Table E-067 Summary and MMRM Analysis of Percent Change from Baseline in Lipid Parameters to All Visits in 24-Week Double-blind Period with Monotherapy (PXL008-014; Efficacy Population)

Parameter		Observed		Percent change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Total Cholesterol (mmol/L)									
Baseline									
Placebo	75	74	5.231 (0.9344)						
Imeglimin 500 mg bid	75	75	5.311 (0.9757)						
Imeglimin 1000 mg bid	73	73	5.455 (1.2120)						
Imeglimin 1500 mg bid	73	73	5.300 (0.8523)						
Week 12									
Placebo	75	66	5.306 (0.8050)	1.398 (10.2894)	1.409 (1.6339)	[-1.8077, 4.6251]			
Imeglimin 500 mg bid	75	71	5.369 (0.8879)	2.547 (11.8289)	2.415 (1.5982)	[-0.7312, 5.5605]	1.006 (1.8118)	[-2.5617, 4.5735]	0.5792
Imeglimin 1000 mg bid	73	67	5.606 (1.2879)	2.141 (12.6555)	3.225 (1.5659)	[0.1426, 6.3078]	1.817 (1.8487)	[-1.8237, 5.4567]	0.3267
Imeglimin 1500 mg bid	73	68	5.272 (0.7903)	-0.077 (10.3826)	0.058 (1.6197)	[-3.1306, 3.2461]	-1.351 (1.8363)	[-4.9669, 2.2650]	0.4626
Week 24									
Placebo	75	65	5.432 (0.9935)	3.405 (11.5469)	3.406 (1.7663)	[-0.0698, 6.8813]			
Imeglimin 500 mg bid	75	70	5.574 (0.9132)	6.474 (13.7584)	6.490 (1.7339)	[3.0785, 9.9010]	3.084 (2.0371)	[-0.9272, 7.0953]	0.1313
Imeglimin 1000 mg bid	73	65	5.749 (1.1635)	4.973 (12.1191)	6.183 (1.7073)	[2.8234, 9.5426]	2.777 (2.0821)	[-1.3227, 6.8772]	0.1834
Imeglimin 1500 mg bid	73	67	5.308 (0.9358)	0.369 (13.2655)	0.432 (1.7488)	[-3.0088, 3.8735]	-2.973 (2.0639)	[-7.0375, 1.0907]	0.1509
LOCF Endpoint									
Placebo	75	66	5.427 (0.9867)	3.345 (11.4682)					
Imeglimin 500 mg bid	75	72	5.558 (0.9060)	6.212 (13.6540)					
Imeglimin 1000 mg bid	73	68	5.734 (1.1484)	4.881 (11.9753)					
Imeglimin 1500 mg bid	73	68	5.295 (0.9346)	0.223 (13.2210)					
LDL-C (mmol/L)									
Baseline									
Placebo	75	69	3.143 (0.7574)						
Imeglimin 500 mg bid	75	72	3.127 (0.8607)						
Imeglimin 1000 mg bid	73	72	3.337 (1.1106)						

Parameter		Observed		Percent change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Imeglimin 1500 mg bid	73	69	3.062 (0.6882)						
Week 12									
Placebo	75	63	3.161 (0.6969)	0.510 (13.0609)	2.952 (2.6087)	[-2.1851, 8.0891]			
Imeglimin 500 mg bid	75	68	3.188 (0.8277)	4.203 (17.0605)	5.821 (2.5040)	[0.8903, 10.7515]	2.869 (2.7872)	[-2.6206, 8.3584]	0.3043
Imeglimin 1000 mg bid	73	66	3.485 (1.1921)	3.129 (17.8273)	6.669 (2.4068)	[1.9298, 11.4089]	3.717 (2.8292)	[-1.8550, 9.2897]	0.1901
Imeglimin 1500 mg bid	73	64	3.090 (0.7299)	1.340 (17.2321)	3.029 (2.5426)	[-1.9782, 8.0355]	0.077 (2.8246)	[-5.4866, 5.6399]	0.9784
Week 24									
Placebo	75	62	3.192 (0.7991)	1.363 (16.5176)	3.693 (3.0445)	[-2.2975, 9.6844]			
Imeglimin 500 mg bid	75	69	3.322 (0.8129)	8.455 (22.6795)	10.490 (2.9093)	[4.7657, 16.2135]	6.796 (3.5127)	[-0.1228, 13.7150]	0.0542
Imeglimin 1000 mg bid	73	63	3.561 (1.1298)	5.259 (17.5737)	9.043 (2.8564)	[3.4218, 14.6645]	5.350 (3.5843)	[-1.7097, 12.4091]	0.1368
Imeglimin 1500 mg bid	73	64	3.103 (0.8405)	3.065 (25.2978)	4.613 (2.9790)	[-1.2491, 10.4748]	0.919 (3.5859)	[-6.1434, 7.9822]	0.7979
LOCF Endpoint									
Placebo	75	64	3.192 (0.7886)	1.209 (16.4234)					
Imeglimin 500 mg bid	75	71	3.294 (0.8239)	8.283 (22.4692)					
Imeglimin 1000 mg bid	73	67	3.546 (1.1050)	5.198 (17.4659)					
Imeglimin 1500 mg bid	73	66	3.092 (0.8302)	2.792 (24.9873)					
HDL-C (mmol/L)									
Baseline									
Placebo	75	74	1.291 (0.3898)						
Imeglimin 500 mg bid	75	75	1.392 (0.4232)						
Imeglimin 1000 mg bid	73	73	1.459 (0.3862)						
Imeglimin 1500 mg bid	73	73	1.385 (0.4076)						
Week 12									
Placebo	75	66	1.351 (0.3891)	5.289 (13.2170)	5.895 (2.0930)	[1.7756, 10.0150]			
Imeglimin 500 mg bid	75	71	1.398 (0.3998)	1.325 (15.5602)	3.060 (2.0386)	[-0.9526, 7.0723]	-2.835 (2.3351)	[-7.4331, 1.7622]	0.2257
Imeglimin 1000 mg bid	73	67	1.483 (0.4120)	1.835 (15.5037)	4.089 (2.0100)	[0.1329, 8.0456]	-1.806 (2.3880)	[-6.5077, 2.8956]	0.4501
Imeglimin 1500 mg bid	73	68	1.337 (0.3828)	-1.391 (12.5883)	0.125 (2.0687)	[-3.9467, 4.1969]	-5.770 (2.3632)	[-10.4232, -1.1172]	0.0153
Week 24									
Placebo	75	65	1.387 (0.4113)	7.635 (15.4607)	8.449 (2.1807)	[4.1579, 12.7401]			

Parameter		Observed		Percent change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Imeglimin 500 mg bid	75	70	1.453 (0.4409)	5.496 (14.6854)	7.279 (2.1355)	[3.0770, 11.4803]	-1.170 (2.4841)	[-6.0614, 3.7207]	0.6379
Imeglimin 1000 mg bid	73	65	1.526 (0.4090)	5.509 (15.6126)	7.502 (2.1060)	[3.3576, 11.6463]	-0.947 (2.5450)	[-5.9579, 4.0638]	0.7101
Imeglimin 1500 mg bid	73	67	1.405 (0.4196)	3.453 (13.6579)	4.906 (2.1545)	[0.6661, 9.1454]	-3.543 (2.5147)	[-8.4947, 1.4082]	0.1600
LOCF Endpoint									
Placebo	75	66	1.383 (0.4092)	7.903 (15.4942)					
Imeglimin 500 mg bid	75	72	1.460 (0.4398)	5.485 (14.5183)					
Imeglimin 1000 mg bid	73	68	1.521 (0.4015)	4.867 (15.5622)					
Imeglimin 1500 mg bid	73	68	1.406 (0.4166)	3.309 (13.6074)					
Triglycerides (mmol/L)									
Baseline									
Placebo	75	74	1.954 (1.5504)						
Imeglimin 500 mg bid	75	75	1.840 (1.1764)						
Imeglimin 1000 mg bid	73	73	1.456 (0.6350)						
Imeglimin 1500 mg bid	73	73	1.924 (1.4096)						
Week 12									
Placebo	75	66	1.930 (1.6123)	9.097 (46.7947)	0.473 (7.5105)	[-14.3015, 15.2471]			
Imeglimin 500 mg bid	75	71	1.823 (1.2618)	16.059 (88.5708)	5.976 (7.3011)	[-8.3854, 20.3380]	5.503 (9.2754)	[-12.7589, 23.7659]	0.5535
Imeglimin 1000 mg bid	73	67	1.473 (0.7441)	3.969 (30.0049)	-7.651 (7.3325)	[-22.0765, 6.7744]	-8.124 (9.4457)	[-26.7209, 10.4731]	0.3905
Imeglimin 1500 mg bid	73	68	1.879 (1.1300)	6.441 (33.5297)	-1.909 (7.4342)	[-16.5323, 12.7152]	-2.381 (9.3805)	[-20.8506, 16.0878]	0.7998
Week 24									
Placebo	75	65	1.974 (1.5051)	10.648 (39.6713)	2.158 (5.6678)	[-8.9983, 13.3133]			
Imeglimin 500 mg bid	75	70	1.735 (0.9330)	7.741 (39.7353)	-2.759 (5.6279)	[-13.8353, 8.3168]	-4.917 (6.2621)	[-17.2474, 7.4138]	0.4331
Imeglimin 1000 mg bid	73	65	1.533 (0.9381)	5.394 (35.6389)	-5.931 (5.4775)	[-16.7126, 4.8504]	-8.089 (6.4274)	[-20.7445, 4.5673]	0.2093
Imeglimin 1500 mg bid	73	67	1.795 (1.2730)	-1.194 (36.5297)	-9.325 (5.6279)	[-20.4022, 1.7520]	-11.483 (6.3346)	[-23.9560, 0.9908]	0.0710
LOCF Endpoint									
Placebo	75	66	1.958 (1.4993)	10.676 (39.3656)					
Imeglimin 500 mg bid	75	72	1.745 (0.9222)	7.302 (39.5069)					
Imeglimin 1000 mg bid	73	68	1.527 (0.9214)	6.805 (35.4874)					

Parameter		Observed		Percent change from baseline			Difference vs Placebo		
Visit									
Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Imeglimin 1500 mg bid	73	68	1.779 (1.2702)	-0.714 (36.4719)					

- Abbreviations: MMRM, Mixed Model Repeated Measures; LOCF, Last Observation Carried Forward; bid, Twice a day; SD, standard deviation; SE, standard error; LS, least square; CI, confidence interval; LDL, Low Density Lipoprotein; LDL-C, LDL Cholesterol; HDL, High Density Lipoprotein; HDL-C, HDL Cholesterol
- MMRM model was used with fixed effects for treatment group, visit, randomization strata of HbA1c (< 8.0%, >= 8.0%), randomization strata of previous treatment status, interaction of treatment-by-visit, and baseline value as a covariate, assuming an unstructured covariance matrix.

Control No:<<t-e-067-lipid-014db.sas, 2020-03-06T00:05:19>>

Table E-068 Summary and MMRM Analysis of Percent Change from Baseline in Lipid Parameters to All Visits in 24-Week Double-blind Period with Monotherapy (PXL008-018; Efficacy Population)

Parameter		Observed		Percent change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Total Cholesterol (mmol/L)									
Baseline									
Placebo	106	106	5.198 (0.8385)						
Imeglimin 1000 mg bid	106	106	5.019 (0.9148)						
Week 12									
Placebo	106	103	5.057 (0.8451)	-2.520 (11.7933)	-0.380 (1.6475)	[-3.6264, 2.8672]			
Imeglimin 1000 mg bid	106	105	5.017 (0.9704)	0.490 (11.5074)	1.792 (1.6137)	[-1.3879, 4.9727]	2.172 (1.5372)	[-0.8592, 5.2032]	0.1592
Week 24									
Placebo	106	96	5.123 (0.8351)	-1.254 (12.2694)	0.933 (1.7104)	[-2.4352, 4.3018]			
Imeglimin 1000 mg bid	106	98	5.161 (0.9402)	2.697 (11.9892)	4.257 (1.6723)	[0.9630, 7.5504]	3.323 (1.6384)	[0.0916, 6.5552]	0.0439
LOCF Endpoint									
Placebo	106	103	5.114 (0.8613)	-1.377 (12.6067)					
Imeglimin 1000 mg bid	106	105	5.128 (0.9281)	2.854 (11.7724)					
LDL-C (mmol/L)									
Baseline									
Placebo	106	106	2.998 (0.7631)						
Imeglimin 1000 mg bid	106	106	2.887 (0.8389)						
Week 12									
Placebo	106	103	2.926 (0.7779)	-2.024 (17.5054)	1.992 (2.4219)	[-2.7814, 6.7646]			
Imeglimin 1000 mg bid	106	105	2.946 (0.9028)	3.053 (16.1084)	6.161 (2.3692)	[1.4917, 10.8298]	4.169 (2.2519)	[-0.2712, 8.6095]	0.0656
Week 24									
Placebo	106	96	2.946 (0.7484)	-0.916 (17.3678)	3.114 (2.5827)	[-1.9714, 8.1997]			
Imeglimin 1000 mg bid	106	98	3.041 (0.8421)	6.764 (19.9827)	10.313 (2.5243)	[5.3420, 15.2836]	7.199 (2.5378)	[2.1927, 12.2045]	0.0051
LOCF Endpoint									
Placebo	106	103	2.955 (0.7849)	-1.117 (18.0665)					
Imeglimin 1000 mg bid	106	105	3.033 (0.8330)	7.212 (19.6336)					

Parameter		Observed		Percent change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
HDL-C (mmol/L)									
Baseline									
Placebo	106	106	1.451 (0.4082)						
Imeglimin 1000 mg bid	106	106	1.435 (0.4620)						
Week 12									
Placebo	106	103	1.427 (0.4365)	-0.950 (11.8842)	-2.419 (1.7175)	[-5.8040, 0.9658]			
Imeglimin 1000 mg bid	106	105	1.367 (0.4087)	-3.205 (11.6694)	-4.755 (1.6783)	[-8.0630, -1.4477]	-2.336 (1.5792)	[-5.4502, 0.7777]	0.1406
Week 24									
Placebo	106	96	1.456 (0.4918)	-0.211 (14.2638)	-1.778 (1.8869)	[-5.4924, 1.9369]			
Imeglimin 1000 mg bid	106	98	1.405 (0.4287)	-0.859 (13.6380)	-2.482 (1.8442)	[-6.1131, 1.1484]	-0.705 (1.8957)	[-4.4438, 3.0346]	0.7105
LOCF Endpoint									
Placebo	106	103	1.441 (0.4794)	-0.486 (13.8410)					
Imeglimin 1000 mg bid	106	105	1.394 (0.4201)	-1.261 (13.6507)					
Triglycerides (mmol/L)									
Baseline									
Placebo	106	106	1.771 (1.5363)						
Imeglimin 1000 mg bid	106	106	1.525 (0.7711)						
Week 12									
Placebo	106	103	1.543 (0.8840)	-0.238 (42.7000)	1.016 (5.5586)	[-9.9388, 11.9717]			
Imeglimin 1000 mg bid	106	105	1.549 (0.8241)	5.702 (34.4019)	4.493 (5.4114)	[-6.1720, 15.1585]	3.477 (5.1211)	[-6.6210, 13.5745]	0.4980
Week 24									
Placebo	106	96	1.717 (1.7764)	2.838 (44.1507)	4.215 (6.1143)	[-7.8212, 16.2513]			
Imeglimin 1000 mg bid	106	98	1.563 (0.7803)	7.121 (43.1840)	5.882 (5.9562)	[-5.8432, 17.6078]	1.667 (6.1559)	[-10.4730, 13.8075]	0.7868
LOCF Endpoint									
Placebo	106	103	1.704 (1.7230)	2.563 (43.2146)					

Parameter		Observed		Percent change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Imeglimin 1000 mg bid	106	105	1.533 (0.7669)	6.694 (41.9806)					

- Abbreviations: MMRM, Mixed Model Repeated Measures; LOCF, Last Observation Carried Forward; bid, Twice a day; SD, standard deviation; SE, standard error; LS, least square; CI, confidence interval; LDL, Low Density Lipoprotein; LDL-C, LDL Cholesterol; HDL, High Density Lipoprotein; HDL-C, HDL Cholesterol
- MMRM model was used with fixed effects for treatment group, visit, randomization strata of HbA1c (< 8.0%, >= 8.0%), randomization strata of previous treatment status, interaction of treatment-by-visit, and baseline value as a covariate, assuming an unstructured covariance matrix.

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Table E-069 Summary of Change from Baseline in HbA1c (%) to All Visits in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Efficacy Population)

Parameter Treatment	Observed		Change from baseline		Paired t-test
Visit	n	Mean (SD)	Mean (SD)	[95% CI]	P-value
HbA1c (%)					
Imeglimin (N = 134)					
Baseline	134	7.83 (0.730)			
Week 4	134	7.61 (0.728)	-0.22 (0.274)	[-0.266, -0.172]	<.0001
Week 8	132	7.45 (0.752)	-0.38 (0.442)	[-0.452, -0.300]	<.0001
Week 12	131	7.31 (0.747)	-0.52 (0.571)	[-0.614, -0.417]	<.0001
Week 16	130	7.22 (0.769)	-0.61 (0.618)	[-0.713, -0.499]	<.0001
Week 20	130	7.12 (0.771)	-0.70 (0.593)	[-0.804, -0.598]	<.0001
Week 24	129	7.07 (0.746)	-0.74 (0.611)	[-0.850, -0.637]	<.0001
Week 28	128	7.09 (0.752)	-0.72 (0.629)	[-0.832, -0.612]	<.0001
Week 32	127	7.09 (0.726)	-0.73 (0.599)	[-0.834, -0.624]	<.0001
Week 36	127	7.23 (0.769)	-0.59 (0.625)	[-0.700, -0.480]	<.0001
Week 40	127	7.21 (0.788)	-0.60 (0.632)	[-0.714, -0.492]	<.0001
Week 44	125	7.25 (0.784)	-0.53 (0.707)	[-0.659, -0.408]	<.0001
Week 48	125	7.27 (0.802)	-0.52 (0.721)	[-0.644, -0.389]	<.0001
Week 52	124	7.30 (0.848)	-0.49 (0.751)	[-0.624, -0.357]	<.0001
LOCF Endpoint	134	7.36 (0.920)	-0.46 (0.758)	[-0.594, -0.335]	<.0001
Imeglimin + SU (N = 127)					
Baseline	127	8.63 (0.903)			
Week 4	127	8.32 (0.975)	-0.31 (0.402)	[-0.382, -0.241]	<.0001
Week 8	124	8.09 (0.985)	-0.52 (0.567)	[-0.623, -0.422]	<.0001
Week 12	122	7.92 (0.949)	-0.68 (0.683)	[-0.807, -0.562]	<.0001
Week 16	121	7.84 (0.988)	-0.76 (0.757)	[-0.894, -0.622]	<.0001
Week 20	121	7.75 (1.009)	-0.84 (0.797)	[-0.982, -0.695]	<.0001
Week 24	119	7.77 (0.980)	-0.79 (0.798)	[-0.936, -0.646]	<.0001
Week 28	117	7.82 (0.992)	-0.72 (0.830)	[-0.869, -0.565]	<.0001
Week 32	115	7.86 (1.043)	-0.70 (0.826)	[-0.850, -0.545]	<.0001
Week 36	113	7.98 (1.048)	-0.57 (0.840)	[-0.731, -0.418]	<.0001
Week 40	113	7.96 (1.095)	-0.60 (0.904)	[-0.766, -0.429]	<.0001
Week 44	112	8.02 (1.077)	-0.53 (0.859)	[-0.690, -0.369]	<.0001
Week 48	110	7.91 (0.999)	-0.62 (0.818)	[-0.777, -0.468]	<.0001
Week 52	110	7.92 (1.016)	-0.62 (0.836)	[-0.777, -0.461]	<.0001
LOCF Endpoint	127	8.08 (1.135)	-0.55 (0.871)	[-0.700, -0.394]	<.0001
Imeglimin + GLIN (N = 64)					
Baseline	64	8.48 (0.837)			
Week 4	63	8.14 (0.810)	-0.33 (0.328)	[-0.416, -0.251]	<.0001
Week 8	62	7.90 (0.788)	-0.58 (0.462)	[-0.701, -0.467]	<.0001
Week 12	62	7.68 (0.758)	-0.80 (0.573)	[-0.945, -0.655]	<.0001
Week 16	62	7.56 (0.834)	-0.92 (0.728)	[-1.104, -0.734]	<.0001
Week 20	61	7.47 (0.903)	-1.04 (0.833)	[-1.250, -0.823]	<.0001
Week 24	61	7.55 (0.922)	-0.95 (0.831)	[-1.165, -0.740]	<.0001
Week 28	61	7.68 (0.956)	-0.82 (0.850)	[-1.039, -0.604]	<.0001
Week 32	61	7.71 (0.996)	-0.79 (0.866)	[-1.010, -0.567]	<.0001
Week 36	59	7.84 (1.033)	-0.66 (0.877)	[-0.891, -0.434]	<.0001
Week 40	59	7.82 (1.031)	-0.69 (0.915)	[-0.925, -0.448]	<.0001
Week 44	59	7.92 (1.094)	-0.59 (0.935)	[-0.832, -0.344]	<.0001
Week 48	59	7.83 (1.139)	-0.67 (0.988)	[-0.927, -0.412]	<.0001

Parameter Treatment	Observed		Change from baseline		Paired t-test
Visit	n	Mean (SD)	Mean (SD)	[95% CI]	P-value
Week 52	58	7.76 (1.160)	-0.75 (0.981)	[-1.005, -0.489]	<.0001
LOCF Endpoint	63	7.77 (1.134)	-0.70 (0.968)	[-0.944, -0.456]	<.0001
Imeglimin + BIG (N = 64)					
Baseline	64	8.16 (0.607)			
Week 4	63	7.88 (0.663)	-0.30 (0.271)	[-0.363, -0.227]	<.0001
Week 8	63	7.57 (0.681)	-0.60 (0.466)	[-0.716, -0.481]	<.0001
Week 12	62	7.43 (0.672)	-0.74 (0.545)	[-0.877, -0.600]	<.0001
Week 16	60	7.36 (0.764)	-0.82 (0.694)	[-0.994, -0.636]	<.0001
Week 20	60	7.28 (0.751)	-0.90 (0.659)	[-1.070, -0.730]	<.0001
Week 24	58	7.28 (0.792)	-0.88 (0.661)	[-1.053, -0.705]	<.0001
Week 28	58	7.38 (0.865)	-0.78 (0.750)	[-0.973, -0.579]	<.0001
Week 32	56	7.26 (0.734)	-0.89 (0.615)	[-1.054, -0.725]	<.0001
Week 36	56	7.37 (0.718)	-0.78 (0.615)	[-0.949, -0.619]	<.0001
Week 40	55	7.34 (0.765)	-0.81 (0.711)	[-0.998, -0.613]	<.0001
Week 44	55	7.44 (0.747)	-0.71 (0.684)	[-0.894, -0.524]	<.0001
Week 48	53	7.37 (0.777)	-0.79 (0.722)	[-0.992, -0.593]	<.0001
Week 52	53	7.45 (0.770)	-0.72 (0.697)	[-0.913, -0.529]	<.0001
LOCF Endpoint	63	7.51 (0.850)	-0.66 (0.774)	[-0.855, -0.465]	<.0001
Imeglimin + AGI (N = 64)					
Baseline	64	8.37 (0.771)			
Week 4	64	8.04 (0.753)	-0.33 (0.338)	[-0.409, -0.241]	<.0001
Week 8	64	7.78 (0.729)	-0.59 (0.529)	[-0.718, -0.454]	<.0001
Week 12	64	7.55 (0.635)	-0.81 (0.634)	[-0.972, -0.656]	<.0001
Week 16	63	7.40 (0.655)	-0.97 (0.670)	[-1.143, -0.806]	<.0001
Week 20	63	7.32 (0.660)	-1.05 (0.710)	[-1.228, -0.870]	<.0001
Week 24	62	7.33 (0.698)	-1.04 (0.704)	[-1.222, -0.865]	<.0001
Week 28	62	7.45 (0.689)	-0.92 (0.676)	[-1.088, -0.745]	<.0001
Week 32	61	7.47 (0.737)	-0.91 (0.682)	[-1.084, -0.735]	<.0001
Week 36	61	7.54 (0.806)	-0.83 (0.744)	[-1.022, -0.640]	<.0001
Week 40	61	7.53 (0.850)	-0.85 (0.726)	[-1.034, -0.662]	<.0001
Week 44	60	7.57 (0.805)	-0.77 (0.715)	[-0.955, -0.585]	<.0001
Week 48	60	7.49 (0.780)	-0.85 (0.695)	[-1.030, -0.670]	<.0001
Week 52	60	7.46 (0.790)	-0.88 (0.723)	[-1.063, -0.690]	<.0001
LOCF Endpoint	64	7.51 (0.869)	-0.85 (0.715)	[-1.032, -0.675]	<.0001
Imeglimin + TZD (N = 65)					
Baseline	65	8.72 (0.942)			
Week 4	64	8.38 (0.975)	-0.32 (0.380)	[-0.418, -0.229]	<.0001
Week 8	63	8.06 (0.895)	-0.67 (0.500)	[-0.791, -0.539]	<.0001
Week 12	63	7.77 (0.831)	-0.96 (0.623)	[-1.112, -0.799]	<.0001
Week 16	62	7.67 (0.852)	-1.07 (0.721)	[-1.249, -0.883]	<.0001
Week 20	63	7.57 (0.826)	-1.16 (0.770)	[-1.354, -0.966]	<.0001
Week 24	63	7.56 (0.839)	-1.17 (0.815)	[-1.370, -0.960]	<.0001
Week 28	63	7.61 (0.842)	-1.11 (0.879)	[-1.336, -0.893]	<.0001
Week 32	62	7.65 (0.849)	-1.09 (0.854)	[-1.310, -0.877]	<.0001
Week 36	62	7.74 (0.867)	-1.00 (0.895)	[-1.224, -0.769]	<.0001
Week 40	62	7.72 (0.906)	-1.02 (0.917)	[-1.251, -0.785]	<.0001
Week 44	61	7.87 (0.944)	-0.89 (0.985)	[-1.139, -0.635]	<.0001
Week 48	61	7.81 (0.888)	-0.92 (0.955)	[-1.161, -0.672]	<.0001
Week 52	61	7.82 (0.883)	-0.90 (0.951)	[-1.149, -0.661]	<.0001
LOCF Endpoint	64	7.83 (0.958)	-0.87 (0.974)	[-1.117, -0.630]	<.0001

Parameter Treatment Visit	Observed n	Mean (SD)	Change from baseline Mean (SD)	[95% CI]	Paired t-test P-value
Imeglimin + DPP4-I (N = 63)					
Baseline	63	8.23 (0.750)			
Week 4	62	7.88 (0.778)	-0.36 (0.296)	[-0.440, -0.289]	<.0001
Week 8	60	7.49 (0.705)	-0.74 (0.465)	[-0.860, -0.620]	<.0001
Week 12	59	7.32 (0.636)	-0.92 (0.618)	[-1.081, -0.759]	<.0001
Week 16	59	7.18 (0.622)	-1.06 (0.704)	[-1.243, -0.876]	<.0001
Week 20	58	7.09 (0.679)	-1.16 (0.710)	[-1.342, -0.969]	<.0001
Week 24	58	7.05 (0.734)	-1.19 (0.750)	[-1.392, -0.998]	<.0001
Week 28	56	7.05 (0.762)	-1.19 (0.805)	[-1.410, -0.979]	<.0001
Week 32	57	7.04 (0.783)	-1.21 (0.813)	[-1.423, -0.991]	<.0001
Week 36	57	7.17 (0.816)	-1.08 (0.816)	[-1.299, -0.866]	<.0001
Week 40	56	7.15 (0.852)	-1.09 (0.818)	[-1.314, -0.876]	<.0001
Week 44	56	7.26 (0.863)	-0.99 (0.820)	[-1.207, -0.768]	<.0001
Week 48	56	7.26 (0.863)	-0.99 (0.792)	[-1.199, -0.776]	<.0001
Week 52	55	7.24 (0.841)	-0.97 (0.831)	[-1.190, -0.741]	<.0001
LOCF Endpoint	62	7.33 (0.911)	-0.91 (0.805)	[-1.117, -0.708]	<.0001
Imeglimin + GLP1-RA (N = 70)					
Baseline	70	8.66 (0.848)			
Week 4	69	8.54 (0.931)	-0.13 (0.393)	[-0.225, -0.036]	0.0075
Week 8	64	8.43 (0.928)	-0.18 (0.548)	[-0.320, -0.046]	0.0097
Week 12	64	8.32 (0.982)	-0.29 (0.648)	[-0.448, -0.124]	0.0008
Week 16	62	8.14 (0.901)	-0.42 (0.744)	[-0.613, -0.235]	<.0001
Week 20	61	8.08 (0.932)	-0.48 (0.793)	[-0.682, -0.276]	<.0001
Week 24	61	8.08 (0.919)	-0.47 (0.790)	[-0.673, -0.268]	<.0001
Week 28	59	8.22 (0.938)	-0.34 (0.788)	[-0.546, -0.135]	0.0015
Week 32	57	8.19 (0.992)	-0.35 (0.836)	[-0.576, -0.133]	0.0023
Week 36	56	8.25 (0.997)	-0.28 (0.870)	[-0.517, -0.051]	0.0179
Week 40	56	8.29 (0.996)	-0.25 (0.929)	[-0.499, -0.001]	0.0489
Week 44	53	8.38 (1.054)	-0.17 (0.975)	[-0.435, 0.103]	0.2206
Week 48	51	8.31 (1.058)	-0.22 (0.954)	[-0.488, 0.049]	0.1066
Week 52	51	8.28 (1.069)	-0.25 (0.976)	[-0.527, 0.022]	0.0701
LOCF Endpoint	69	8.53 (1.211)	-0.14 (0.947)	[-0.368, 0.087]	0.2218
Imeglimin + SGLT2-I (N = 63)					
Baseline	63	8.50 (0.748)			
Week 4	63	8.23 (0.665)	-0.27 (0.287)	[-0.342, -0.198]	<.0001
Week 8	63	8.00 (0.686)	-0.50 (0.413)	[-0.607, -0.399]	<.0001
Week 12	63	7.88 (0.648)	-0.62 (0.488)	[-0.740, -0.495]	<.0001
Week 16	63	7.82 (0.733)	-0.68 (0.522)	[-0.809, -0.546]	<.0001
Week 20	62	7.68 (0.658)	-0.78 (0.560)	[-0.921, -0.637]	<.0001
Week 24	62	7.64 (0.687)	-0.82 (0.580)	[-0.968, -0.674]	<.0001
Week 28	62	7.70 (0.725)	-0.76 (0.627)	[-0.917, -0.599]	<.0001
Week 32	62	7.71 (0.747)	-0.75 (0.634)	[-0.914, -0.592]	<.0001
Week 36	62	7.83 (0.808)	-0.63 (0.662)	[-0.799, -0.462]	<.0001
Week 40	62	7.84 (0.794)	-0.62 (0.635)	[-0.784, -0.461]	<.0001
Week 44	61	7.92 (0.772)	-0.55 (0.530)	[-0.683, -0.412]	<.0001
Week 48	61	7.89 (0.774)	-0.58 (0.570)	[-0.723, -0.431]	<.0001
Week 52	61	7.90 (0.781)	-0.58 (0.563)	[-0.720, -0.431]	<.0001

Parameter Treatment Visit	Observed n	 Mean (SD)	Change from baseline Mean (SD)	 [95% CI]	Paired t-test P-value
LOCF Endpoint	63	7.92 (0.852)	-0.58 (0.561)	[-0.721, -0.438]	<.0001

- Abbreviations: LOCF, Last Observation Carried Forward; SD, standard deviation; CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".

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Table E-070 Summary of Change from Baseline in Fasting Plasma Glucose (mg/dL) to All Visits in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Efficacy Population)

Parameter Treatment	Observed		Change from baseline		Paired t-test
Visit	n	Mean (SD)	Mean (SD)	[95% CI]	P-value
Fasting Plasma Glucose (mg/dL)					
Imeglimin (N = 134)					
Baseline	134	163.19 (25.578)			
Week 4	134	150.42 (23.648)	-12.77 (18.522)	[-15.937, -9.607]	<.0001
Week 8	132	147.86 (23.826)	-15.35 (19.240)	[-18.667, -12.041]	<.0001
Week 12	131	144.65 (27.130)	-18.35 (23.392)	[-22.389, -14.302]	<.0001
Week 16	130	145.48 (25.236)	-17.61 (21.305)	[-21.311, -13.917]	<.0001
Week 20	130	144.65 (24.704)	-18.45 (20.996)	[-22.089, -14.802]	<.0001
Week 24	129	142.73 (24.811)	-19.96 (24.620)	[-24.246, -15.668]	<.0001
Week 28	128	145.64 (23.270)	-17.34 (24.439)	[-21.614, -13.066]	<.0001
Week 32	127	149.47 (25.413)	-13.50 (25.534)	[-17.989, -9.021]	<.0001
Week 36	127	150.17 (24.700)	-12.81 (23.512)	[-16.938, -8.681]	<.0001
Week 40	127	152.78 (27.084)	-10.20 (24.670)	[-14.531, -5.867]	<.0001
Week 44	125	152.46 (26.196)	-9.93 (23.850)	[-14.152, -5.708]	<.0001
Week 48	125	150.13 (25.679)	-12.25 (25.614)	[-16.785, -7.716]	<.0001
Week 52	124	150.21 (28.920)	-11.83 (28.053)	[-16.813, -6.840]	<.0001
LOCF Endpoint	134	151.51 (30.445)	-11.68 (27.414)	[-16.367, -6.999]	<.0001
Imeglimin + SU (N = 127)					
Baseline	127	185.13 (37.679)			
Week 4	127	166.30 (38.385)	-18.84 (23.713)	[-23.002, -14.674]	<.0001
Week 8	124	164.42 (34.484)	-20.09 (30.175)	[-25.457, -14.729]	<.0001
Week 12	122	162.36 (35.221)	-21.88 (29.916)	[-27.247, -16.522]	<.0001
Week 16	121	163.03 (35.326)	-20.70 (32.870)	[-26.612, -14.779]	<.0001
Week 20	121	163.75 (38.222)	-19.98 (33.039)	[-25.928, -14.034]	<.0001
Week 24	119	163.94 (35.871)	-19.15 (29.873)	[-24.574, -13.728]	<.0001
Week 28	117	171.86 (38.304)	-10.62 (32.384)	[-16.554, -4.695]	0.0006
Week 32	115	171.30 (34.934)	-11.80 (32.065)	[-17.720, -5.873]	0.0001
Week 36	113	175.93 (37.675)	-7.19 (35.918)	[-13.885, -0.495]	0.0355
Week 40	113	171.63 (36.565)	-11.49 (30.492)	[-17.178, -5.811]	0.0001
Week 44	112	170.15 (33.246)	-13.05 (30.070)	[-18.676, -7.415]	<.0001
Week 48	110	169.69 (33.535)	-13.66 (30.201)	[-19.366, -7.952]	<.0001
Week 52	110	167.40 (35.962)	-15.95 (30.451)	[-21.706, -10.197]	<.0001
LOCF Endpoint	127	171.72 (41.116)	-13.42 (33.950)	[-19.381, -7.458]	<.0001
Imeglimin + GLIN (N = 64)					
Baseline	64	179.76 (33.493)			
Week 4	63	162.20 (30.737)	-17.13 (26.352)	[-23.766, -10.492]	<.0001
Week 8	62	156.88 (27.615)	-22.20 (26.370)	[-28.897, -15.503]	<.0001
Week 12	62	154.18 (30.203)	-24.90 (29.772)	[-32.463, -17.342]	<.0001
Week 16	62	154.59 (29.685)	-24.50 (30.401)	[-32.216, -16.775]	<.0001
Week 20	61	159.07 (31.999)	-21.09 (28.654)	[-28.426, -13.748]	<.0001
Week 24	61	161.11 (31.491)	-19.05 (30.005)	[-26.734, -11.365]	<.0001
Week 28	61	165.86 (29.371)	-14.29 (28.517)	[-21.598, -6.991]	0.0002
Week 32	61	167.63 (37.880)	-12.52 (35.492)	[-21.612, -3.432]	0.0077
Week 36	59	167.97 (35.556)	-11.54 (30.359)	[-19.454, -3.631]	0.0050
Week 40	59	168.31 (36.912)	-11.21 (30.751)	[-19.220, -3.193]	0.0069
Week 44	59	166.96 (34.454)	-12.55 (28.819)	[-20.060, -5.040]	0.0014
Week 48	59	164.58 (39.955)	-14.93 (35.597)	[-24.208, -5.655]	0.0021

Parameter Treatment Visit	Observed n	 Mean (SD)	Change from baseline Mean (SD)	 [95% CI]	Paired t-test P-value
Week 52	58	162.79 (40.435)	-17.27 (34.131)	[-26.244, -8.296]	0.0003
LOCF Endpoint	63	162.40 (39.295)	-16.93 (35.252)	[-25.807, -8.051]	0.0003
Imeglimin + BIG (N = 64)					
Baseline	64	174.86 (30.714)			
Week 4	63	157.16 (31.757)	-18.24 (26.585)	[-24.940, -11.549]	<.0001
Week 8	63	149.93 (27.709)	-25.48 (21.871)	[-30.987, -19.971]	<.0001
Week 12	62	148.54 (28.721)	-26.91 (29.244)	[-34.334, -19.480]	<.0001
Week 16	60	148.06 (32.490)	-26.75 (27.265)	[-33.796, -19.710]	<.0001
Week 20	60	151.57 (36.360)	-23.24 (30.840)	[-31.207, -15.273]	<.0001
Week 24	58	148.44 (35.085)	-25.31 (28.297)	[-32.755, -17.875]	<.0001
Week 28	58	153.85 (37.633)	-19.91 (29.007)	[-27.537, -12.283]	<.0001
Week 32	56	151.85 (32.234)	-22.00 (23.185)	[-28.214, -15.796]	<.0001
Week 36	56	155.22 (35.396)	-18.63 (30.927)	[-26.909, -10.344]	<.0001
Week 40	55	154.31 (31.243)	-19.46 (25.084)	[-26.238, -12.676]	<.0001
Week 44	55	154.90 (30.509)	-18.87 (24.050)	[-25.369, -12.365]	<.0001
Week 48	53	153.27 (29.785)	-21.14 (24.659)	[-27.940, -14.346]	<.0001
Week 52	53	148.85 (31.606)	-25.56 (25.088)	[-32.477, -18.647]	<.0001
LOCF Endpoint	63	152.02 (34.930)	-23.39 (31.847)	[-31.412, -15.371]	<.0001
Imeglimin + AGI (N = 64)					
Baseline	64	173.93 (31.336)			
Week 4	64	156.37 (24.781)	-17.57 (18.993)	[-22.309, -12.821]	<.0001
Week 8	64	153.64 (23.914)	-20.30 (25.812)	[-26.743, -13.848]	<.0001
Week 12	64	150.04 (21.162)	-23.90 (27.184)	[-30.689, -17.108]	<.0001
Week 16	63	149.93 (25.177)	-24.08 (29.290)	[-31.455, -16.701]	<.0001
Week 20	63	153.50 (29.576)	-20.50 (29.764)	[-27.999, -13.008]	<.0001
Week 24	62	152.44 (27.573)	-21.56 (29.592)	[-29.075, -14.046]	<.0001
Week 28	62	158.77 (28.911)	-15.23 (28.258)	[-22.402, -8.050]	<.0001
Week 32	61	156.03 (29.778)	-17.87 (28.368)	[-25.133, -10.603]	<.0001
Week 36	61	157.00 (28.250)	-16.89 (29.859)	[-24.541, -9.246]	<.0001
Week 40	61	156.29 (33.618)	-17.60 (31.015)	[-25.545, -9.659]	<.0001
Week 44	60	159.89 (32.758)	-13.66 (29.764)	[-21.351, -5.973]	0.0008
Week 48	60	154.87 (31.078)	-18.68 (31.520)	[-26.819, -10.534]	<.0001
Week 52	60	153.19 (30.817)	-20.36 (28.701)	[-27.772, -12.943]	<.0001
LOCF Endpoint	64	153.67 (32.110)	-20.27 (29.393)	[-27.610, -12.925]	<.0001
Imeglimin + TZD (N = 65)					
Baseline	65	171.62 (32.202)			
Week 4	64	157.61 (28.216)	-13.65 (20.817)	[-18.852, -8.453]	<.0001
Week 8	63	147.76 (26.964)	-24.31 (26.085)	[-30.876, -17.737]	<.0001
Week 12	63	147.44 (29.688)	-24.62 (27.095)	[-31.445, -17.798]	<.0001
Week 16	62	148.63 (26.062)	-23.54 (29.726)	[-31.086, -15.987]	<.0001
Week 20	63	150.67 (27.661)	-21.39 (29.273)	[-28.762, -14.018]	<.0001
Week 24	63	146.67 (26.340)	-25.39 (28.409)	[-32.548, -18.239]	<.0001
Week 28	63	153.85 (28.255)	-18.22 (30.632)	[-25.930, -10.501]	<.0001
Week 32	62	153.89 (26.317)	-18.28 (28.941)	[-25.627, -10.928]	<.0001
Week 36	62	156.53 (28.868)	-15.63 (30.496)	[-23.378, -7.888]	0.0002
Week 40	62	158.51 (33.019)	-13.66 (34.802)	[-22.495, -4.819]	0.0030
Week 44	62	155.34 (31.603)	-16.82 (29.617)	[-24.346, -9.303]	<.0001
Week 48	61	154.55 (27.397)	-17.10 (30.263)	[-24.851, -9.349]	<.0001
Week 52	61	154.40 (32.437)	-17.25 (32.434)	[-25.554, -8.941]	0.0001
LOCF Endpoint	64	154.29 (32.961)	-16.97 (32.245)	[-25.028, -8.920]	<.0001

Parameter Treatment Visit	Observed n	 Mean (SD)	Change from baseline Mean (SD)	 [95% CI]	Paired t-test P-value
Imeglimin + DPP4-I (N = 63)					
Baseline	63	180.10 (32.963)			
Week 4	62	154.61 (36.323)	-25.83 (33.018)	[-34.217, -17.447]	<.0001
Week 8	60	150.16 (27.986)	-30.69 (26.419)	[-37.511, -23.862]	<.0001
Week 12	59	146.87 (27.165)	-34.23 (23.170)	[-40.268, -28.191]	<.0001
Week 16	59	148.92 (28.244)	-32.18 (27.117)	[-39.251, -25.117]	<.0001
Week 20	58	146.98 (24.547)	-34.20 (26.338)	[-41.124, -27.273]	<.0001
Week 24	58	146.83 (27.757)	-34.35 (26.242)	[-41.254, -27.454]	<.0001
Week 28	56	151.11 (29.649)	-30.63 (27.496)	[-37.990, -23.263]	<.0001
Week 32	57	149.34 (30.062)	-31.86 (25.795)	[-38.703, -25.015]	<.0001
Week 36	57	149.85 (30.277)	-31.35 (28.416)	[-38.893, -23.814]	<.0001
Week 40	56	154.16 (33.133)	-26.89 (24.751)	[-33.523, -20.266]	<.0001
Week 44	56	158.25 (33.220)	-22.81 (28.647)	[-30.481, -15.137]	<.0001
Week 48	56	154.77 (35.032)	-26.28 (27.157)	[-33.556, -19.011]	<.0001
Week 52	55	152.61 (35.326)	-27.15 (28.958)	[-34.983, -19.326]	<.0001
LOCF Endpoint	62	157.52 (43.975)	-22.93 (36.572)	[-32.214, -13.639]	<.0001
Imeglimin + GLP1-RA (N = 70)					
Baseline	70	191.04 (39.655)			
Week 4	69	173.76 (37.923)	-17.21 (32.303)	[-24.966, -9.446]	<.0001
Week 8	64	165.15 (33.675)	-22.32 (31.765)	[-30.257, -14.388]	<.0001
Week 12	64	166.19 (36.217)	-21.28 (30.529)	[-28.907, -13.655]	<.0001
Week 16	62	168.82 (33.986)	-17.35 (37.475)	[-26.864, -7.830]	0.0006
Week 20	61	169.73 (35.360)	-16.51 (38.575)	[-26.389, -6.630]	0.0014
Week 24	61	164.06 (31.218)	-22.18 (36.898)	[-31.630, -12.730]	<.0001
Week 28	59	172.31 (35.670)	-15.57 (37.579)	[-25.366, -5.780]	0.0023
Week 32	57	169.47 (34.704)	-19.41 (39.621)	[-29.919, -8.893]	0.0005
Week 36	56	175.27 (38.287)	-12.61 (37.265)	[-22.590, -2.631]	0.0142
Week 40	56	170.09 (37.738)	-17.79 (39.078)	[-28.256, -7.325]	0.0012
Week 44	53	173.87 (35.674)	-13.32 (40.377)	[-24.454, -2.195]	0.0199
Week 48	51	167.09 (32.219)	-18.51 (36.527)	[-28.783, -8.237]	0.0007
Week 52	51	164.97 (32.236)	-20.63 (39.792)	[-31.821, -9.438]	0.0005
LOCF Endpoint	69	175.61 (42.674)	-15.35 (45.254)	[-26.224, -4.481]	0.0063
Imeglimin + SGLT2-I (N = 63)					
Baseline	63	165.57 (27.745)			
Week 4	63	157.85 (24.722)	-7.72 (23.475)	[-13.633, -1.809]	0.0113
Week 8	63	153.56 (23.790)	-12.01 (23.828)	[-18.011, -6.009]	0.0002
Week 12	63	149.76 (26.138)	-15.81 (22.791)	[-21.554, -10.074]	<.0001
Week 16	63	151.47 (30.654)	-14.10 (23.573)	[-20.035, -8.161]	<.0001
Week 20	62	151.88 (28.383)	-13.22 (20.652)	[-18.466, -7.977]	<.0001
Week 24	62	150.63 (25.651)	-14.47 (21.311)	[-19.883, -9.059]	<.0001
Week 28	62	152.96 (26.117)	-12.15 (24.005)	[-18.242, -6.050]	0.0002
Week 32	62	153.02 (27.697)	-12.09 (24.285)	[-18.255, -5.921]	0.0002
Week 36	62	158.16 (25.950)	-6.94 (23.788)	[-12.986, -0.904]	0.0250
Week 40	62	156.04 (27.068)	-9.07 (25.154)	[-15.454, -2.678]	0.0062
Week 44	61	159.66 (27.916)	-5.67 (21.985)	[-11.301, -0.040]	0.0485
Week 48	61	156.29 (30.179)	-9.04 (25.621)	[-15.599, -2.476]	0.0078
Week 52	61	152.72 (26.740)	-12.61 (22.410)	[-18.350, -6.871]	<.0001

Parameter Treatment	Observed		Change from baseline		Paired t-test
Visit	n	Mean (SD)	Mean (SD)	[95% CI]	P-value
LOCF Endpoint	63	153.85 (29.511)	-11.72 (23.942)	[-17.754, -5.695]	0.0002

- Abbreviations: LOCF, Last Observation Carried Forward; SD, standard deviation; CI, confidence interval; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".

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Table E-071 Summary of Change from Baseline in Insulin-Related Parameters to All Visits in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Efficacy Population)

Parameter Treatment Visit	Observed n	 Mean (SD)	Change from baseline Mean (SD)	 [95% CI]	Paired t-test P-value
Fasting Insulin (uIU/mL)					
Imeglimin (N = 134)					
Baseline	134	5.836 (3.8789)			
Week 12	130	5.356 (4.2863)	-0.450 (2.8253)	[-0.9399, 0.0407]	0.0719
Week 24	129	5.548 (3.8867)	-0.271 (2.5825)	[-0.7214, 0.1784]	0.2347
Week 40	127	5.233 (3.3680)	-0.576 (2.5707)	[-1.0278, -0.1249]	0.0128
Week 52	124	5.426 (3.5880)	-0.405 (2.8008)	[-0.9031, 0.0926]	0.1097
LOCF Endpoint	131	5.337 (3.5429)	-0.437 (2.8031)	[-0.9219, 0.0471]	0.0764
Imeglimin + SU (N = 127)					
Baseline	127	5.655 (4.2044)			
Week 12	122	5.358 (3.5673)	-0.360 (2.5167)	[-0.8112, 0.0910]	0.1166
Week 24	119	5.257 (3.4773)	-0.414 (2.3577)	[-0.8424, 0.0135]	0.0576
Week 40	113	5.201 (3.7743)	-0.323 (2.3152)	[-0.7546, 0.1084]	0.1408
Week 52	110	5.152 (3.7101)	-0.284 (2.2205)	[-0.7035, 0.1357]	0.1827
LOCF Endpoint	122	5.398 (3.8474)	-0.320 (2.2890)	[-0.7299, 0.0907]	0.1256
Imeglimin + GLIN (N = 64)					
Baseline	64	5.764 (5.1130)			
Week 12	62	5.533 (4.2840)	-0.287 (2.2939)	[-0.8695, 0.2956]	0.3285
Week 24	61	5.693 (4.6415)	-0.166 (2.5176)	[-0.8112, 0.4784]	0.6076
Week 40	59	5.272 (3.9112)	-0.536 (2.9479)	[-1.3043, 0.2321]	0.1678
Week 52	58	5.325 (4.0689)	-0.543 (2.6650)	[-1.2438, 0.1576]	0.1262
LOCF Endpoint	62	5.437 (4.2616)	-0.382 (2.8051)	[-1.0948, 0.3300]	0.2873
Imeglimin + BIG (N = 64)					
Baseline	64	5.562 (3.9001)			
Week 12	62	4.841 (3.1005)	-0.804 (2.2479)	[-1.3744, -0.2327]	0.0066
Week 24	58	5.112 (3.1629)	-0.541 (2.3543)	[-1.1604, 0.0777]	0.0853
Week 40	55	4.705 (2.4680)	-1.082 (2.7561)	[-1.8269, -0.3368]	0.0052
Week 52	53	4.650 (2.6591)	-0.928 (2.4422)	[-1.6011, -0.2548]	0.0078
LOCF Endpoint	62	4.685 (2.7488)	-0.960 (2.4072)	[-1.5711, -0.3485]	0.0026
Imeglimin + AGI (N = 64)					
Baseline	64	5.620 (3.8386)			
Week 12	64	5.429 (3.6527)	-0.191 (2.3412)	[-0.7762, 0.3934]	0.5155
Week 24	62	5.513 (3.4418)	-0.167 (2.3619)	[-0.7672, 0.4324]	0.5788
Week 40	61	5.318 (3.7103)	-0.385 (2.8738)	[-1.1208, 0.3513]	0.2999
Week 52	60	5.114 (3.3436)	-0.647 (2.8953)	[-1.3948, 0.1011]	0.0888
LOCF Endpoint	64	5.033 (3.2679)	-0.587 (2.8248)	[-1.2925, 0.1188]	0.1015
Imeglimin + TZD (N = 65)					
Baseline	65	4.726 (2.8832)			
Week 12	63	4.495 (2.5589)	-0.270 (1.8989)	[-0.7487, 0.2078]	0.2626
Week 24	63	4.690 (2.6103)	-0.075 (1.9229)	[-0.5592, 0.4094]	0.7582
Week 40	62	4.437 (2.3438)	-0.240 (1.8523)	[-0.7102, 0.2306]	0.3120
Week 52	61	5.199 (3.4295)	0.493 (2.1041)	[-0.0463, 1.0315]	0.0724
LOCF Endpoint	63	5.183 (3.3782)	0.418 (2.1740)	[-0.1297, 0.9653]	0.1323
Imeglimin + DPP4-I (N = 63)					
Baseline	63	5.680 (4.3290)			
Week 12	59	5.412 (4.3932)	-0.347 (2.8879)	[-1.0992, 0.4060]	0.3604
Week 24	58	5.762 (4.9140)	0.058 (3.7039)	[-0.9156, 1.0322]	0.9050

Parameter Treatment	Observed		Change from baseline		Paired t-test
Visit	n	Mean (SD)	Mean (SD)	[95% CI]	P-value
Week 40	56	4.909 (3.5276)	-0.803 (3.2671)	[-1.6776, 0.0723]	0.0714
Week 52	55	5.372 (4.0917)	-0.391 (2.8876)	[-1.1721, 0.3892]	0.3192
LOCF Endpoint	59	5.435 (4.1030)	-0.323 (2.8217)	[-1.0586, 0.4121]	0.3826
Imeglimin + GLP1-RA (N = 70)					
Baseline	70	6.841 (7.1200)			
Week 12	64	6.249 (4.4512)	-0.553 (5.5634)	[-1.9423, 0.8370]	0.4298
Week 24	61	5.586 (4.0176)	-1.097 (6.2430)	[-2.6955, 0.5023]	0.1752
Week 40	56	5.336 (3.3692)	-1.286 (6.0457)	[-2.9046, 0.3335]	0.1173
Week 52	51	5.458 (3.3202)	-1.354 (7.1085)	[-3.3530, 0.6456]	0.1799
LOCF Endpoint	64	5.810 (3.9113)	-0.991 (6.4804)	[-2.6102, 0.6273]	0.2256
Imeglimin + SGLT2-I (N = 63)					
Baseline	63	5.419 (4.1608)			
Week 12	62	5.443 (4.5210)	-0.016 (3.1230)	[-0.8092, 0.7770]	0.9677
Week 24	62	5.478 (4.2356)	0.009 (2.5421)	[-0.6369, 0.6543]	0.9786
Week 40	62	4.899 (3.0509)	-0.570 (2.4423)	[-1.1906, 0.0499]	0.0708
Week 52	60	4.698 (3.2494)	-0.745 (2.5934)	[-1.4145, -0.0745]	0.0300
LOCF Endpoint	63	4.642 (3.2057)	-0.777 (2.5545)	[-1.4199, -0.1332]	0.0188
C-peptide (pmol/L)					
Imeglimin (N = 134)					
Baseline	134	598.3 (249.52)			
Week 12	131	556.5 (233.42)	-39.9 (142.05)	[-64.45, -15.34]	0.0016
Week 24	129	524.0 (219.36)	-74.7 (143.55)	[-99.75, -49.74]	<.0001
Week 40	127	562.4 (235.72)	-35.8 (153.01)	[-62.71, -8.97]	0.0093
Week 52	124	524.1 (230.23)	-78.4 (138.09)	[-102.96, -53.87]	<.0001
LOCF Endpoint	131	521.9 (231.57)	-74.6 (144.23)	[-99.50, -49.63]	<.0001
Imeglimin + SU (N = 127)					
Baseline	127	587.0 (242.78)			
Week 12	122	557.6 (220.38)	-33.1 (119.12)	[-54.47, -11.77]	0.0026
Week 24	119	549.8 (230.80)	-38.5 (123.64)	[-60.93, -16.04]	0.0009
Week 40	113	541.5 (252.44)	-39.1 (116.02)	[-60.72, -17.47]	0.0005
Week 52	110	514.3 (244.20)	-62.6 (144.61)	[-89.94, -35.28]	<.0001
LOCF Endpoint	122	532.0 (248.59)	-58.8 (145.89)	[-84.91, -32.61]	<.0001
Imeglimin + GLIN (N = 64)					
Baseline	64	575.6 (255.57)			
Week 12	62	530.5 (214.63)	-47.3 (132.77)	[-80.97, -13.54]	0.0068
Week 24	61	538.8 (232.20)	-41.8 (148.33)	[-79.74, -3.77]	0.0318
Week 40	59	529.0 (240.11)	-46.6 (144.70)	[-84.27, -8.85]	0.0164
Week 52	58	505.2 (223.86)	-73.1 (149.05)	[-112.33, -33.95]	0.0004
LOCF Endpoint	62	515.6 (231.62)	-62.1 (156.40)	[-101.86, -22.43]	0.0027
Imeglimin + BIG (N = 64)					
Baseline	64	540.8 (201.30)			
Week 12	62	512.3 (173.97)	-32.8 (117.82)	[-62.74, -2.90]	0.0321
Week 24	58	493.0 (180.20)	-53.1 (126.48)	[-86.40, -19.88]	0.0022
Week 40	55	508.6 (156.45)	-43.4 (157.90)	[-86.07, -0.70]	0.0465
Week 52	53	465.7 (166.31)	-80.2 (118.29)	[-112.79, -47.58]	<.0001
LOCF Endpoint	62	465.3 (168.13)	-79.9 (116.06)	[-109.38, -50.43]	<.0001
Imeglimin + AGI (N = 64)					

Parameter Treatment Visit	Observed n	 Mean (SD)	Change from baseline Mean (SD)	 [95% CI]	Paired t-test P-value
Baseline	64	546.9 (208.09)			
Week 12	64	537.8 (226.56)	-9.0 (176.88)	[-53.23, 35.14]	0.6838
Week 24	62	522.3 (240.08)	-29.4 (190.56)	[-77.76, 19.02]	0.2296
Week 40	61	512.6 (240.70)	-42.5 (184.06)	[-89.66, 4.62]	0.0762
Week 52	60	486.1 (206.76)	-74.6 (169.68)	[-118.45, -30.78]	0.0012
LOCF Endpoint	64	478.9 (202.79)	-68.0 (168.62)	[-110.10, -25.86]	0.0020
Imeglimin + TZD (N = 65)					
Baseline	65	507.7 (182.72)			
Week 12	63	500.2 (196.35)	-10.7 (123.44)	[-41.82, 20.36]	0.4928
Week 24	63	488.9 (171.49)	-22.0 (110.74)	[-49.94, 5.84]	0.1191
Week 40	62	463.8 (170.13)	-38.3 (121.84)	[-69.20, -7.32]	0.0162
Week 52	61	458.4 (187.07)	-45.1 (113.82)	[-74.27, -15.96]	0.0030
LOCF Endpoint	63	462.2 (185.41)	-48.8 (124.63)	[-80.15, -17.37]	0.0029
Imeglimin + DPP4-I (N = 63)					
Baseline	63	545.5 (211.26)			
Week 12	59	521.9 (214.08)	-24.8 (118.36)	[-55.66, 6.03]	0.1127
Week 24	58	505.4 (217.94)	-38.4 (166.70)	[-82.19, 5.47]	0.0850
Week 40	56	499.6 (220.28)	-42.8 (136.05)	[-79.24, -6.37]	0.0221
Week 52	55	486.2 (211.62)	-59.5 (158.34)	[-102.33, -16.72]	0.0073
LOCF Endpoint	59	495.1 (219.71)	-51.6 (157.67)	[-92.72, -10.54]	0.0147
Imeglimin + GLP1-RA (N = 70)					
Baseline	70	651.8 (279.40)			
Week 12	64	604.3 (223.17)	-44.5 (187.19)	[-91.24, 2.27]	0.0619
Week 24	61	555.8 (229.29)	-80.0 (220.46)	[-136.50, -23.57]	0.0062
Week 40	56	537.2 (222.01)	-94.7 (210.00)	[-150.95, -38.48]	0.0014
Week 52	51	546.4 (214.23)	-92.5 (243.71)	[-161.00, -23.91]	0.0092
LOCF Endpoint	64	572.8 (234.80)	-76.0 (227.14)	[-132.71, -19.23]	0.0095
Imeglimin + SGLT2-I (N = 63)					
Baseline	63	569.8 (299.63)			
Week 12	63	550.7 (265.75)	-19.2 (192.35)	[-67.62, 29.27]	0.4318
Week 24	62	541.4 (243.28)	-31.3 (182.01)	[-77.54, 14.90]	0.1804
Week 40	62	538.8 (220.78)	-33.9 (206.06)	[-86.25, 18.41]	0.1998
Week 52	60	495.0 (232.51)	-72.9 (193.18)	[-122.82, -23.01]	0.0049
LOCF Endpoint	63	498.7 (229.93)	-71.2 (190.40)	[-119.11, -23.21]	0.0043
HOMA-IR					
Imeglimin (N = 134)					
Baseline	134	2.3930 (1.74208)			
Week 24	129	2.0116 (1.56382)	-0.3675 (1.25144)	[-0.58552, -0.14949]	0.0011
Week 52	124	2.0488 (1.46742)	-0.3260 (1.34519)	[-0.56516, -0.08692]	0.0079
LOCF Endpoint	129	2.0398 (1.45923)	-0.3394 (1.33719)	[-0.57233, -0.10643]	0.0046
Imeglimin + SU (N = 127)					
Baseline	127	2.6331 (2.11409)			
Week 24	119	2.2148 (1.65507)	-0.3932 (1.28071)	[-0.62566, -0.16069]	0.0011

Parameter Treatment Visit	Observed n	Mean (SD)	Change from baseline Mean (SD)	[95% CI]	Paired t-test P-value
Week 52	110	2.2277 (1.92801)	-0.2510 (1.26854)	[-0.49076, -0.01132]	0.0403
LOCF Endpoint	119	2.3281 (1.98760)	-0.2798 (1.29068)	[-0.51415, -0.04555]	0.0196
Imeglimin + GLIN (N = 64)					
Baseline	64	2.6327 (2.40824)			
Week 24	61	2.3327 (2.02930)	-0.3482 (1.45089)	[-0.71984, 0.02334]	0.0657
Week 52	58	2.1733 (1.76419)	-0.5079 (1.59121)	[-0.92627, -0.08949]	0.0182
LOCF Endpoint	61	2.2469 (1.87918)	-0.4340 (1.63123)	[-0.85179, -0.01624]	0.0420
Imeglimin + BIG (N = 64)					
Baseline	64	2.4167 (1.69594)			
Week 24	58	1.9062 (1.30119)	-0.5248 (1.22838)	[-0.84776, -0.20179]	0.0019
Week 52	53	1.7300 (1.11072)	-0.6853 (1.27100)	[-1.03563, -0.33497]	0.0003
LOCF Endpoint	58	1.7283 (1.08058)	-0.7027 (1.27903)	[-1.03896, -0.36635]	0.0001
Imeglimin + AGI (N = 64)					
Baseline	63	2.4320 (1.63392)			
Week 24	62	2.0901 (1.36339)	-0.3533 (1.07227)	[-0.62792, -0.07868]	0.0126
Week 52	60	2.0122 (1.60615)	-0.4641 (1.30117)	[-0.80322, -0.12505]	0.0082
LOCF Endpoint	62	1.9964 (1.58859)	-0.4479 (1.28414)	[-0.77679, -0.11902]	0.0084
Imeglimin + TZD (N = 65)					
Baseline	65	1.9866 (1.19588)			
Week 24	63	1.6849 (0.95996)	-0.3227 (0.93977)	[-0.55941, -0.08605]	0.0083
Week 52	61	1.9520 (1.27510)	-0.0291 (0.97916)	[-0.27986, 0.22169]	0.8173
LOCF Endpoint	63	1.9254 (1.26553)	-0.0822 (1.02212)	[-0.33965, 0.17518]	0.5254
Imeglimin + DPP4-I (N = 63)					
Baseline	63	2.5675 (2.06929)			
Week 24	58	2.1452 (1.89008)	-0.4504 (1.67777)	[-0.89159, -0.00930]	0.0455
Week 52	55	2.1034 (1.70055)	-0.5089 (1.51142)	[-0.91748, -0.10030]	0.0156
LOCF Endpoint	58	2.1134 (1.68628)	-0.4822 (1.47773)	[-0.87077, -0.09367]	0.0159
Imeglimin + GLP1-RA (N = 70)					
Baseline	70	3.4361 (4.43326)			
Week 24	61	2.3465 (2.05407)	-0.9394 (3.89092)	[-1.93590, 0.05712]	0.0642
Week 52	51	2.3037 (1.61480)	-1.0498 (4.44028)	[-2.29861, 0.19908]	0.0976
LOCF Endpoint	61	2.3956 (1.82548)	-0.8903 (4.08575)	[-1.93670, 0.15611]	0.0940

Parameter Treatment Visit	Observed n	Mean (SD)	Change from baseline Mean (SD)	[95% CI]	Paired t-test P-value
Imeglimin + SGLT2-I (N = 63)					
Baseline	63	2.2551 (1.79802)			
Week 24	61	2.0867 (1.69008)	-0.1811 (1.26211)	[-0.50437, 0.14211]	0.2668
Week 52	60	1.8173 (1.35756)	-0.4385 (1.24136)	[-0.75921, -0.11786]	0.0082
LOCF Endpoint	62	1.8327 (1.36953)	-0.4409 (1.22093)	[-0.75094, -0.13083]	0.0061
HOMA-B (%)					
Imeglimin (N = 134)					
Baseline	134	21.9054 (15.62979)			
Week 24	129	26.3234 (22.08193)	4.3537 (12.81060)	[2.12192, 6.58545]	0.0002
Week 52	124	23.5628 (16.28402)	1.4180 (9.72891)	[-0.31142, 3.14738]	0.1072
LOCF Endpoint	129	23.3052 (16.13517)	1.3354 (9.57586)	[-0.33280, 3.00367]	0.1157
Imeglimin + SU (N = 127)					
Baseline	127	17.9899 (15.19508)			
Week 24	119	24.4339 (52.68220)	6.0811 (52.08052)	[-3.37311, 15.53538]	0.2053
Week 52	110	18.9156 (13.43076)	1.3147 (8.52785)	[-0.29688, 2.92619]	0.1088
LOCF Endpoint	119	19.4446 (13.61892)	1.0918 (9.40407)	[-0.61533, 2.79893]	0.2078
Imeglimin + GLIN (N = 64)					
Baseline	64	18.4103 (16.15717)			
Week 24	61	22.0432 (17.80909)	3.4670 (9.69661)	[0.98357, 5.95040]	0.0070
Week 52	58	24.3099 (29.83126)	5.6275 (23.95645)	[-0.67151, 11.92654]	0.0789
LOCF Endpoint	61	24.3940 (29.40073)	5.8179 (23.53089)	[-0.20867, 11.84441]	0.0582
Imeglimin + BIG (N = 64)					
Baseline	64	18.9228 (14.18966)			
Week 24	58	305.6570 (2144.33849)	286.1656 (2144.03598)	[-277.57995, 849.91109]	0.3137
Week 52	53	21.8531 (16.01588)	2.7303 (6.72049)	[0.87789, 4.58268]	0.0047
LOCF Endpoint	58	22.0088 (16.52426)	2.5174 (6.88555)	[0.70695, 4.32788]	0.0073
Imeglimin + AGI (N = 64)					
Baseline	63	20.5917 (21.39695)			
Week 24	62	25.3559 (27.16840)	4.5084 (11.18540)	[1.64368, 7.37311]	0.0026

Parameter Treatment Visit	Observed n	Mean (SD)	Change from baseline Mean (SD)	[95% CI]	Paired t-test P-value
Week 52	60	22.1415 (15.67219)	0.8935 (12.54654)	[-2.37612, 4.16317]	0.5865
LOCF Endpoint	62	21.7899 (15.56357)	0.9159 (12.33972)	[-2.24443, 4.07627]	0.5643
Imeglimin + TZD (N = 65)					
Baseline	65	17.0525 (12.03362)			
Week 24	63	22.6563 (16.25983)	5.5748 (7.70642)	[3.63399, 7.51566]	<.0001
Week 52	61	23.4881 (18.67623)	6.5566 (11.14113)	[3.70321, 9.40997]	<.0001
LOCF Endpoint	63	23.4721 (18.60920)	6.3907 (11.00519)	[3.61903, 9.16227]	<.0001
Imeglimin + DPP4-I (N = 63)					
Baseline	63	18.1849 (13.31663)			
Week 24	58	25.5883 (20.53031)	7.5066 (13.91511)	[3.84778, 11.16536]	0.0001
Week 52	55	23.1224 (19.81789)	4.7298 (12.62267)	[1.31738, 8.14215]	0.0075
LOCF Endpoint	58	23.1411 (19.88237)	5.0594 (12.62160)	[1.74075, 8.37811]	0.0034
Imeglimin + GLP1-RA (N = 70)					
Baseline	70	19.5868 (15.41910)			
Week 24	61	20.6686 (12.89117)	0.8815 (14.74886)	[-2.89590, 4.65882]	0.6424
Week 52	51	20.0686 (11.19609)	0.0458 (14.84781)	[-4.13023, 4.22180]	0.9825
LOCF Endpoint	61	20.8356 (13.65718)	1.0484 (15.45122)	[-2.90885, 5.00564]	0.5981
Imeglimin + SGLT2-I (N = 63)					
Baseline	63	19.6933 (15.53126)			
Week 24	61	22.9880 (17.70562)	3.1009 (9.17558)	[0.75089, 5.45084]	0.0106
Week 52	60	19.4080 (12.77077)	-0.5149 (8.39780)	[-2.68428, 1.65448]	0.6366
LOCF Endpoint	62	19.4592 (12.62238)	-0.4502 (8.26762)	[-2.54974, 1.64942]	0.6696

- Abbreviations: LOCF, Last Observation Carried Forward; SD, standard deviation; CI, confidence interval; HOMA, Homeostasis model assessment; HOMA-IR, HOMA of insulin resistance; HOMA-B, HOMA of beta-cell function; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".

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Table E-072 Summary of Percent Change from Baseline in Lipid Parameters to All Visits in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Efficacy Population)

Parameter Treatment	Observed		Percent change from baseline		Paired t-test
Visit	n	Mean (SD)	Mean (SD)	[95% CI]	P-value
Total Cholesterol (mmol/L)					
Imeglimin (N = 134)					
Baseline	134	5.211 (0.8419)			
Week 12	132	5.248 (0.9360)	0.980 (12.1282)	[-1.1081, 3.0684]	0.3549
Week 24	129	5.197 (0.7991)	0.460 (11.9497)	[-1.6214, 2.5422]	0.6624
Week 40	127	5.315 (0.8992)	2.490 (12.6273)	[0.2722, 4.7071]	0.0281
Week 52	124	5.240 (0.9155)	0.896 (11.9325)	[-1.2254, 3.0168]	0.4048
LOCF Endpoint	132	5.250 (0.9307)	0.960 (11.9048)	[-1.0894, 3.0102]	0.3557
Imeglimin + SU (N = 127)					
Baseline	127	5.089 (0.8636)			
Week 12	122	5.054 (0.8911)	0.229 (12.4866)	[-2.0093, 2.4669]	0.8399
Week 24	119	5.073 (0.8707)	0.875 (14.1528)	[-1.6944, 3.4440]	0.5015
Week 40	113	5.043 (0.8849)	0.965 (14.4738)	[-1.7324, 3.6632]	0.4798
Week 52	110	5.025 (0.8853)	0.350 (13.3237)	[-2.1674, 2.8682]	0.7832
LOCF Endpoint	122	5.054 (0.8760)	0.494 (12.8782)	[-1.8143, 2.8022]	0.6726
Imeglimin + GLIN (N = 64)					
Baseline	64	5.107 (0.9774)			
Week 12	62	5.061 (0.9041)	0.213 (11.2573)	[-2.6453, 3.0723]	0.8818
Week 24	61	5.143 (1.0307)	1.478 (11.0285)	[-1.3464, 4.3026]	0.2994
Week 40	59	5.153 (1.0770)	1.579 (12.0387)	[-1.5586, 4.7160]	0.3180
Week 52	58	5.238 (1.0474)	3.436 (11.8639)	[0.3165, 6.5554]	0.0315
LOCF Endpoint	62	5.224 (1.0190)	3.146 (11.5915)	[0.2023, 6.0897]	0.0366
Imeglimin + BIG (N = 64)					
Baseline	64	5.038 (0.7969)			
Week 12	62	4.716 (0.7860)	-5.628 (9.3886)	[-8.0125, -3.2440]	<.0001
Week 24	58	4.760 (0.7844)	-4.797 (9.7081)	[-7.3494, -2.2442]	0.0004
Week 40	55	4.850 (0.8763)	-3.291 (12.4227)	[-6.6493, 0.0674]	0.0546
Week 52	53	4.860 (0.9130)	-2.864 (11.9130)	[-6.1473, 0.4199]	0.0860
LOCF Endpoint	62	4.830 (0.9015)	-3.473 (11.5152)	[-6.3975, -0.5489]	0.0207
Imeglimin + AGI (N = 64)					
Baseline	64	4.955 (0.7759)			
Week 12	64	4.881 (0.6585)	-0.721 (9.8113)	[-3.1713, 1.7302]	0.5589
Week 24	62	4.793 (0.6757)	-2.047 (11.3703)	[-4.9343, 0.8408]	0.1615
Week 40	61	4.983 (0.8001)	1.423 (12.3552)	[-1.7409, 4.5877]	0.3718
Week 52	60	4.912 (0.6734)	0.218 (12.0233)	[-2.8883, 3.3236]	0.8890
LOCF Endpoint	64	4.914 (0.6592)	0.249 (12.0906)	[-2.7714, 3.2689]	0.8698
Imeglimin + TZD (N = 65)					
Baseline	65	5.076 (0.8872)			
Week 12	63	5.133 (0.9794)	0.790 (11.8266)	[-2.1888, 3.7682]	0.5980
Week 24	63	5.226 (0.9384)	2.558 (12.1689)	[-0.5067, 5.6227]	0.1003
Week 40	62	5.204 (0.9407)	2.286 (11.3648)	[-0.6001, 5.1721]	0.1184
Week 52	61	5.055 (0.8770)	0.046 (11.4713)	[-2.8917, 2.9842]	0.9750
LOCF Endpoint	63	5.100 (0.9813)	-0.015 (11.7887)	[-2.9841, 2.9538]	0.9919
Imeglimin + DPP4-I (N = 63)					
Baseline	63	5.058 (0.8249)			
Week 12	59	4.799 (0.7466)	-4.544 (11.2994)	[-7.4886, -1.5993]	0.0031
Week 24	58	4.905 (0.8997)	-3.167 (11.8620)	[-6.2860, -0.0481]	0.0467

Parameter Treatment	Observed		Percent change from baseline		Paired t-test
Visit	n	Mean (SD)	Mean (SD)	[95% CI]	P-value
Week 40	57	4.914 (0.9084)	-2.244 (13.3536)	[-5.7869, 1.2995]	0.2099
Week 52	55	4.943 (0.8572)	-1.387 (12.3741)	[-4.7319, 1.9585]	0.4096
LOCF Endpoint	59	4.960 (0.8578)	-1.530 (12.0248)	[-4.6642, 1.6032]	0.3323
Imeglimin + GLP1-RA (N = 70)					
Baseline	70	5.025 (1.0103)			
Week 12	64	5.019 (1.0074)	0.288 (11.6727)	[-2.6274, 3.2041]	0.8440
Week 24	61	5.008 (0.9204)	1.349 (12.9092)	[-1.9570, 4.6554]	0.4176
Week 40	56	5.183 (0.9653)	4.499 (14.7994)	[0.5362, 8.4628]	0.0268
Week 52	51	5.084 (1.0403)	1.896 (13.9571)	[-2.0291, 5.8219]	0.3365
LOCF Endpoint	64	5.139 (1.1118)	2.489 (14.1829)	[-1.0535, 6.0321]	0.1652
Imeglimin + SGLT2-I (N = 63)					
Baseline	63	5.461 (0.9249)			
Week 12	63	5.374 (0.9940)	-1.461 (9.0624)	[-3.7430, 0.8217]	0.2056
Week 24	62	5.371 (0.9353)	-1.250 (10.0069)	[-3.7908, 1.2917]	0.3294
Week 40	62	5.517 (1.1580)	1.265 (11.4308)	[-1.6378, 4.1680]	0.3869
Week 52	61	5.477 (0.9194)	1.054 (11.5134)	[-1.8943, 4.0032]	0.4772
LOCF Endpoint	63	5.463 (0.9081)	0.703 (11.5944)	[-2.2168, 3.6232]	0.6319
LDL-C (mmol/L)					
Imeglimin (N = 134)					
Baseline	134	3.059 (0.7334)			
Week 12	132	3.145 (0.8649)	3.204 (18.2602)	[0.0595, 6.3477]	0.0459
Week 24	129	3.096 (0.7556)	2.239 (16.9189)	[-0.7085, 5.1864]	0.1353
Week 40	127	3.179 (0.8379)	4.833 (18.5767)	[1.5710, 8.0953]	0.0040
Week 52	124	3.082 (0.8692)	1.389 (20.0006)	[-2.1666, 4.9440]	0.4409
LOCF Endpoint	132	3.103 (0.8837)	1.583 (19.7399)	[-1.8160, 4.9818]	0.3586
Imeglimin + SU (N = 127)					
Baseline	127	2.864 (0.7064)			
Week 12	122	2.895 (0.7796)	3.398 (22.8509)	[-0.6980, 7.4935]	0.1031
Week 24	119	2.921 (0.7832)	4.248 (21.7579)	[0.2985, 8.1979]	0.0353
Week 40	113	2.957 (0.8027)	6.926 (24.3321)	[2.3902, 11.4608]	0.0031
Week 52	110	2.893 (0.7505)	4.011 (20.1474)	[0.2035, 7.8181]	0.0391
LOCF Endpoint	122	2.926 (0.7466)	4.947 (20.1482)	[1.3359, 8.5586]	0.0077
Imeglimin + GLIN (N = 64)					
Baseline	64	2.954 (0.8056)			
Week 12	62	3.008 (0.7987)	2.473 (16.9091)	[-1.8208, 6.7673]	0.2539
Week 24	61	3.079 (0.8410)	5.145 (18.1351)	[0.5001, 9.7893]	0.0305
Week 40	59	3.045 (0.8413)	3.987 (16.9440)	[-0.4286, 8.4026]	0.0759
Week 52	58	3.131 (0.7936)	7.567 (16.5430)	[3.2168, 11.9163]	0.0010
LOCF Endpoint	62	3.117 (0.7717)	6.647 (16.4317)	[2.4739, 10.8196]	0.0023
Imeglimin + BIG (N = 64)					
Baseline	64	2.832 (0.6973)			
Week 12	62	2.663 (0.6247)	-4.184 (13.7313)	[-7.6714, -0.6972]	0.0195
Week 24	58	2.686 (0.6863)	-3.423 (14.1857)	[-7.1534, 0.3065]	0.0713
Week 40	55	2.750 (0.7783)	-1.046 (19.2221)	[-6.2423, 4.1507]	0.6882
Week 52	53	2.776 (0.8098)	-0.339 (18.3116)	[-5.3860, 4.7086]	0.8934
LOCF Endpoint	62	2.745 (0.7661)	-1.571 (17.8113)	[-6.0945, 2.9519]	0.4899
Imeglimin + AGI (N = 64)					

Parameter Treatment Visit	Observed n	 Mean (SD)	Percent change from baseline Mean (SD)	 [95% CI]	Paired t-test P-value
Baseline	64	2.889 (0.7431)			
Week 12	64	2.853 (0.6442)	0.985 (17.7435)	[-3.4476, 5.4168]	0.6586
Week 24	62	2.819 (0.6990)	-0.322 (17.6097)	[-4.7938, 4.1502]	0.8861
Week 40	61	2.919 (0.7349)	3.639 (21.1232)	[-1.7712, 9.0487]	0.1836
Week 52	60	2.898 (0.6798)	2.366 (17.0933)	[-2.0495, 6.7819]	0.2880
LOCF Endpoint	64	2.883 (0.6795)	1.655 (16.8960)	[-2.5655, 5.8755]	0.4362
Imeglimin + TZD (N = 65)					
Baseline	65	2.952 (0.7728)			
Week 12	63	3.041 (0.8518)	3.457 (24.2473)	[-2.6491, 9.5641]	0.2621
Week 24	63	3.127 (0.8840)	5.235 (21.5885)	[-0.2024, 10.6716]	0.0589
Week 40	62	3.118 (0.8200)	5.272 (18.2310)	[0.6419, 9.9015]	0.0263
Week 52	61	2.948 (0.8126)	-0.087 (17.6998)	[-4.6203, 4.4460]	0.9695
LOCF Endpoint	63	2.977 (0.8936)	-0.447 (18.0983)	[-5.0054, 4.1106]	0.8451
Imeglimin + DPP4-I (N = 63)					
Baseline	63	2.868 (0.6549)			
Week 12	59	2.708 (0.6100)	-4.706 (14.9651)	[-8.6061, -0.8062]	0.0189
Week 24	58	2.782 (0.6854)	-3.098 (16.1345)	[-7.3407, 1.1440]	0.1491
Week 40	57	2.834 (0.6966)	-0.070 (18.4025)	[-4.9524, 4.8133]	0.9773
Week 52	55	2.805 (0.6230)	0.179 (18.5860)	[-4.8459, 5.2031]	0.9435
LOCF Endpoint	59	2.833 (0.6487)	-0.006 (17.9635)	[-4.6869, 4.6757]	0.9981
Imeglimin + GLP1-RA (N = 70)					
Baseline	70	2.795 (0.8014)			
Week 12	64	2.794 (0.7788)	1.853 (19.7381)	[-3.0770, 6.7839]	0.4553
Week 24	61	2.840 (0.7421)	5.752 (23.3971)	[-0.2403, 11.7443]	0.0596
Week 40	56	2.882 (0.7168)	6.166 (18.9891)	[1.0804, 11.2511]	0.0184
Week 52	51	2.935 (0.8161)	7.048 (21.3791)	[1.0352, 13.0612]	0.0225
LOCF Endpoint	64	2.954 (0.8911)	6.898 (21.5827)	[1.5071, 12.2895]	0.0130
Imeglimin + SGLT2-I (N = 63)					
Baseline	63	3.031 (0.8653)			
Week 12	63	3.044 (0.9411)	2.020 (21.4585)	[-3.3847, 7.4238]	0.4579
Week 24	62	2.977 (0.7860)	1.600 (23.4528)	[-4.3560, 7.5558]	0.5931
Week 40	62	3.070 (0.7096)	6.631 (32.0328)	[-1.5037, 14.7659]	0.1083
Week 52	61	3.127 (0.8477)	6.070 (21.7836)	[0.4914, 11.6495]	0.0335
LOCF Endpoint	63	3.114 (0.8490)	5.363 (21.9228)	[-0.1586, 10.8838]	0.0567
HDL-C (mmol/L)					
Imeglimin (N = 134)					
Baseline	134	1.462 (0.4340)			
Week 12	132	1.400 (0.4080)	-3.688 (10.9115)	[-5.5668, -1.8093]	0.0002
Week 24	129	1.357 (0.3899)	-6.307 (12.8748)	[-8.5500, -4.0641]	<.0001
Week 40	127	1.433 (0.4261)	-1.616 (14.1163)	[-4.0945, 0.8633]	0.1995
Week 52	124	1.422 (0.4388)	-2.852 (12.0412)	[-4.9927, -0.7118]	0.0094
LOCF Endpoint	132	1.419 (0.4335)	-2.682 (12.1426)	[-4.7723, -0.5907]	0.0123
Imeglimin + SU (N = 127)					
Baseline	127	1.425 (0.3900)			
Week 12	122	1.358 (0.3644)	-3.779 (11.4144)	[-5.8244, -1.7326]	0.0004
Week 24	119	1.385 (0.3825)	-2.112 (13.1533)	[-4.5001, 0.2754]	0.0824
Week 40	113	1.383 (0.3554)	-1.189 (12.5016)	[-3.5192, 1.1411]	0.3142

Parameter Treatment	Observed		Percent change from baseline		Paired t-test
Visit	n	Mean (SD)	Mean (SD)	[95% CI]	P-value
Week 52	110	1.400 (0.3671)	-1.036 (12.6487)	[-3.4263, 1.3542]	0.3922
LOCF Endpoint	122	1.397 (0.3707)	-0.863 (12.4176)	[-3.0887, 1.3628]	0.4442
Imeglimin + GLIN (N = 64)					
Baseline	64	1.338 (0.3459)			
Week 12	62	1.312 (0.2738)	-0.703 (10.2201)	[-3.2984, 1.8925]	0.5901
Week 24	61	1.333 (0.3184)	0.581 (12.8258)	[-2.7037, 3.8660]	0.7246
Week 40	59	1.346 (0.3392)	1.206 (12.9550)	[-2.1704, 4.5818]	0.4776
Week 52	58	1.385 (0.3865)	3.653 (12.2362)	[0.4352, 6.8699]	0.0268
LOCF Endpoint	62	1.383 (0.3759)	3.353 (12.0371)	[0.2965, 6.4102]	0.0321
Imeglimin + BIG (N = 64)					
Baseline	64	1.436 (0.3386)			
Week 12	62	1.302 (0.3050)	-7.861 (10.8241)	[-10.6095, -5.1119]	<.0001
Week 24	58	1.285 (0.3271)	-8.953 (10.8981)	[-11.8186, -6.0876]	<.0001
Week 40	55	1.277 (0.2871)	-7.949 (12.7946)	[-11.4079, -4.4901]	<.0001
Week 52	53	1.348 (0.3501)	-3.589 (12.6245)	[-7.0684, -0.1090]	0.0435
LOCF Endpoint	62	1.356 (0.3533)	-4.069 (12.5796)	[-7.2637, -0.8744]	0.0134
Imeglimin + AGI (N = 64)					
Baseline	64	1.398 (0.4020)			
Week 12	64	1.372 (0.4136)	-1.461 (11.7439)	[-4.3949, 1.4722]	0.3233
Week 24	62	1.340 (0.3818)	-2.840 (11.2479)	[-5.6964, 0.0164]	0.0513
Week 40	61	1.381 (0.4022)	-0.478 (13.3181)	[-3.8885, 2.9334]	0.7804
Week 52	60	1.366 (0.3982)	-1.010 (13.4306)	[-4.4796, 2.4594]	0.5624
LOCF Endpoint	64	1.359 (0.3905)	-1.947 (13.7501)	[-5.3816, 1.4878]	0.2616
Imeglimin + TZD (N = 65)					
Baseline	65	1.450 (0.4024)			
Week 12	63	1.397 (0.3732)	-2.261 (9.9328)	[-4.7623, 0.2408]	0.0757
Week 24	63	1.417 (0.4111)	-1.150 (11.3444)	[-4.0068, 1.7073]	0.4242
Week 40	62	1.439 (0.4358)	0.155 (12.4542)	[-3.0074, 3.3182]	0.9221
Week 52	61	1.431 (0.4205)	-0.562 (12.6332)	[-3.7974, 2.6736]	0.7295
LOCF Endpoint	63	1.425 (0.4170)	-0.549 (12.5464)	[-3.7089, 2.6107]	0.7295
Imeglimin + DPP4-I (N = 63)					
Baseline	63	1.517 (0.4068)			
Week 12	59	1.423 (0.3537)	-4.056 (11.5316)	[-7.0610, -1.0507]	0.0090
Week 24	58	1.403 (0.3867)	-5.736 (11.8933)	[-8.8629, -2.6086]	0.0005
Week 40	57	1.438 (0.3901)	-2.558 (15.0249)	[-6.5449, 1.4284]	0.2039
Week 52	55	1.481 (0.3918)	0.024 (14.2345)	[-3.8237, 3.8725]	0.9899
LOCF Endpoint	59	1.473 (0.3879)	-0.906 (14.6323)	[-4.7194, 2.9070]	0.6361
Imeglimin + GLP1-RA (N = 70)					
Baseline	70	1.400 (0.3535)			
Week 12	64	1.354 (0.3322)	-2.014 (12.8260)	[-5.2181, 1.1895]	0.2136
Week 24	61	1.369 (0.3462)	-2.308 (12.7902)	[-5.5842, 0.9672]	0.1638
Week 40	56	1.391 (0.3683)	-0.450 (17.6981)	[-5.1893, 4.2898]	0.8499
Week 52	51	1.424 (0.3514)	1.326 (12.8224)	[-2.2801, 4.9326]	0.4636
LOCF Endpoint	64	1.401 (0.3288)	1.464 (12.8333)	[-1.7420, 4.6693]	0.3650
Imeglimin + SGLT2-I (N = 63)					

Parameter Treatment Visit	Observed n	Mean (SD)	Percent change from baseline Mean (SD)	[95% CI]	Paired t-test P-value
Baseline	63	1.577 (0.4834)			
Week 12	63	1.482 (0.4076)	-4.512 (12.4490)	[-7.6467, -1.3763]	0.0055
Week 24	62	1.481 (0.4585)	-5.897 (11.6984)	[-8.8682, -2.9265]	0.0002
Week 40	62	1.506 (0.4739)	-4.221 (13.8976)	[-7.7500, -0.6914]	0.0199
Week 52	61	1.550 (0.4564)	-0.753 (13.3428)	[-4.1698, 2.6647]	0.6611
LOCF Endpoint	63	1.542 (0.4515)	-0.989 (13.4115)	[-4.3667, 2.3886]	0.5604
Triglycerides (mmol/L)					
Imeglimin (N = 134)					
Baseline	134	1.539 (0.8948)			
Week 12	132	1.566 (0.9719)	6.035 (31.2346)	[0.6573, 11.4135]	0.0281
Week 24	129	1.711 (1.3297)	13.461 (42.0949)	[6.1279, 20.7948]	0.0004
Week 40	127	1.623 (1.4512)	7.946 (40.3184)	[0.8662, 15.0265]	0.0281
Week 52	124	1.720 (1.8601)	13.127 (51.9999)	[3.8838, 22.3707]	0.0057
LOCF Endpoint	132	1.698 (1.8073)	12.260 (50.9026)	[3.4953, 21.0244]	0.0065
Imeglimin + SU (N = 127)					
Baseline	127	1.810 (1.4703)			
Week 12	122	1.872 (1.7444)	11.589 (60.8267)	[0.6865, 22.4915]	0.0374
Week 24	119	1.704 (1.0660)	8.683 (43.6153)	[0.7656, 16.6007]	0.0319
Week 40	113	1.582 (1.0450)	-0.987 (33.8405)	[-7.2949, 5.3203]	0.7570
Week 52	110	1.635 (1.4160)	1.956 (40.9955)	[-5.7911, 9.7030]	0.6178
LOCF Endpoint	122	1.628 (1.3631)	-0.463 (40.4895)	[-7.7207, 6.7939]	0.8996
Imeglimin + GLIN (N = 64)					
Baseline	64	1.917 (1.6381)			
Week 12	62	1.656 (0.9738)	6.705 (39.5740)	[-3.3453, 16.7546]	0.1872
Week 24	61	1.626 (1.0236)	3.473 (39.1761)	[-6.5604, 13.5066]	0.4914
Week 40	59	1.851 (3.2491)	1.897 (59.9500)	[-13.7260, 17.5201]	0.8088
Week 52	58	1.735 (1.9210)	-2.114 (37.6113)	[-12.0035, 7.7753]	0.6702
LOCF Endpoint	62	1.728 (1.8719)	-0.347 (38.4715)	[-10.1169, 9.4230]	0.9436
Imeglimin + BIG (N = 64)					
Baseline	64	1.733 (1.0768)			
Week 12	62	1.712 (1.1164)	3.935 (41.7954)	[-6.6789, 14.5492]	0.4613
Week 24	58	1.764 (1.1301)	4.236 (37.8850)	[-5.7258, 14.1969]	0.3981
Week 40	55	1.893 (1.4307)	6.492 (53.3168)	[-7.9218, 20.9053]	0.3705
Week 52	53	1.660 (1.0538)	-4.552 (31.1789)	[-13.1462, 4.0417]	0.2927
LOCF Endpoint	62	1.636 (1.0664)	-3.591 (30.0120)	[-11.2128, 4.0304]	0.3498
Imeglimin + AGI (N = 64)					
Baseline	64	1.502 (0.9980)			
Week 12	64	1.474 (0.9506)	4.458 (33.4720)	[-3.9028, 12.8193]	0.2907
Week 24	62	1.385 (0.6540)	1.903 (34.7517)	[-6.9227, 10.7278]	0.6679
Week 40	61	1.674 (1.7136)	27.630 (155.2084)	[-12.1206, 67.3808]	0.1696
Week 52	60	1.450 (0.9454)	4.211 (42.8374)	[-6.8548, 15.2774]	0.4494
LOCF Endpoint	64	1.618 (1.7019)	21.756 (147.9196)	[-15.1930, 58.7055]	0.2438
Imeglimin + TZD (N = 65)					
Baseline	65	1.496 (0.8279)			
Week 12	63	1.602 (1.1659)	4.159 (34.6238)	[-4.5612, 12.8786]	0.3441
Week 24	63	1.607 (1.3834)	3.537 (42.7206)	[-7.2223, 14.2958]	0.5135

Parameter Treatment Visit	Observed n	 Mean (SD)	Percent change from baseline Mean (SD)	 [95% CI]	Paired t-test P-value
Week 40	62	1.428 (0.8545)	-1.052 (42.6105)	[-11.8726, 9.7695]	0.8466
Week 52	61	1.478 (0.9026)	1.290 (34.5823)	[-7.5670, 10.1469]	0.7718
LOCF Endpoint	63	1.538 (0.9777)	2.527 (36.1780)	[-6.5840, 11.6386]	0.5813
Imeglimin + DPP4-I (N = 63)					
Baseline	63	1.491 (0.9466)			
Week 12	59	1.500 (1.0604)	3.833 (29.7558)	[-3.9210, 11.5878]	0.3265
Week 24	58	1.593 (1.1552)	9.722 (42.6397)	[-1.4891, 20.9340]	0.0879
Week 40	57	1.441 (0.9485)	2.927 (48.2402)	[-9.8726, 15.7271]	0.6486
Week 52	55	1.456 (0.9430)	-1.812 (30.5132)	[-10.0607, 6.4370]	0.6614
LOCF Endpoint	59	1.448 (0.9113)	-0.582 (29.9270)	[-8.3813, 7.2167]	0.8817
Imeglimin + GLP1-RA (N = 70)					
Baseline	70	1.903 (1.6651)			
Week 12	64	1.905 (1.2954)	14.519 (66.9429)	[-2.2031, 31.2405]	0.0876
Week 24	61	1.810 (1.1062)	13.960 (47.8550)	[1.7042, 26.2167]	0.0263
Week 40	56	2.123 (2.2226)	25.780 (71.6416)	[6.5944, 44.9659]	0.0094
Week 52	51	1.677 (1.4392)	1.147 (37.2450)	[-9.3285, 11.6222]	0.8268
LOCF Endpoint	64	1.851 (1.8046)	2.678 (40.6063)	[-7.4647, 12.8216]	0.5996
Imeglimin + SGLT2-I (N = 63)					
Baseline	63	2.071 (1.6843)			
Week 12	63	1.969 (1.4077)	12.869 (51.1770)	[-0.0198, 25.7577]	0.0503
Week 24	62	2.255 (2.2586)	15.714 (55.2515)	[1.6824, 29.7449]	0.0288
Week 40	62	2.419 (3.2804)	22.381 (71.0435)	[4.3396, 40.4230]	0.0159
Week 52	61	1.990 (1.8181)	9.801 (47.9943)	[-2.4914, 22.0924]	0.1160
LOCF Endpoint	63	1.996 (1.8014)	8.633 (47.7754)	[-3.3989, 20.6653]	0.1565

- Abbreviations: LOCF, Last Observation Carried Forward; SD, standard deviation; CI, confidence interval; LDL, Low Density Lipoprotein; LDL-C, LDL Cholesterol; HDL, High Density Lipoprotein; HDL-C, HDL Cholesterol; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".

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Table E-073 Summary of Change from Baseline in HbA1c (%) to All Visits in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Efficacy Population)

Parameter Treatment	Observed		Change from baseline		Paired t-test
Visit	n	Mean (SD)	Mean (SD)	[95% CI]	P-value
HbA1c (%)					
Placebo/Imeglimin + Insulin (N = 101)					
Baseline	101	8.72 (0.987)			
Week 4	100	8.45 (0.893)	-0.25 (0.361)	[-0.319, -0.175]	<.0001
Week 8	100	8.31 (0.866)	-0.40 (0.533)	[-0.501, -0.289]	<.0001
Week 12	100	8.26 (0.834)	-0.44 (0.654)	[-0.566, -0.306]	<.0001
Week 16	97	8.24 (0.825)	-0.45 (0.744)	[-0.600, -0.301]	<.0001
Week 20	97	8.23 (0.805)	-0.46 (0.820)	[-0.629, -0.299]	<.0001
Week 24	96	8.17 (0.746)	-0.51 (0.780)	[-0.672, -0.355]	<.0001
Week 28	95	8.13 (0.733)	-0.53 (0.789)	[-0.693, -0.372]	<.0001
Week 32	94	8.11 (0.742)	-0.56 (0.819)	[-0.733, -0.397]	<.0001
Week 36	93	8.13 (0.775)	-0.55 (0.862)	[-0.731, -0.376]	<.0001
LOCF Endpoint	100	8.15 (0.767)	-0.55 (0.840)	[-0.713, -0.379]	<.0001
Imeglimin/Imeglimin + Insulin (N = 108)					
Baseline	108	8.74 (0.721)			
Week 4	108	8.42 (0.812)	-0.32 (0.352)	[-0.385, -0.250]	<.0001
Week 8	107	8.20 (0.826)	-0.54 (0.524)	[-0.642, -0.442]	<.0001
Week 12	107	8.08 (0.909)	-0.66 (0.697)	[-0.793, -0.526]	<.0001
Week 16	107	8.06 (0.965)	-0.68 (0.765)	[-0.822, -0.529]	<.0001
Week 20	107	8.01 (0.906)	-0.73 (0.728)	[-0.869, -0.590]	<.0001
Week 24	107	8.06 (0.946)	-0.68 (0.790)	[-0.827, -0.524]	<.0001
Week 28	107	8.16 (0.945)	-0.58 (0.801)	[-0.729, -0.422]	<.0001
Week 32	107	8.20 (0.990)	-0.54 (0.850)	[-0.706, -0.380]	<.0001
Week 36	105	8.15 (0.991)	-0.59 (0.877)	[-0.756, -0.417]	<.0001
Week 40	105	8.08 (0.943)	-0.66 (0.851)	[-0.824, -0.494]	<.0001
Week 44	103	8.00 (0.881)	-0.71 (0.823)	[-0.875, -0.554]	<.0001
Week 48	103	8.00 (0.880)	-0.71 (0.853)	[-0.879, -0.546]	<.0001
Week 52	103	8.01 (0.820)	-0.70 (0.862)	[-0.871, -0.535]	<.0001
LOCF Endpoint	108	8.08 (0.922)	-0.66 (0.914)	[-0.832, -0.483]	<.0001
Imeglimin + Insulin Total (N = 209)					
Baseline	209	8.73 (0.858)			
Week 4	208	8.44 (0.850)	-0.28 (0.358)	[-0.333, -0.235]	<.0001
Week 8	207	8.25 (0.845)	-0.47 (0.532)	[-0.544, -0.398]	<.0001
Week 12	207	8.17 (0.876)	-0.55 (0.684)	[-0.645, -0.458]	<.0001
Week 16	204	8.15 (0.903)	-0.57 (0.762)	[-0.674, -0.463]	<.0001
Week 20	204	8.11 (0.864)	-0.60 (0.783)	[-0.711, -0.495]	<.0001
Week 24	203	8.11 (0.857)	-0.60 (0.788)	[-0.708, -0.490]	<.0001
Week 28	202	8.15 (0.850)	-0.56 (0.794)	[-0.666, -0.445]	<.0001
Week 32	201	8.16 (0.881)	-0.55 (0.834)	[-0.669, -0.437]	<.0001
Week 36	198	8.14 (0.894)	-0.57 (0.868)	[-0.693, -0.450]	<.0001
Week 40	105	8.08 (0.943)	-0.66 (0.851)	[-0.824, -0.494]	<.0001
Week 44	103	8.00 (0.881)	-0.71 (0.823)	[-0.875, -0.554]	<.0001
Week 48	103	8.00 (0.880)	-0.71 (0.853)	[-0.879, -0.546]	<.0001
Week 52	103	8.01 (0.820)	-0.70 (0.862)	[-0.871, -0.535]	<.0001

Parameter Treatment	Observed		Change from baseline		Paired t-test
Visit	n	Mean (SD)	Mean (SD)	[95% CI]	P-value
LOCF Endpoint	208	8.12 (0.849)	-0.60 (0.879)	[-0.724, -0.484]	<.0001

- Abbreviations: LOCF, Last Observation Carried Forward; SD, standard deviation; CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c)
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- For "Placebo/Imeglimin + Insulin" group, baseline was defined as last visit with non-missing value prior to or at the day of first dose of Investigational Medicinal Product (IMP) in open-label treatment period. For "Imeglimin/Imeglimin + Insulin" group, baseline was the same as for the double-blind treatment period.

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Table E-074 Summary of Change from Baseline in Fasting Plasma Glucose (mg/dL) to All Visits in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Efficacy Population)

Parameter Treatment	Observed		Change from baseline		Paired t-test
Visit	n	Mean (SD)	Mean (SD)	[95% CI]	P-value
Fasting Plasma Glucose (mg/dL)					
Placebo/Imeglimin + Insulin (N = 101)					
Baseline	101	147.09 (40.389)			
Week 4	99	138.52 (36.530)	-7.04 (35.041)	[-14.031, -0.054]	0.0483
Week 8	99	148.04 (41.662)	2.37 (37.929)	[-5.199, 9.931]	0.5363
Week 12	100	145.73 (36.975)	-0.52 (36.699)	[-7.804, 6.760]	0.8871
Week 16	97	145.20 (36.602)	-0.30 (39.911)	[-8.341, 7.747]	0.9417
Week 20	97	141.17 (40.635)	-4.33 (41.318)	[-12.655, 4.000]	0.3049
Week 24	96	140.93 (34.743)	-4.71 (39.418)	[-12.697, 3.276]	0.2446
Week 28	94	142.67 (33.259)	-2.89 (37.717)	[-10.619, 4.831]	0.4588
Week 32	94	140.94 (34.764)	-4.75 (43.499)	[-13.662, 4.156]	0.2922
Week 36	93	145.09 (42.440)	-0.39 (44.651)	[-9.583, 8.808]	0.9335
LOCF Endpoint	100	145.82 (41.516)	-0.43 (44.492)	[-9.261, 8.396]	0.9228
Imeglimin/Imeglimin + Insulin (N = 108)					
Baseline	108	153.03 (37.690)			
Week 4	108	138.99 (31.714)	-14.05 (29.264)	[-19.628, -8.463]	<.0001
Week 8	107	140.82 (37.713)	-11.82 (40.406)	[-19.564, -4.075]	0.0031
Week 12	107	140.96 (37.012)	-11.68 (36.937)	[-18.764, -4.605]	0.0014
Week 16	107	143.40 (37.670)	-9.24 (35.578)	[-16.063, -2.424]	0.0084
Week 20	107	144.85 (35.518)	-7.80 (37.395)	[-14.963, -0.628]	0.0333
Week 24	106	144.75 (34.399)	-7.85 (37.288)	[-15.033, -0.671]	0.0324
Week 28	107	145.51 (32.528)	-7.14 (36.017)	[-14.042, -0.236]	0.0428
Week 32	106	142.36 (37.268)	-10.16 (34.537)	[-16.815, -3.512]	0.0031
Week 36	104	145.61 (33.945)	-7.90 (43.875)	[-16.432, 0.633]	0.0692
Week 40	104	141.06 (33.169)	-11.43 (40.424)	[-19.294, -3.572]	0.0048
Week 44	103	140.28 (32.775)	-11.95 (40.340)	[-19.830, -4.062]	0.0033
Week 48	103	138.65 (36.129)	-13.57 (38.176)	[-21.034, -6.112]	0.0005
Week 52	103	146.73 (36.897)	-5.49 (46.581)	[-14.596, 3.612]	0.2342
LOCF Endpoint	108	145.33 (36.861)	-7.71 (47.986)	[-16.860, 1.447]	0.0980
Imeglimin + Insulin Total (N = 209)					
Baseline	209	150.16 (39.037)			
Week 4	207	138.76 (34.019)	-10.70 (32.268)	[-15.118, -6.274]	<.0001
Week 8	206	144.29 (39.727)	-5.00 (39.779)	[-10.467, 0.462]	0.0726
Week 12	207	143.26 (36.981)	-6.29 (37.156)	[-11.384, -1.201]	0.0157
Week 16	204	144.26 (37.086)	-4.99 (37.872)	[-10.218, 0.239]	0.0613
Week 20	204	143.10 (37.987)	-6.15 (39.249)	[-11.565, -0.728]	0.0264
Week 24	202	142.94 (34.530)	-6.36 (38.252)	[-11.666, -1.052]	0.0191
Week 28	201	144.18 (32.820)	-5.15 (36.790)	[-10.271, -0.037]	0.0484
Week 32	200	141.69 (36.029)	-7.62 (38.999)	[-13.059, -2.183]	0.0063
Week 36	197	145.37 (38.092)	-4.35 (44.290)	[-10.576, 1.870]	0.1693
Week 40	104	141.06 (33.169)	-11.43 (40.424)	[-19.294, -3.572]	0.0048
Week 44	103	140.28 (32.775)	-11.95 (40.340)	[-19.830, -4.062]	0.0033
Week 48	103	138.65 (36.129)	-13.57 (38.176)	[-21.034, -6.112]	0.0005
Week 52	103	146.73 (36.897)	-5.49 (46.581)	[-14.596, 3.612]	0.2342

Parameter Treatment Visit	Observed n	 Mean (SD)	Change from baseline Mean (SD)	 [95% CI]	Paired t-test P-value
LOCF Endpoint	208	145.56 (39.073)	-4.21 (46.371)	[-10.548, 2.129]	0.1919

- Abbreviations: LOCF, Last Observation Carried Forward; SD, standard deviation; CI, confidence interval
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- For "Placebo/Imeglimin + Insulin" group, baseline was defined as last visit with non-missing value prior to or at the day of first dose of Investigational Medicinal Product (IMP) in open-label treatment period. For "Imeglimin/Imeglimin + Insulin" group, baseline was the same as for the double-blind treatment period.

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Table E-075 Subgroup Analysis of Change from Baseline in HbA1c (%) to Week 24 (LOCF) by Various Characteristics in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Efficacy Population)

Parameter	Study 014								Study 018				Pooled (Studies 014+018)			
	Placebo		Imeglimin 500 mg bid		Imeglimin 1000 mg bid		Imeglimin 1500 mg bid		Placebo		Imeglimin 1000 mg bid		Placebo		Imeglimin 1000 mg bid	
Subgroup	N = 75		N = 75		N = 73		N = 73		N = 106		N = 106		N = 181		N = 179	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
HbA1c (%)																
BMI at baseline																
< 25 kg/m2	36	0.40 (0.761)	39	-0.21 (0.634)	39	-0.55 (0.506)	26	-0.63 (0.471)	58	0.13 (0.532)	51	-0.79 (0.540)	94	0.23 (0.639)	90	-0.69 (0.536)
>= 25 kg/m2	39	0.34 (1.043)	36	0.02 (0.607)	34	-0.42 (0.639)	47	-0.48 (0.810)	48	0.15 (0.761)	54	-0.64 (0.706)	87	0.24 (0.898)	88	-0.55 (0.685)
>= 25 to < 30 kg/m2	25	0.48 (1.121)	22	0.06 (0.532)	26	-0.43 (0.672)	33	-0.58 (0.598)	39	0.08 (0.607)	39	-0.71 (0.549)	64	0.24 (0.860)	65	-0.60 (0.611)
>= 30 kg/m2	14	0.09 (0.869)	14	-0.05 (0.726)	8	-0.38 (0.555)	14	-0.26 (1.169)	9	0.44 (1.237)	15	-0.45 (1.008)	23	0.23 (1.017)	23	-0.43 (0.864)
HbA1c at baseline																
< 8.0%	45	0.37 (0.759)	47	-0.12 (0.539)	44	-0.52 (0.447)	42	-0.36 (0.592)	61	0.07 (0.544)	62	-0.52 (0.550)	106	0.20 (0.658)	106	-0.52 (0.507)
>= 8.0%	30	0.37 (1.119)	28	-0.07 (0.763)	29	-0.45 (0.728)	31	-0.77 (0.790)	45	0.23 (0.753)	43	-1.00 (0.641)	75	0.28 (0.912)	72	-0.78 (0.725)
>= 8.0 to < 9.0%	23	0.42 (1.116)	20	-0.21 (0.797)	24	-0.51 (0.703)	28	-0.73 (0.767)	36	0.16 (0.752)	26	-0.93 (0.552)	59	0.26 (0.911)	50	-0.73 (0.657)
>= 9.0%	7	0.19 (1.199)	8	0.28 (0.573)	5	-0.16 (0.862)	3	-1.20 (1.058)	9	0.52 (0.722)	17	-1.11 (0.761)	16	0.38 (0.940)	22	-0.90 (0.866)
Duration of type 2 diabetes																
< 5 years	39	0.40 (1.049)	32	-0.10 (0.511)	36	-0.54 (0.558)	41	-0.57 (0.657)	50	0.08 (0.641)	40	-0.79 (0.593)	89	0.22 (0.855)	76	-0.67 (0.586)
>= 5 years	36	0.33 (0.751)	43	-0.10 (0.707)	37	-0.45 (0.589)	32	-0.49 (0.777)	56	0.19 (0.644)	65	-0.67 (0.656)	92	0.25 (0.688)	102	-0.59 (0.639)
Complication of diabetes																
Yes	18	0.06 (0.793)	17	-0.23 (0.655)	17	-0.41 (0.565)	15	-0.28 (0.637)	13	0.15 (0.570)	14	-0.55 (0.572)	31	0.10 (0.699)	31	-0.47 (0.563)

Parameter Subgroup Category	Study 014 Placebo N = 75 n	Mean (SD)	Imeglimin 500 mg bid N = 75 n	Mean (SD)	Imeglimin 1000 mg bid N = 73 n	Mean (SD)	Imeglimin 1500 mg bid N = 73 n	Mean (SD)	Study 018 Placebo N = 106 n	Mean (SD)	Imeglimin 1000 mg bid N = 106 n	Mean (SD)	Pooled (Studies 014+018) Placebo N = 181 n	Mean (SD)	Imeglimin 1000 mg bid N = 179 n	Mean (SD)
No	57	0.47 (0.932)	58	-0.06 (0.620)	56	-0.52 (0.576)	58	-0.60 (0.715)	93	0.13 (0.655)	91	-0.74 (0.641)	150	0.26 (0.786)	147	-0.66 (0.624)
Metabolic syndrome at baseline																
Yes	41	0.49 (1.110)	35	-0.03 (0.605)	24	-0.50 (0.456)	44	-0.47 (0.814)	43	0.07 (0.670)	53	-0.70 (0.749)	84	0.27 (0.931)	77	-0.64 (0.675)
No	34	0.22 (0.579)	40	-0.16 (0.648)	49	-0.49 (0.625)	29	-0.63 (0.506)	63	0.19 (0.624)	52	-0.73 (0.495)	97	0.20 (0.606)	101	-0.61 (0.571)
Previous treatment status																
Treatment naive	34	0.05 (0.718)	33	-0.30 (0.601)	33	-0.65 (0.489)	29	-0.59 (0.910)	77	0.05 (0.628)	75	-0.81 (0.604)	111	0.05 (0.653)	108	-0.76 (0.574)
Previously treated	41	0.63 (0.978)	42	0.06 (0.609)	40	-0.36 (0.606)	44	-0.50 (0.545)	29	0.36 (0.641)	30	-0.46 (0.644)	70	0.52 (0.860)	70	-0.40 (0.620)
FPG at baseline																
< 160 mg/dL	44	0.27 (0.867)	40	-0.21 (0.613)	38	-0.49 (0.603)	39	-0.41 (0.627)	61	0.13 (0.511)	49	-0.60 (0.408)	105	0.19 (0.683)	87	-0.55 (0.502)
>= 160 mg/dL	31	0.51 (0.970)	35	0.02 (0.629)	35	-0.49 (0.544)	34	-0.68 (0.777)	45	0.15 (0.793)	56	-0.82 (0.767)	76	0.30 (0.882)	91	-0.69 (0.705)
HOMA-IR at baseline																
< 2.5	27	0.30 (0.786)	32	-0.24 (0.595)	34	-0.43 (0.625)	22	-0.50 (0.493)	64	0.10 (0.570)	67	-0.64 (0.538)	91	0.16 (0.643)	101	-0.57 (0.575)
>= 2.5 to < 4.0	20	0.22 (0.678)	16	0.09 (0.583)	16	-0.56 (0.385)	13	-0.59 (0.459)	27	0.17 (0.658)	19	-1.03 (0.567)	47	0.19 (0.660)	35	-0.81 (0.540)
>= 4.0	27	0.54 (1.168)	27	-0.05 (0.674)	23	-0.54 (0.608)	38	-0.53 (0.876)	15	0.21 (0.904)	19	-0.65 (0.898)	42	0.43 (1.082)	42	-0.59 (0.745)
Missing	1	0.40 (.)	0	.	0	.	0	.	0	.	0	.	1	0.40 (.)	0	.
HOMA-B at baseline																
< 30.0%	34	0.38 (0.920)	43	-0.13 (0.631)	48	-0.43 (0.601)	32	-0.60 (0.514)	78	0.15 (0.641)	85	-0.75 (0.666)	112	0.22 (0.740)	133	-0.63 (0.659)

Parameter Subgroup	Study 014 Placebo N = 75		Imeglimin 500 mg bid N = 75		Imeglimin 1000 mg bid N = 73		Imeglimin 1500 mg bid N = 73		Study 018 Placebo N = 106		Imeglimin 1000 mg bid N = 106		Pooled (Studies 014+018) Placebo N = 181		Imeglimin 1000 mg bid N = 179	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
>= 30.0%	40	0.36 (0.930)	32	-0.07 (0.631)	25	-0.61 (0.500)	41	-0.49 (0.832)	28	0.10 (0.657)	20	-0.58 (0.455)	68	0.25 (0.833)	45	-0.60 (0.476)
Missing	1	0.40 (.)	0	.	0	.	0	.	0	.	0	.	1	0.40 (.)	0	.
QUICKI at baseline																
< 0.33	44	0.39 (1.016)	41	0.00 (0.653)	38	-0.53 (0.518)	47	-0.56 (0.811)	37	0.22 (0.766)	30	-0.83 (0.794)	81	0.31 (0.909)	68	-0.66 (0.666)
>= 0.33	30	0.33 (0.772)	34	-0.21 (0.584)	35	-0.45 (0.629)	26	-0.49 (0.478)	69	0.09 (0.567)	75	-0.67 (0.555)	99	0.17 (0.641)	110	-0.60 (0.586)
Missing	1	0.40 (.)	0	.	0	.	0	.	0	.	0	.	1	0.40 (.)	0	.

- Abbreviations: LOCF, Last Observation Carried Forward; bid, Twice a day; SD, standard deviation; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); BMI, body mass index; FPG, Fasting Plasma Glucose; HOMA, Homeostasis model assessment; HOMA-IR, HOMA of insulin resistance; HOMA-B, HOMA of beta-cell function; QUICKI, Quantitative Insulin Sensitivity Check Index
- Complication of diabetes is defined as any MedDRA Preferred Term (PT) of medical history which are included in High-Level Group Term (HLGT) of diabetic complication.
- Metabolic Syndrome is defined as an excessive waist circumference (>= 85 cm in men and >= 90 cm in women) as well as the presence of two or more of the following symptoms: (1) Hypertension: systolic blood pressure >= 130 mmHg, or diastolic blood pressure >= 85 mmHg; (2) Glucose intolerance: fasting glucose >= 110 mg/dL; (3) Dyslipidemia: triglyceride >= 150 mg/dL, or HDL cholesterol < 40 mg/dL.

Control No:<<t-e-075-subhb-24wdb.sas, 2020-03-06T00:05:32>>

Table E-076 Subgroup Analysis of Change from Baseline in Fasting Plasma Glucose (mg/dL) to Week 24 (LOCF) by Various Characteristics in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Efficacy Population)

Parameter	Study 014								Study 018				Pooled (Studies 014+018)			
	Placebo		Imeglimin 500 mg bid		Imeglimin 1000 mg bid		Imeglimin 1500 mg bid		Placebo		Imeglimin 1000 mg bid		Placebo		Imeglimin 1000 mg bid	
Subgroup	N = 75		N = 75		N = 73		N = 73		N = 106		N = 106		N = 181		N = 179	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Fasting Plasma Glucose (mg/dL)																
BMI at baseline																
< 25 kg/m2	36	13.39 (31.206)	39	5.26 (24.933)	39	-11.79 (20.724)	26	-16.58 (24.612)	58	5.16 (26.455)	51	-17.84 (20.072)	94	8.31 (28.489)	90	-15.22 (20.464)
>= 25 kg/m2	39	13.54 (37.145)	36	2.67 (27.992)	34	-11.59 (22.817)	47	-10.28 (28.878)	48	5.63 (25.042)	54	-8.34 (28.721)	87	9.18 (31.113)	88	-9.60 (26.505)
>= 25 to < 30 kg/m2	25	15.36 (40.957)	22	8.59 (27.947)	26	-13.73 (23.899)	33	-16.94 (26.837)	39	5.27 (21.754)	39	-9.05 (20.762)	64	9.21 (30.808)	65	-10.92 (22.009)
>= 30 kg/m2	14	10.29 (30.307)	14	-6.64 (26.366)	8	-4.63 (18.493)	14	5.43 (28.278)	9	7.21 (37.854)	15	-6.49 (44.133)	23	9.08 (32.653)	23	-5.84 (36.730)
HbA1c at baseline																
< 8.0%	45	12.67 (28.432)	47	5.72 (19.407)	44	-12.32 (18.866)	42	-11.26 (19.276)	61	5.20 (21.536)	62	-6.65 (24.297)	106	8.37 (24.850)	106	-9.01 (22.284)
>= 8.0%	30	14.67 (41.885)	28	1.14 (35.213)	29	-10.76 (25.462)	31	-14.23 (35.953)	45	5.60 (30.726)	43	-22.04 (24.010)	75	9.23 (35.621)	72	-17.49 (25.054)
>= 8.0 to < 9.0%	23	15.91 (39.926)	20	0.15 (34.002)	24	-9.25 (25.693)	28	-13.29 (35.288)	36	5.15 (27.173)	26	-20.86 (24.692)	59	9.35 (32.836)	50	-15.29 (25.597)
>= 9.0%	7	10.57 (51.078)	8	3.63 (40.433)	5	-18.00 (25.758)	3	-23.00 (49.508)	9	7.41 (44.243)	17	-23.84 (23.554)	16	8.79 (45.719)	22	-22.52 (23.566)
Duration of type 2 diabetes																
< 5 years	39	11.62 (37.437)	32	1.75 (18.979)	36	-10.47 (25.113)	41	-10.93 (28.463)	50	2.41 (26.136)	40	-12.66 (21.423)	89	6.45 (31.728)	76	-11.62 (23.112)
>= 5 years	36	15.47 (30.697)	43	5.70 (30.753)	37	-12.89 (17.734)	32	-14.56 (26.352)	56	8.01 (25.252)	65	-13.14 (27.479)	92	10.93 (27.591)	102	-13.05 (24.302)
Complication of diabetes																

Parameter Subgroup		Study 014 Placebo N = 75		Imeglimin 500 mg bid N = 75		Imeglimin 1000 mg bid N = 73		Imeglimin 1500 mg bid N = 73		Study 018 Placebo N = 106		Imeglimin 1000 mg bid N = 106		Pooled (Studies 014+018) Placebo N = 181		Imeglimin 1000 mg bid N = 179	
Category		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Yes		18	6.28 (26.166)	17	-0.12 (25.673)	17	-8.71 (19.643)	15	-10.67 (30.810)	13	3.88 (25.688)	14	-8.36 (22.015)	31	5.27 (25.561)	31	-8.55 (20.392)
No		57	15.74 (36.266)	58	5.22 (26.574)	56	-12.61 (22.209)	58	-13.00 (26.759)	93	5.58 (25.838)	91	-13.66 (25.731)	150	9.44 (30.512)	147	-13.26 (24.377)
Metabolic syndrome at baseline																	
Yes		41	15.78 (40.660)	35	2.14 (30.513)	24	-10.92 (25.035)	44	-12.05 (28.268)	43	4.48 (28.869)	53	-13.73 (28.697)	84	10.00 (35.366)	77	-12.85 (27.475)
No		34	10.68 (24.559)	40	5.65 (22.238)	49	-12.08 (19.929)	29	-13.24 (26.582)	63	5.98 (23.525)	52	-12.16 (21.393)	97	7.62 (23.871)	101	-12.12 (20.593)
Previous treatment status																	
Treatment naive		34	3.76 (27.016)	33	6.45 (28.024)	33	-9.76 (20.562)	29	-12.07 (27.638)	77	2.11 (21.734)	75	-16.57 (23.614)	111	2.61 (23.365)	108	-14.49 (22.848)
Previously treated		41	21.51 (37.609)	42	2.10 (25.032)	40	-13.30 (22.500)	44	-12.82 (27.607)	29	14.04 (32.989)	30	-3.90 (27.244)	70	18.42 (35.712)	70	-9.27 (24.901)
FPG at baseline																	
< 160 mg/dL		44	17.07 (32.132)	40	9.28 (20.946)	38	-5.24 (17.049)	39	-1.54 (22.705)	61	11.31 (20.525)	49	-3.42 (13.127)	105	13.72 (26.040)	87	-4.21 (14.902)
>= 160 mg/dL		31	8.35 (36.851)	35	-2.00 (30.530)	35	-18.71 (23.910)	34	-25.12 (27.237)	45	-2.68 (29.781)	56	-21.30 (30.032)	76	1.82 (33.065)	91	-20.30 (27.726)
HOMA-IR at baseline																	
< 2.5		27	11.30 (28.555)	32	10.88 (25.993)	34	-9.26 (19.891)	22	-10.41 (19.025)	64	7.80 (26.460)	67	-9.84 (21.287)	91	8.84 (26.986)	101	-9.65 (20.730)
>= 2.5 to < 4.0		20	10.70 (32.645)	16	4.00 (23.594)	16	-18.56 (27.773)	13	-6.15 (22.901)	27	4.00 (21.569)	19	-24.94 (17.807)	47	6.85 (26.727)	35	-22.02 (22.772)
>= 4.0		27	18.70 (40.806)	27	-4.11 (26.739)	23	-10.52 (18.935)	38	-15.92 (32.554)	15	-2.52 (29.040)	19	-11.95 (38.887)	42	11.12 (38.077)	42	-11.17 (29.271)
Missing		1	-14.00 (.)	0	.	0	.	0	.	0	.	0	.	1	-14.00 (.)	0	.
HOMA-B at baseline																	

Parameter Subgroup	Study 014 Placebo N = 75		Imeglimin 500 mg bid N = 75		Imeglimin 1000 mg bid N = 73		Imeglimin 1500 mg bid N = 73		Study 018 Placebo N = 106		Imeglimin 1000 mg bid N = 106		Pooled (Studies 014+018) Placebo N = 181		Imeglimin 1000 mg bid N = 179	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
< 30.0%	34	13.62 (34.292)	43	5.28 (25.463)	48	-14.60 (21.388)	32	-16.34 (27.032)	78	5.10 (24.730)	85	-14.03 (25.182)	112	7.69 (28.094)	133	-14.24 (23.801)
>= 30.0%	40	14.03 (34.694)	32	2.31 (27.697)	25	-6.12 (21.232)	41	-9.54 (27.697)	28	6.11 (28.714)	20	-8.38 (25.593)	68	10.77 (32.377)	45	-7.12 (23.022)
Missing	1	-14.00 (.)	0	.	0	.	0	.	0	.	0	.	1	-14.00 (.)	0	.
QUICKI at baseline																
< 0.33	44	13.75 (37.237)	41	-0.46 (25.912)	38	-13.00 (22.703)	47	-14.45 (31.144)	37	1.61 (25.242)	30	-17.78 (33.420)	81	8.20 (32.697)	68	-15.11 (27.817)
>= 0.33	30	13.97 (30.015)	34	9.41 (26.113)	35	-10.29 (20.506)	26	-9.04 (19.040)	69	7.39 (25.904)	75	-11.03 (21.074)	99	9.38 (27.229)	110	-10.79 (20.804)
Missing	1	-14.00 (.)	0	.	0	.	0	.	0	.	0	.	1	-14.00 (.)	0	.

- Abbreviations: LOCF, Last Observation Carried Forward; bid, Twice a day; SD, standard deviation; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); BMI, body mass index; FPG, Fasting Plasma Glucose; HOMA, Homeostasis model assessment; HOMA-IR, HOMA of insulin resistance; HOMA-B, HOMA of beta-cell function; QUICKI, Quantitative Insulin Sensitivity Check Index
- Complication of diabetes is defined as any MedDRA Preferred Term (PT) of medical history which are included in High-Level Group Term (HLGT) of diabetic complication.
- Metabolic Syndrome is defined as an excessive waist circumference (>= 85 cm in men and >= 90 cm in women) as well as the presence of two or more of the following symptoms: (1) Hypertension: systolic blood pressure >= 130 mmHg, or diastolic blood pressure >= 85 mmHg; (2) Glucose intolerance: fasting glucose >= 110 mg/dL; (3) Dyslipidemia: triglyceride >= 150 mg/dL, or HDL cholesterol < 40 mg/dL.

Control No:<<t-e-076-subgl-24wdb.sas, 2020-03-06T00:05:36>>

Table E-077 Subgroup Analysis of Change from Baseline in HbA1c (%) to Week 52 (LOCF) by Various Characteristics in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Efficacy Population)

Parameter / Subgroup	Imeglimin N = 134		Imeglimin + SU N = 127		Imeglimin + GLIN N = 64		Imeglimin + BIG N = 64		Imeglimin + AGI N = 64		Imeglimin + TZD N = 65		Imeglimin + DPP4-I N = 63		Imeglimin + GLP1-RA N = 70		Imeglimin + SGLT2-I N = 63	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
HbA1c (%)																		
BMI at baseline																		
< 25 kg/m2	67	-0.54 (0.747)	65	-0.75 (0.664)	35	-0.78 (0.832)	21	-0.57 (0.477)	31	-0.76 (0.736)	24	-0.64 (1.127)	38	-0.92 (0.700)	26	-0.20 (0.865)	32	-0.68 (0.621)
>= 25 kg/m2	67	-0.39 (0.767)	62	-0.33 (1.006)	28	-0.60 (1.123)	42	-0.70 (0.888)	33	-0.94 (0.694)	40	-1.01 (0.855)	24	-0.90 (0.965)	43	-0.10 (1.001)	31	-0.48 (0.481)
>= 25 to < 30 kg/m2	51	-0.42 (0.708)	43	-0.55 (1.044)	17	-0.37 (0.810)	29	-0.53 (0.882)	26	-1.09 (0.557)	24	-1.19 (0.901)	22	-0.99 (0.967)	31	-0.12 (1.120)	24	-0.48 (0.523)
>= 30 kg/m2	16	-0.31 (0.951)	19	0.16 (0.723)	11	-0.95 (1.461)	13	-1.09 (0.803)	7	-0.40 (0.918)	16	-0.75 (0.730)	2	0.00 (0.141)	12	-0.05 (0.633)	7	-0.46 (0.331)
HbA1c at baseline																		
< 8.0%	89	-0.34 (0.684)	33	-0.37 (0.733)	23	-0.62 (0.648)	25	-0.53 (0.537)	20	-0.63 (0.659)	16	-0.52 (0.660)	23	-0.63 (0.500)	17	-0.26 (0.771)	16	-0.46 (0.334)
>= 8.0%	45	-0.70 (0.843)	94	-0.61 (0.909)	40	-0.75 (1.117)	38	-0.75 (0.892)	44	-0.96 (0.722)	48	-0.99 (1.038)	39	-1.08 (0.907)	52	-0.10 (1.001)	47	-0.62 (0.618)
>= 8.0 to < 9.0%	34	-0.71 (0.808)	52	-0.50 (0.880)	22	-0.66 (1.237)	32	-0.61 (0.828)	31	-0.79 (0.519)	24	-0.60 (0.822)	28	-0.96 (0.864)	25	0.10 (0.760)	31	-0.53 (0.554)
>= 9.0%	11	-0.69 (0.984)	42	-0.75 (0.937)	18	-0.84 (0.976)	6	-1.50 (0.914)	13	-1.35 (0.977)	24	-1.39 (1.094)	11	-1.37 (0.988)	27	-0.29 (1.165)	16	-0.80 (0.710)
Duration of type 2 diabetes																		
< 5 years	72	-0.41 (0.753)	23	-0.08 (0.907)	18	-0.63 (1.040)	21	-0.89 (0.769)	26	-0.75 (0.673)	20	-0.82 (0.877)	19	-0.93 (1.101)	15	-0.03 (0.915)	12	-0.35 (0.326)
>= 5 years	62	-0.53 (0.763)	104	-0.65 (0.832)	45	-0.73 (0.949)	42	-0.55 (0.759)	38	-0.93 (0.742)	44	-0.90 (1.024)	43	-0.91 (0.650)	54	-0.17 (0.962)	51	-0.63 (0.593)
Complication of diabetes																		
Yes	23	-0.52 (0.740)	46	-0.66 (0.769)	24	-0.50 (0.811)	24	-0.62 (0.922)	16	-1.04 (0.803)	10	-0.46 (0.458)	22	-0.88 (0.806)	31	-0.23 (1.008)	16	-0.68 (0.626)

Parameter Subgroup	Imeglimin N = 134		Imeglimin + SU N = 127		Imeglimin + GLIN N = 64		Imeglimin + BIG N = 64		Imeglimin + AGI N = 64		Imeglimin + TZD N = 65		Imeglimin + DPP4-I N = 63		Imeglimin + GLP1-RA N = 70		Imeglimin + SGLT2-I N = 63	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
No	111	-0.45 (0.764)	81	-0.48 (0.922)	39	-0.82 (1.045)	39	-0.68 (0.679)	48	-0.79 (0.681)	54	-0.95 (1.027)	40	-0.93 (0.815)	38	-0.07 (0.901)	47	-0.54 (0.540)
Metabolic syndrome at baseline																		
Yes	62	-0.26 (0.896)	64	-0.48 (0.968)	27	-0.64 (1.061)	36	-0.68 (0.871)	32	-0.91 (0.769)	32	-0.97 (0.889)	25	-0.92 (0.964)	38	-0.08 (1.015)	31	-0.55 (0.516)
No	72	-0.64 (0.565)	63	-0.62 (0.761)	36	-0.75 (0.905)	27	-0.64 (0.637)	32	-0.80 (0.664)	32	-0.78 (1.058)	37	-0.91 (0.692)	31	-0.22 (0.867)	32	-0.61 (0.609)
Previous treatment status																		
Treatment naive	134	-0.46 (0.758)	0	.	0	.	0	.	0	.	0	.	0	.	0	.	0	.
Previously treated	0	.	127	-0.55 (0.871)	63	-0.70 (0.968)	63	-0.66 (0.774)	64	-0.85 (0.715)	64	-0.87 (0.974)	62	-0.91 (0.805)	69	-0.14 (0.947)	63	-0.58 (0.561)
FPG at baseline																		
< 160 mg/dL	63	-0.40 (0.653)	29	-0.38 (0.944)	20	-0.71 (0.857)	17	-0.64 (0.659)	20	-0.81 (0.696)	26	-0.74 (0.821)	19	-0.85 (0.536)	14	-0.02 (0.917)	33	-0.62 (0.510)
>= 160 mg/dL	71	-0.52 (0.841)	98	-0.60 (0.846)	43	-0.70 (1.025)	46	-0.67 (0.819)	44	-0.87 (0.731)	38	-0.96 (1.068)	43	-0.94 (0.904)	55	-0.17 (0.960)	30	-0.53 (0.618)
HOMA-IR at baseline																		
< 2.5	89	-0.47 (0.657)	80	-0.60 (0.863)	41	-0.65 (0.872)	40	-0.59 (0.748)	39	-0.74 (0.645)	47	-0.75 (0.991)	37	-0.80 (0.497)	36	-0.13 (0.953)	42	-0.64 (0.587)
>= 2.5 to < 4.0	25	-0.51 (0.592)	17	-0.53 (1.088)	10	-0.74 (0.795)	14	-0.41 (0.631)	17	-0.87 (0.718)	11	-1.03 (0.911)	14	-0.43 (0.749)	20	-0.55 (0.941)	12	-0.56 (0.626)
>= 4.0	20	-0.39 (1.252)	30	-0.43 (0.769)	12	-0.83 (1.403)	9	-1.37 (0.753)	7	-1.39 (0.960)	6	-1.57 (0.700)	11	-1.91 (0.934)	13	0.45 (0.613)	9	-0.33 (0.224)
Missing	0	.	0	.	0	.	0	.	1	-1.20 (.)	0	.	0	.	0	.	0	.
HOMA-B at baseline																		
< 30.0%	108	-0.45 (0.776)	108	-0.62 (0.843)	52	-0.60 (0.832)	52	-0.62 (0.740)	53	-0.83 (0.716)	56	-0.86 (1.018)	51	-0.83 (0.760)	58	-0.18 (0.964)	55	-0.58 (0.584)

Parameter Subgroup	Imeglimin N = 134		Imeglimin + SU N = 127		Imeglimin + GLIN N = 64		Imeglimin + BIG N = 64		Imeglimin + AGI N = 64		Imeglimin + TZD N = 65		Imeglimin + DPP4-I N = 63		Imeglimin + GLP1-RA N = 70		Imeglimin + SGLT2-I N = 63	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
>= 30.0%	26	-0.51 (0.690)	19	-0.13 (0.933)	11	-1.16 (1.413)	11	-0.85 (0.934)	10	-0.94 (0.766)	8	-1.00 (0.614)	11	-1.31 (0.927)	11	0.08 (0.859)	8	-0.60 (0.400)
Missing	0	.	0	.	0	.	0	.	1	-1.20 (.)	0	.	0	.	0	.	0	.
QUICKI at baseline																		
< 0.33	42	-0.49 (0.950)	45	-0.47 (0.903)	19	-0.81 (1.230)	22	-0.78 (0.838)	22	-1.04 (0.845)	13	-1.28 (0.805)	24	-1.08 (1.133)	27	-0.01 (0.872)	17	-0.40 (0.334)
>= 0.33	92	-0.46 (0.658)	82	-0.59 (0.855)	44	-0.65 (0.843)	41	-0.60 (0.739)	41	-0.75 (0.630)	51	-0.77 (0.993)	38	-0.81 (0.491)	42	-0.23 (0.993)	46	-0.65 (0.615)
Missing	0	.	0	.	0	.	0	.	1	-1.20 (.)	0	.	0	.	0	.	0	.

- Abbreviations: LOCF, Last Observation Carried Forward; SD, standard deviation; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); BMI, body mass index; FPG, Fasting Plasma Glucose; HOMA, Homeostasis model assessment; HOMA-IR, HOMA of insulin resistance; HOMA-B, HOMA of beta-cell function; QUICKI, Quantitative Insulin Sensitivity Check Index; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- Complication of diabetes is defined as any MedDRA Preferred Term (PT) of medical history which are included in High-Level Group Term (HLGT) of diabetic complication.
- Metabolic Syndrome is defined as an excessive waist circumference (>= 85 cm in men and >= 90 cm in women) as well as the presence of two or more of the following symptoms: (1) Hypertension: systolic blood pressure >= 130 mmHg, or diastolic blood pressure >= 85 mmHg; (2) Glucose intolerance: fasting glucose >= 110 mg/dL; (3) Dyslipidemia: triglyceride >= 150 mg/dL, or HDL cholesterol < 40 mg/dL.

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Table E-078 Subgroup Analysis of Change from Baseline in Fasting Plasma Glucose (mg/dL) to Week 52 (LOCF) by Various Characteristics in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Efficacy Population)

Parameter Subgroup	Imeglimin N = 134		Imeglimin + SU N = 127		Imeglimin + GLIN N = 64		Imeglimin + BIG N = 64		Imeglimin + AGI N = 64		Imeglimin + TZD N = 65		Imeglimin + DPP4-I N = 63		Imeglimin + GLP1-RA N = 70		Imeglimin + SGLT2-I N = 63	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Fasting Plasma Glucose (mg/dL)																		
BMI at baseline																		
< 25 kg/m2	67	-14.90 (30.288)	65	-17.66 (33.051)	35	-13.49 (35.565)	21	-26.42 (22.482)	31	-21.56 (28.224)	24	-14.64 (41.292)	38	-27.12 (28.272)	26	-22.73 (44.285)	32	-11.88 (23.600)
>= 25 kg/m2	67	-8.47 (24.001)	62	-8.98 (34.576)	28	-21.23 (35.017)	42	-21.88 (35.779)	33	-19.05 (30.838)	40	-18.38 (25.858)	24	-16.29 (46.761)	43	-10.89 (45.764)	31	-11.56 (24.679)
>= 25 to < 30 kg/m2	51	-7.42 (24.724)	43	-15.63 (32.231)	17	-16.32 (27.518)	29	-16.84 (37.748)	26	-22.45 (25.707)	24	-20.49 (24.718)	22	-15.80 (48.751)	31	-9.88 (49.874)	24	-10.28 (27.262)
>= 30 kg/m2	16	-11.82 (21.936)	19	6.07 (35.816)	11	-28.82 (44.663)	13	-33.12 (29.166)	7	-6.43 (45.634)	16	-15.20 (27.995)	2	-21.62 (17.835)	12	-13.51 (34.675)	7	-15.96 (12.926)
HbA1c at baseline																		
< 8.0%	89	-8.32 (24.903)	33	-6.71 (22.878)	23	-11.98 (27.320)	25	-22.20 (26.456)	20	-12.34 (29.063)	16	-8.11 (20.456)	23	-18.25 (18.471)	17	-18.44 (26.899)	16	-13.29 (21.437)
>= 8.0%	45	-18.34 (31.034)	94	-15.77 (36.877)	40	-19.77 (39.139)	38	-24.18 (35.270)	44	-23.87 (29.156)	48	-19.93 (34.992)	39	-25.68 (43.915)	52	-14.34 (49.994)	47	-11.19 (24.932)
>= 8.0 to < 9.0%	34	-19.50 (30.873)	52	-15.52 (34.108)	22	-29.23 (42.411)	32	-17.73 (34.515)	31	-22.03 (21.330)	24	-18.32 (22.699)	28	-18.02 (44.406)	25	-7.35 (43.790)	31	-13.48 (22.010)
>= 9.0%	11	-14.74 (32.765)	42	-16.09 (40.465)	18	-8.21 (32.169)	6	-58.55 (11.662)	13	-28.27 (43.346)	24	-21.54 (44.513)	11	-45.20 (37.691)	27	-20.82 (55.154)	16	-6.76 (30.092)
Duration of type 2 diabetes																		
< 5 years	72	-10.28 (28.478)	23	-0.16 (36.977)	18	-17.92 (27.185)	21	-30.97 (29.748)	26	-14.27 (32.631)	20	-20.54 (25.096)	19	-24.37 (35.325)	15	-5.52 (49.062)	12	-8.41 (19.590)
>= 5 years	62	-13.31 (26.260)	104	-16.35 (32.710)	45	-16.53 (38.275)	42	-19.60 (32.526)	38	-24.37 (26.628)	44	-15.35 (35.163)	43	-22.29 (37.502)	54	-18.08 (44.236)	51	-12.50 (24.962)
Complication of diabetes																		

Parameter Subgroup	Imeglimin N = 134		Imeglimin + SU N = 127		Imeglimin + GLIN N = 64		Imeglimin + BIG N = 64		Imeglimin + AGI N = 64		Imeglimin + TZD N = 65		Imeglimin + DPP4-I N = 63		Imeglimin + GLP1-RA N = 70		Imeglimin + SGLT2-I N = 63	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Yes	23	-13.94 (15.153)	46	-14.45 (26.208)	24	-17.64 (35.874)	24	-16.44 (38.902)	16	-35.47 (30.223)	10	3.78 (30.567)	22	-22.19 (49.169)	31	-16.16 (48.521)	16	-19.37 (25.736)
No	111	-11.22 (29.350)	81	-12.83 (37.789)	39	-16.49 (35.329)	39	-27.67 (26.259)	48	-15.20 (27.598)	54	-20.82 (31.319)	40	-23.33 (28.103)	38	-14.70 (43.058)	47	-9.12 (23.008)
Metabolic syndrome at baseline																		
Yes	62	-6.94 (33.358)	64	-14.53 (33.452)	27	-24.02 (32.589)	36	-24.37 (35.318)	32	-18.18 (31.402)	32	-16.66 (27.547)	25	-25.58 (30.320)	38	-17.21 (44.638)	31	-16.16 (23.441)
No	72	-15.76 (20.377)	63	-12.30 (34.680)	36	-11.61 (36.668)	27	-22.09 (27.137)	32	-22.35 (27.581)	32	-17.28 (36.796)	37	-21.13 (40.562)	31	-13.08 (46.634)	32	-7.43 (24.000)
Previous treatment status																		
Treatment naive	134	-11.68 (27.414)	0	.	0	.	0	.	0	.	0	.	0	.	0	.	0	.
Previously treated	0	.	127	-13.42 (33.950)	63	-16.93 (35.252)	63	-23.39 (31.847)	64	-20.27 (29.393)	64	-16.97 (32.245)	62	-22.93 (36.572)	69	-15.35 (45.254)	63	-11.72 (23.942)
FPG at baseline																		
< 160 mg/dL	63	-4.69 (20.337)	29	2.80 (26.119)	20	-0.27 (28.088)	17	-11.02 (24.889)	20	-11.89 (29.087)	26	-5.34 (14.973)	19	-14.79 (14.741)	14	22.26 (38.888)	33	-4.31 (15.392)
>= 160 mg/dL	71	-17.89 (31.280)	98	-18.22 (34.618)	43	-24.68 (35.832)	46	-27.96 (33.136)	44	-24.08 (29.060)	38	-24.94 (38.190)	43	-26.52 (42.501)	55	-24.93 (41.888)	30	-19.88 (28.858)
HOMA-IR at baseline																		
< 2.5	89	-10.36 (22.908)	80	-13.78 (31.787)	41	-8.13 (30.566)	40	-18.33 (30.327)	39	-18.80 (28.147)	47	-11.73 (31.341)	37	-21.18 (23.917)	36	-6.81 (46.855)	42	-7.03 (23.408)
>= 2.5 to < 4.0	25	-13.55 (15.629)	17	-10.49 (37.770)	10	-25.22 (34.830)	14	-27.02 (37.604)	17	-16.00 (32.614)	11	-25.88 (33.630)	14	2.06 (47.956)	20	-22.61 (45.544)	12	-21.77 (24.419)
>= 4.0	20	-15.22 (49.955)	30	-14.11 (38.240)	12	-40.08 (40.968)	9	-40.23 (24.669)	7	-37.58 (28.111)	6	-41.74 (25.155)	11	-60.60 (25.760)	13	-27.85 (37.966)	9	-20.22 (21.596)
Missing	0	.	0	.	0	.	0	.	1	-28.82 (.)	0	.	0	.	0	.	0	.
HOMA-B at baseline																		

Parameter Subgroup	Imeglimin N = 134		Imeglimin + SU N = 127		Imeglimin + GLIN N = 64		Imeglimin + BIG N = 64		Imeglimin + AGI N = 64		Imeglimin + TZD N = 65		Imeglimin + DPP4-I N = 63		Imeglimin + GLP1-RA N = 70		Imeglimin + SGLT2-I N = 63	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
< 30.0%	108	-11.36 (29.441)	108	-16.58 (33.094)	52	-13.17 (32.181)	52	-23.80 (31.934)	53	-22.67 (27.709)	56	-17.05 (34.071)	51	-21.58 (38.767)	58	-16.03 (46.094)	55	-11.53 (23.960)
>= 30.0%	26	-13.03 (16.910)	19	4.55 (34.010)	11	-34.72 (44.736)	11	-21.45 (32.900)	10	-6.67 (36.931)	8	-16.44 (15.360)	11	-29.15 (24.342)	11	-11.79 (42.414)	8	-13.06 (25.419)
Missing	0	.	0	.	0	.	0	.	1	-28.82 (.)	0	.	0	.	0	.	0	.
QUICKI at baseline																		
< 0.33	42	-15.66 (35.621)	45	-12.89 (38.267)	19	-32.05 (40.103)	22	-31.77 (33.889)	22	-22.52 (33.730)	13	-37.83 (24.941)	24	-24.85 (51.268)	27	-22.49 (40.291)	17	-17.59 (17.145)
>= 0.33	92	-9.87 (22.717)	82	-13.71 (31.579)	44	-10.40 (31.208)	41	-18.89 (30.162)	41	-18.85 (27.509)	51	-11.66 (31.918)	38	-21.71 (23.819)	42	-10.77 (48.084)	46	-9.56 (25.835)
Missing	0	.	0	.	0	.	0	.	1	-28.82 (.)	0	.	0	.	0	.	0	.

- Abbreviations: LOCF, Last Observation Carried Forward; SD, standard deviation; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); BMI, body mass index; FPG, Fasting Plasma Glucose; HOMA, Homeostasis model assessment; HOMA-IR, HOMA of insulin resistance; HOMA-B, HOMA of beta-cell function; QUICKI, Quantitative Insulin Sensitivity Check Index; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- Complication of diabetes is defined as any MedDRA Preferred Term (PT) of medical history which are included in High-Level Group Term (HLGT) of diabetic complication.
- Metabolic Syndrome is defined as an excessive waist circumference (>= 85 cm in men and >= 90 cm in women) as well as the presence of two or more of the following symptoms: (1) Hypertension: systolic blood pressure >= 130 mmHg, or diastolic blood pressure >= 85 mmHg; (2) Glucose intolerance: fasting glucose >= 110 mg/dL; (3) Dyslipidemia: triglyceride >= 150 mg/dL, or HDL cholesterol < 40 mg/dL.

Control No:<<t-e-078-subgl-019lt.sas, 2020-03-06T00:04:52>>

Table E-079 Subgroup Analysis of Change from Baseline in HbA1c (%) to Week 16 (LOCF) by Various Characteristics in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Efficacy Population)

Parameter Subgroup	Placebo + Insulin N = 106		Imeglimin 1000 mg bid + Insulin N = 108	
Category	n	Mean (SD)	n	Mean (SD)
HbA1c (%)				
BMI at baseline				
< 25 kg/m2	59	-0.19 (0.567)	56	-0.95 (0.647)
>= 25 kg/m2	46	0.08 (0.825)	52	-0.38 (0.770)
>= 25 to < 30 kg/m2	35	0.06 (0.718)	44	-0.45 (0.725)
>= 30 kg/m2	11	0.15 (1.143)	8	0.00 (0.944)
HbA1c at baseline				
< 8.0%	16	0.07 (0.502)	16	-0.37 (0.723)
>= 8.0%	89	-0.10 (0.732)	92	-0.73 (0.759)
>= 8.0 to < 9.0%	43	-0.13 (0.677)	53	-0.68 (0.657)
>= 9.0%	46	-0.06 (0.785)	39	-0.79 (0.884)
Duration of type 2 diabetes				
< 5 years	12	0.42 (1.060)	16	-0.58 (0.822)
>= 5 years	93	-0.14 (0.623)	92	-0.69 (0.754)
Complication of diabetes				
Yes	51	-0.08 (0.640)	45	-0.56 (0.840)
No	54	-0.06 (0.762)	63	-0.76 (0.696)
Metabolic syndrome at baseline				
Yes	48	0.01 (0.776)	39	-0.53 (0.745)
No	57	-0.14 (0.633)	69	-0.76 (0.763)
Previous treatment status				
Insulin monotherapy	84	-0.11 (0.626)	87	-0.70 (0.754)
Insulin in combination with 1 OHA	21	0.08 (0.954)	21	-0.57 (0.803)
FPG at baseline				
< 160 mg/dL	67	-0.13 (0.591)	61	-0.70 (0.698)
>= 160 mg/dL	38	0.03 (0.865)	47	-0.65 (0.844)

- Abbreviations: LOCF, Last Observation Carried Forward; bid, Twice a day; SD, standard deviation; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); BMI, body mass index; FPG, Fasting Plasma Glucose; 1 OHA, Patients on insulin in combination with one oral hypoglycemic agent
- Complication of diabetes is defined as any MedDRA Preferred Term (PT) of medical history which are included in High-Level Group Term (HLGT) of diabetic complication.
- Metabolic Syndrome is defined as an excessive waist circumference (>= 85 cm in men and >= 90 cm in women) as well as the presence of two or more of the following symptoms: (1) Hypertension: systolic blood pressure >= 130 mmHg, or diastolic blood pressure >= 85 mmHg; (2) Glucose intolerance: fasting glucose >= 110 mg/dL; (3) Dyslipidemia: triglyceride >= 150 mg/dL, or HDL cholesterol < 40 mg/dL.

Control No:<<t-e-079-subhb-020db.sas, 2020-03-06T00:06:07>>

Table E-080 Subgroup Analysis of Change from Baseline in Fasting Plasma Glucose (mg/dL) to Week 16 (LOCF) by Various Characteristics in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Efficacy Population)

Parameter Subgroup	Placebo + Insulin N = 106		Imeglimin 1000 mg bid + Insulin N = 108	
Category	n	Mean (SD)	n	Mean (SD)
Fasting Plasma Glucose (mg/dL)				
BMI at baseline				
< 25 kg/m2	59	-0.67 (36.183)	56	-15.47 (25.533)
>= 25 kg/m2	46	5.21 (33.775)	52	-3.33 (43.391)
>= 25 to < 30 kg/m2	35	8.39 (35.389)	44	1.64 (40.890)
>= 30 kg/m2	11	-4.91 (26.964)	8	-30.63 (49.394)
HbA1c at baseline				
< 8.0%	16	4.84 (21.606)	16	4.73 (25.545)
>= 8.0%	89	1.38 (37.080)	92	-12.12 (36.645)
>= 8.0 to < 9.0%	43	0.13 (35.735)	53	-7.58 (30.806)
>= 9.0%	46	2.55 (38.653)	39	-18.29 (43.003)
Duration of type 2 diabetes				
< 5 years	12	-6.91 (42.673)	16	-3.83 (28.719)
>= 5 years	93	3.04 (34.116)	92	-10.63 (36.743)
Complication of diabetes				
Yes	51	5.30 (39.413)	45	-7.13 (36.278)
No	54	-1.30 (30.514)	63	-11.41 (35.348)
Metabolic syndrome at baseline				
Yes	48	5.44 (34.687)	39	-11.83 (44.629)
No	57	-1.07 (35.483)	69	-8.38 (29.673)
Previous treatment status				
Insulin monotherapy	84	2.17 (34.487)	87	-9.40 (36.113)
Insulin in combination with 1 OHA	21	0.86 (38.351)	21	-10.55 (34.406)
FPG at baseline				
< 160 mg/dL	67	10.70 (32.709)	61	-0.12 (26.614)
>= 160 mg/dL	38	-13.61 (34.179)	47	-21.96 (41.882)

- Abbreviations: LOCF, Last Observation Carried Forward; bid, Twice a day; SD, standard deviation; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); BMI, body mass index; FPG, Fasting Plasma Glucose; 1 OHA, Patients on insulin in combination with one oral hypoglycemic agent
- Complication of diabetes is defined as any MedDRA Preferred Term (PT) of medical history which are included in High-Level Group Term (HLGT) of diabetic complication.
- Metabolic Syndrome is defined as an excessive waist circumference (>= 85 cm in men and >= 90 cm in women) as well as the presence of two or more of the following symptoms: (1) Hypertension: systolic blood pressure >= 130 mmHg, or diastolic blood pressure >= 85 mmHg; (2) Glucose intolerance: fasting glucose >= 110 mg/dL; (3) Dyslipidemia: triglyceride >= 150 mg/dL, or HDL cholesterol < 40 mg/dL.

Control No:<<t-e-080-subgl-020db.sas, 2020-03-06T00:06:04>>

Table E-081 Subgroup Analysis of Change from Baseline in HbA1c (%) to Week 52 (LOCF) by Various Characteristics in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Efficacy Population)

Parameter Subgroup	Placebo/Imeglimin + Insulin N = 101		Imeglimin/Imeglimin + Insulin N = 108		Imeglimin + Insulin Total N = 209	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
HbA1c (%)						
BMI at baseline						
< 25 kg/m2	58	-0.31 (0.866)	56	-0.75 (0.844)	114	-0.53 (0.880)
>= 25 kg/m2	42	-0.88 (0.686)	52	-0.55 (0.981)	94	-0.70 (0.873)
>= 25 to < 30 kg/m2	32	-0.90 (0.667)	44	-0.54 (0.877)	76	-0.69 (0.811)
>= 30 kg/m2	10	-0.80 (0.777)	8	-0.65 (1.512)	18	-0.73 (1.126)
HbA1c at baseline						
< 8.0%	16	-0.25 (0.726)	16	-0.05 (0.705)	32	-0.15 (0.711)
>= 8.0%	84	-0.60 (0.853)	92	-0.76 (0.908)	176	-0.69 (0.883)
>= 8.0 to < 9.0%	41	-0.36 (0.754)	53	-0.60 (0.776)	94	-0.50 (0.772)
>= 9.0%	43	-0.83 (0.885)	39	-0.98 (1.032)	82	-0.90 (0.954)
Duration of type 2 diabetes						
< 5 years	10	-0.50 (1.034)	16	-0.34 (1.003)	26	-0.40 (0.997)
>= 5 years	90	-0.55 (0.823)	92	-0.71 (0.892)	182	-0.63 (0.860)
Complication of diabetes						
Yes	48	-0.58 (0.791)	45	-0.46 (0.971)	93	-0.52 (0.879)
No	52	-0.52 (0.891)	63	-0.80 (0.851)	115	-0.67 (0.877)
Metabolic syndrome at baseline						
Yes	45	-0.72 (0.761)	39	-0.78 (0.972)	84	-0.75 (0.861)
No	55	-0.40 (0.881)	69	-0.59 (0.879)	124	-0.51 (0.882)
Previous treatment status						
Insulin monotherapy	83	-0.55 (0.832)	87	-0.64 (0.954)	170	-0.60 (0.895)
Insulin in combination with 1 OHA	17	-0.51 (0.905)	21	-0.72 (0.741)	38	-0.63 (0.814)
FPG at baseline						
< 160 mg/dL	65	-0.43 (0.806)	61	-0.44 (0.885)	126	-0.44 (0.842)
>= 160 mg/dL	35	-0.75 (0.876)	47	-0.94 (0.880)	82	-0.86 (0.878)

- Abbreviations: LOCF, Last Observation Carried Forward; SD, standard deviation; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); BMI, body mass index; FPG, Fasting Plasma Glucose; 1 OHA, Patients on insulin in combination with one oral hypoglycemic agent
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- For "Placebo/Imeglimin + Insulin" group, baseline was defined as last visit with non-missing value prior to or at the day of first dose of Investigational Medicinal Product (IMP) in open-label treatment period. For "Imeglimin/Imeglimin + Insulin" group, baseline was the same as for the double-blind treatment period.
- Complication of diabetes is defined as any MedDRA Preferred Term (PT) of medical history which are included in High-Level Group Term (HLGT) of diabetic complication.
- Metabolic Syndrome is defined as an excessive waist circumference (>= 85 cm in men and >= 90 cm in women) as well as the presence of two or more of the following symptoms: (1) Hypertension: systolic blood pressure >= 130 mmHg, or diastolic blood pressure >= 85 mmHg; (2) Glucose intolerance: fasting glucose >= 110 mg/dL; (3) Dyslipidemia: triglyceride >= 150 mg/dL, or HDL cholesterol < 40 mg/dL.

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Table E-082 Subgroup Analysis of Change from Baseline in Fasting Plasma Glucose (mg/dL) to Week 52 (LOCF) by Various Characteristics in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Efficacy Population)

Parameter Subgroup	Placebo/Imeglimin + Insulin N = 101		Imeglimin/Imeglimin + Insulin N = 108		Imeglimin + Insulin Total N = 209	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Fasting Plasma Glucose (mg/dL)						
BMI at baseline						
< 25 kg/m2	58	10.06 (42.054)	56	-8.94 (44.891)	114	0.73 (44.318)
>= 25 kg/m2	42	-14.93 (44.160)	52	-6.37 (51.519)	94	-10.20 (48.307)
>= 25 to < 30 kg/m2	32	-16.95 (46.627)	44	-1.43 (51.248)	76	-7.96 (49.637)
>= 30 kg/m2	10	-8.47 (36.529)	8	-33.55 (46.978)	18	-19.62 (42.186)
HbA1c at baseline						
< 8.0%	16	14.41 (46.311)	16	9.57 (24.123)	32	11.99 (36.406)
>= 8.0%	84	-3.26 (43.852)	92	-10.71 (50.497)	176	-7.16 (47.455)
>= 8.0 to < 9.0%	41	0.92 (38.175)	53	3.54 (54.613)	94	2.40 (47.918)
>= 9.0%	43	-7.25 (48.775)	39	-30.07 (36.840)	82	-18.10 (44.741)
Duration of type 2 diabetes						
< 5 years	10	-0.90 (58.205)	16	4.28 (59.047)	26	2.29 (57.604)
>= 5 years	90	-0.38 (43.120)	92	-9.79 (45.860)	182	-5.14 (44.653)
Complication of diabetes						
Yes	48	-6.19 (42.739)	45	-0.92 (51.378)	93	-3.64 (46.932)
No	52	4.88 (45.818)	63	-12.55 (45.203)	115	-4.67 (46.113)
Metabolic syndrome at baseline						
Yes	45	-9.81 (46.810)	39	-22.82 (40.172)	84	-15.85 (44.080)
No	55	7.24 (41.360)	69	0.84 (50.163)	124	3.68 (46.394)
Previous treatment status						
Insulin monotherapy	83	-0.82 (43.274)	87	-5.63 (50.205)	170	-3.29 (46.873)
Insulin in combination with 1 OHA	17	1.48 (51.444)	21	-16.30 (37.208)	38	-8.34 (44.419)
FPG at baseline						
< 160 mg/dL	65	0.36 (36.679)	61	11.05 (47.400)	126	5.53 (42.379)
>= 160 mg/dL	35	-1.90 (56.817)	47	-32.04 (36.796)	82	-19.18 (48.466)

- Abbreviations: LOCF, Last Observation Carried Forward; SD, standard deviation; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); BMI, body mass index; FPG, Fasting Plasma Glucose; 1 OHA, Patients on insulin in combination with one oral hypoglycemic agent
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- For "Placebo/Imeglimin + Insulin" group, baseline was defined as last visit with non-missing value prior to or at the day of first dose of Investigational Medicinal Product (IMP) in open-label treatment period. For "Imeglimin/Imeglimin + Insulin" group, baseline was the same as for the double-blind treatment period.
- Complication of diabetes is defined as any MedDRA Preferred Term (PT) of medical history which are included in High-Level Group Term (HLGT) of diabetic complication.
- Metabolic Syndrome is defined as an excessive waist circumference (>= 85 cm in men and >= 90 cm in women) as well as the presence of two or more of the following symptoms: (1) Hypertension: systolic blood pressure >= 130 mmHg, or diastolic blood pressure >= 85 mmHg; (2) Glucose intolerance: fasting glucose >= 110 mg/dL; (3) Dyslipidemia: triglyceride >= 150 mg/dL, or HDL cholesterol < 40 mg/dL.

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Table E-085 Subgroup and MMRM Analysis of Change from Baseline in HbA1c (%) to All Visits by Age Group in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Efficacy Population)

Age		Observed		Change from baseline			Difference vs Placebo		
Visit									
Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
< 65 years									
Baseline									
Placebo	105	105	7.98 (0.696)						
Imeglimin 1000 mg bid	97	97	8.01 (0.782)						
Week 4									
Placebo	105	104	8.01 (0.786)	0.05 (0.317)	0.06 (0.028)	[0.000, 0.110]			
Imeglimin 1000 mg bid	97	96	7.79 (0.783)	-0.23 (0.245)	-0.22 (0.029)	[-0.282, -0.167]	-0.28 (0.040)	[-0.359, -0.200]	<.0001
Week 8									
Placebo	105	103	8.07 (0.821)	0.12 (0.423)	0.14 (0.040)	[0.056, 0.216]			
Imeglimin 1000 mg bid	97	95	7.57 (0.755)	-0.44 (0.378)	-0.43 (0.042)	[-0.515, -0.349]	-0.57 (0.058)	[-0.683, -0.453]	<.0001
Week 12									
Placebo	105	100	8.06 (0.827)	0.16 (0.564)	0.20 (0.055)	[0.088, 0.306]			
Imeglimin 1000 mg bid	97	95	7.49 (0.789)	-0.52 (0.512)	-0.51 (0.057)	[-0.623, -0.397]	-0.71 (0.079)	[-0.863, -0.550]	<.0001
Week 16									
Placebo	105	97	8.01 (0.816)	0.13 (0.630)	0.22 (0.066)	[0.094, 0.354]			
Imeglimin 1000 mg bid	97	94	7.40 (0.824)	-0.61 (0.533)	-0.58 (0.068)	[-0.716, -0.447]	-0.81 (0.095)	[-0.992, -0.618]	<.0001
Week 20									
Placebo	105	96	8.02 (0.878)	0.14 (0.701)	0.26 (0.076)	[0.115, 0.413]			
Imeglimin 1000 mg bid	97	93	7.37 (0.865)	-0.64 (0.610)	-0.61 (0.078)	[-0.759, -0.451]	-0.87 (0.108)	[-1.083, -0.655]	<.0001
Week 24									
Placebo	105	93	8.01 (0.922)	0.17 (0.812)	0.32 (0.084)	[0.159, 0.489]			
Imeglimin 1000 mg bid	97	91	7.39 (0.778)	-0.61 (0.633)	-0.55 (0.086)	[-0.720, -0.379]	-0.87 (0.120)	[-1.111, -0.636]	<.0001
LOCF Endpoint									
Placebo	105	105	8.27 (1.158)	0.29 (0.880)					
Imeglimin 1000 mg bid	97	96	7.47 (0.897)	-0.55 (0.694)					
>= 65 years									

Age		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Baseline									
Placebo	76	76	7.82 (0.648)						
Imeglimin 1000 mg bid	82	82	7.84 (0.633)						
Week 4									
Placebo	76	76	7.86 (0.761)	0.04 (0.269)	0.04 (0.031)	[-0.021, 0.101]			
Imeglimin 1000 mg bid	82	82	7.56 (0.654)	-0.27 (0.259)	-0.27 (0.030)	[-0.327, -0.209]	-0.31 (0.042)	[-0.391, -0.224]	<.0001
Week 8									
Placebo	76	76	7.89 (0.904)	0.07 (0.446)	0.07 (0.051)	[-0.027, 0.173]			
Imeglimin 1000 mg bid	82	80	7.36 (0.642)	-0.46 (0.426)	-0.46 (0.049)	[-0.559, -0.366]	-0.54 (0.070)	[-0.674, -0.397]	<.0001
Week 12									
Placebo	76	71	7.82 (0.769)	0.07 (0.474)	0.11 (0.057)	[-0.005, 0.222]			
Imeglimin 1000 mg bid	82	78	7.21 (0.620)	-0.62 (0.470)	-0.61 (0.055)	[-0.718, -0.499]	-0.72 (0.079)	[-0.874, -0.561]	<.0001
Week 16									
Placebo	76	68	7.75 (0.722)	0.01 (0.462)	0.08 (0.058)	[-0.035, 0.195]			
Imeglimin 1000 mg bid	82	76	7.12 (0.671)	-0.71 (0.465)	-0.71 (0.056)	[-0.820, -0.600]	-0.79 (0.080)	[-0.949, -0.632]	<.0001
Week 20									
Placebo	76	68	7.77 (0.702)	0.04 (0.483)	0.10 (0.060)	[-0.015, 0.223]			
Imeglimin 1000 mg bid	82	75	7.06 (0.624)	-0.75 (0.478)	-0.74 (0.058)	[-0.850, -0.622]	-0.84 (0.083)	[-1.005, -0.677]	<.0001
Week 24									
Placebo	76	68	7.82 (0.737)	0.09 (0.534)	0.15 (0.065)	[0.025, 0.282]			
Imeglimin 1000 mg bid	82	73	7.09 (0.672)	-0.73 (0.514)	-0.72 (0.062)	[-0.843, -0.596]	-0.87 (0.090)	[-1.050, -0.695]	<.0001
LOCF Endpoint									
Placebo	76	76	7.97 (0.947)	0.15 (0.588)					
Imeglimin 1000 mg bid	82	82	7.13 (0.696)	-0.71 (0.502)					
< 75 years									
Baseline									
Placebo	168	168	7.92 (0.664)						
Imeglimin 1000 mg bid	170	170	7.93 (0.728)						
Week 4									

Age		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Placebo	168	167	7.95 (0.748)	0.04 (0.294)	0.04 (0.021)	[0.003, 0.086]			
Imeglimin 1000 mg bid	170	169	7.68 (0.741)	-0.25 (0.252)	-0.25 (0.021)	[-0.287, -0.204]	-0.29 (0.030)	[-0.349, -0.231]	<.0001
Week 8									
Placebo	168	166	7.98 (0.811)	0.09 (0.421)	0.10 (0.032)	[0.037, 0.165]			
Imeglimin 1000 mg bid	170	167	7.46 (0.713)	-0.46 (0.399)	-0.45 (0.032)	[-0.515, -0.388]	-0.55 (0.046)	[-0.642, -0.463]	<.0001
Week 12									
Placebo	168	159	7.97 (0.812)	0.12 (0.540)	0.15 (0.041)	[0.069, 0.231]			
Imeglimin 1000 mg bid	170	166	7.35 (0.730)	-0.57 (0.500)	-0.56 (0.041)	[-0.641, -0.480]	-0.71 (0.058)	[-0.825, -0.596]	<.0001
Week 16									
Placebo	168	153	7.91 (0.789)	0.08 (0.582)	0.16 (0.047)	[0.065, 0.248]			
Imeglimin 1000 mg bid	170	163	7.26 (0.765)	-0.66 (0.499)	-0.65 (0.046)	[-0.738, -0.557]	-0.80 (0.065)	[-0.933, -0.676]	<.0001
Week 20									
Placebo	168	152	7.92 (0.825)	0.09 (0.637)	0.19 (0.052)	[0.087, 0.292]			
Imeglimin 1000 mg bid	170	161	7.23 (0.782)	-0.69 (0.559)	-0.67 (0.051)	[-0.772, -0.570]	-0.86 (0.073)	[-1.005, -0.716]	<.0001
Week 24									
Placebo	168	149	7.94 (0.863)	0.14 (0.727)	0.25 (0.058)	[0.134, 0.361]			
Imeglimin 1000 mg bid	170	159	7.24 (0.745)	-0.67 (0.586)	-0.63 (0.057)	[-0.743, -0.520]	-0.88 (0.081)	[-1.038, -0.720]	<.0001
LOCF Endpoint									
Placebo	168	168	8.15 (1.063)	0.23 (0.784)					
Imeglimin 1000 mg bid	170	169	7.31 (0.836)	-0.63 (0.625)					
>= 75 years									
Baseline									
Placebo	13	13	7.87 (0.875)						
Imeglimin 1000 mg bid	9	9	7.99 (0.613)						
Week 4									
Placebo	13	13	7.95 (1.130)	0.08 (0.344)	-0.03 (0.156)	[-0.355, 0.295]			
Imeglimin 1000 mg bid	9	9	7.77 (0.612)	-0.22 (0.268)	-0.29 (0.128)	[-0.560, -0.023]	-0.26 (0.148)	[-0.573, 0.051]	0.0954
Week 8									
Placebo	13	13	8.07 (1.383)	0.20 (0.570)	0.09 (0.193)	[-0.314, 0.484]			

Age		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Imeglimin 1000 mg bid	9	8	7.71 (0.669)	-0.26 (0.389)	-0.41 (0.185)	[-0.796, -0.022]	-0.49 (0.237)	[-0.992, 0.003]	0.0513
Week 12									
Placebo	13	12	7.79 (0.796)	0.11 (0.368)	0.13 (0.200)	[-0.281, 0.548]			
Imeglimin 1000 mg bid	9	7	7.60 (0.733)	-0.41 (0.363)	-0.52 (0.194)	[-0.927, -0.104]	-0.65 (0.250)	[-1.182, -0.116]	0.0203
Week 16									
Placebo	13	12	7.78 (0.782)	0.09 (0.370)	0.16 (0.240)	[-0.342, 0.659]			
Imeglimin 1000 mg bid	9	7	7.54 (0.911)	-0.47 (0.642)	-0.57 (0.252)	[-1.108, -0.036]	-0.73 (0.329)	[-1.434, -0.028]	0.0426
Week 20									
Placebo	13	12	7.80 (0.717)	0.12 (0.369)	0.14 (0.211)	[-0.302, 0.578]			
Imeglimin 1000 mg bid	9	7	7.44 (0.772)	-0.57 (0.509)	-0.68 (0.214)	[-1.131, -0.221]	-0.81 (0.274)	[-1.403, -0.226]	0.0103
Week 24									
Placebo	13	12	7.81 (0.717)	0.13 (0.409)	0.13 (0.207)	[-0.304, 0.560]			
Imeglimin 1000 mg bid	9	5	7.70 (0.682)	-0.52 (0.581)	-0.68 (0.224)	[-1.150, -0.207]	-0.81 (0.276)	[-1.398, -0.214]	0.0111
LOCF Endpoint									
Placebo	13	13	8.13 (1.350)	0.26 (0.629)					
Imeglimin 1000 mg bid	9	9	7.44 (0.631)	-0.54 (0.456)					

- Abbreviations: MMRM, Mixed Model Repeated Measures; LOCF, Last Observation Carried Forward; bid, Twice a day; SD, standard deviation; SE, standard error; LS, least square; CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c)
- MMRM model was used with fixed effects for treatment group, visit, study, interaction of treatment-by-visit, and baseline HbA1c as a covariate, assuming an unstructured covariance matrix.

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Table E-086 Subgroup and MMRM Analysis of Change from Baseline in HbA1c (%) to All Visits by Sex in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Efficacy Population)

Sex		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Male									
Baseline									
Placebo	126	126	7.87 (0.657)						
Imeglimin 1000 mg bid	137	137	8.00 (0.741)						
Week 4									
Placebo	126	125	7.90 (0.717)	0.04 (0.286)	0.05 (0.024)	[0.002, 0.098]			
Imeglimin 1000 mg bid	137	137	7.74 (0.757)	-0.25 (0.252)	-0.25 (0.024)	[-0.295, -0.202]	-0.30 (0.033)	[-0.364, -0.232]	<.0001
Week 8									
Placebo	126	124	7.90 (0.757)	0.06 (0.387)	0.08 (0.037)	[0.006, 0.153]			
Imeglimin 1000 mg bid	137	136	7.54 (0.731)	-0.44 (0.421)	-0.44 (0.036)	[-0.507, -0.366]	-0.52 (0.051)	[-0.617, -0.414]	<.0001
Week 12									
Placebo	126	121	7.94 (0.796)	0.11 (0.487)	0.13 (0.046)	[0.037, 0.220]			
Imeglimin 1000 mg bid	137	135	7.42 (0.754)	-0.56 (0.527)	-0.55 (0.044)	[-0.638, -0.463]	-0.68 (0.064)	[-0.805, -0.553]	<.0001
Week 16									
Placebo	126	118	7.87 (0.761)	0.05 (0.478)	0.11 (0.050)	[0.006, 0.204]			
Imeglimin 1000 mg bid	137	133	7.33 (0.805)	-0.66 (0.534)	-0.64 (0.048)	[-0.732, -0.543]	-0.74 (0.069)	[-0.879, -0.606]	<.0001
Week 20									
Placebo	126	118	7.91 (0.807)	0.09 (0.549)	0.14 (0.055)	[0.033, 0.251]			
Imeglimin 1000 mg bid	137	131	7.29 (0.826)	-0.69 (0.581)	-0.66 (0.053)	[-0.768, -0.561]	-0.81 (0.076)	[-0.956, -0.657]	<.0001
Week 24									
Placebo	126	115	7.92 (0.839)	0.13 (0.658)	0.21 (0.063)	[0.082, 0.329]			
Imeglimin 1000 mg bid	137	128	7.30 (0.782)	-0.68 (0.613)	-0.63 (0.060)	[-0.746, -0.511]	-0.83 (0.086)	[-1.004, -0.664]	<.0001
LOCF Endpoint									
Placebo	126	126	8.07 (1.019)	0.20 (0.713)					
Imeglimin 1000 mg bid	137	137	7.37 (0.877)	-0.63 (0.657)					
Female									

Sex		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Baseline									
Placebo	55	55	8.01 (0.723)						
Imeglimin 1000 mg bid	42	42	7.73 (0.616)						
Week 4									
Placebo	55	55	8.06 (0.896)	0.05 (0.322)	0.03 (0.041)	[-0.046, 0.115]			
Imeglimin 1000 mg bid	42	41	7.51 (0.623)	-0.23 (0.255)	-0.23 (0.047)	[-0.322, -0.137]	-0.26 (0.063)	[-0.388, -0.140]	<.0001
Week 8									
Placebo	55	55	8.19 (1.035)	0.18 (0.516)	0.17 (0.061)	[0.044, 0.287]			
Imeglimin 1000 mg bid	42	39	7.23 (0.587)	-0.47 (0.316)	-0.48 (0.071)	[-0.622, -0.339]	-0.65 (0.094)	[-0.833, -0.459]	<.0001
Week 12									
Placebo	55	50	8.01 (0.848)	0.15 (0.624)	0.22 (0.081)	[0.062, 0.384]			
Imeglimin 1000 mg bid	42	38	7.14 (0.590)	-0.56 (0.364)	-0.57 (0.094)	[-0.757, -0.383]	-0.79 (0.124)	[-1.041, -0.546]	<.0001
Week 16									
Placebo	55	47	7.97 (0.854)	0.16 (0.750)	0.30 (0.097)	[0.110, 0.498]			
Imeglimin 1000 mg bid	42	37	7.06 (0.593)	-0.63 (0.389)	-0.66 (0.113)	[-0.881, -0.431]	-0.96 (0.150)	[-1.257, -0.662]	<.0001
Week 20									
Placebo	55	46	7.93 (0.849)	0.12 (0.780)	0.33 (0.111)	[0.109, 0.553]			
Imeglimin 1000 mg bid	42	37	7.03 (0.551)	-0.66 (0.461)	-0.69 (0.129)	[-0.945, -0.432]	-1.02 (0.170)	[-1.359, -0.680]	<.0001
Week 24									
Placebo	55	46	7.96 (0.891)	0.15 (0.826)	0.36 (0.117)	[0.131, 0.597]			
Imeglimin 1000 mg bid	42	36	7.09 (0.575)	-0.61 (0.473)	-0.64 (0.134)	[-0.910, -0.374]	-1.01 (0.178)	[-1.361, -0.650]	<.0001
LOCF Endpoint									
Placebo	55	55	8.32 (1.206)	0.31 (0.896)					
Imeglimin 1000 mg bid	42	41	7.13 (0.596)	-0.60 (0.460)					

- Abbreviations: MMRM, Mixed Model Repeated Measures; LOCF, Last Observation Carried Forward; bid, Twice a day; SD, standard deviation; SE, standard error; LS, least square; CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c)
- MMRM model was used with fixed effects for treatment group, visit, study, interaction of treatment-by-visit, and baseline HbA1c as a covariate, assuming an unstructured covariance matrix.

Control No:<<t-e-086-subhb-24wdb.sas, 2020-03-06T00:16:02>>

Table E-087 Subgroup and MMRM Analysis of Change from Baseline in HbA1c (%) to All Visits by eGFR CKD Stage in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Efficacy Population)

CKD		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Stage 1									
Baseline									
Placebo	16	16	8.06 (0.747)						
Imeglimin 1000 mg bid	21	21	8.12 (0.569)						
Week 4									
Placebo	16	16	8.05 (0.819)	-0.01 (0.211)	0.00 (0.072)	[-0.150, 0.143]			
Imeglimin 1000 mg bid	21	21	7.92 (0.602)	-0.20 (0.323)	-0.19 (0.063)	[-0.323, -0.067]	-0.19 (0.096)	[-0.387, 0.004]	0.0544
Week 8									
Placebo	16	16	8.19 (0.822)	0.13 (0.209)	0.13 (0.106)	[-0.081, 0.349]			
Imeglimin 1000 mg bid	21	21	7.79 (0.749)	-0.33 (0.526)	-0.33 (0.092)	[-0.516, -0.140]	-0.46 (0.141)	[-0.748, -0.176]	0.0024
Week 12									
Placebo	16	15	8.12 (0.702)	0.15 (0.239)	0.17 (0.137)	[-0.109, 0.448]			
Imeglimin 1000 mg bid	21	21	7.75 (0.873)	-0.37 (0.689)	-0.37 (0.119)	[-0.613, -0.130]	-0.54 (0.182)	[-0.910, -0.171]	0.0053
Week 16									
Placebo	16	15	8.05 (0.661)	0.09 (0.437)	0.10 (0.132)	[-0.172, 0.369]			
Imeglimin 1000 mg bid	21	20	7.58 (0.724)	-0.55 (0.448)	-0.47 (0.114)	[-0.702, -0.235]	-0.57 (0.175)	[-0.925, -0.210]	0.0030
Week 20									
Placebo	16	15	8.13 (0.662)	0.16 (0.368)	0.17 (0.124)	[-0.086, 0.422]			
Imeglimin 1000 mg bid	21	20	7.50 (0.718)	-0.63 (0.482)	-0.56 (0.107)	[-0.783, -0.345]	-0.73 (0.164)	[-1.068, -0.396]	0.0001
Week 24									
Placebo	16	14	8.00 (0.411)	0.14 (0.318)	0.17 (0.131)	[-0.098, 0.439]			
Imeglimin 1000 mg bid	21	20	7.54 (0.788)	-0.60 (0.538)	-0.53 (0.112)	[-0.756, -0.296]	-0.70 (0.173)	[-1.051, -0.343]	0.0004
LOCF Endpoint									
Placebo	16	16	8.22 (0.716)	0.16 (0.310)					
Imeglimin 1000 mg bid	21	21	7.65 (0.925)	-0.47 (0.772)					
Stage 2									

CKD		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Baseline									
Placebo	136	136	7.93 (0.677)						
Imeglimin 1000 mg bid	130	130	7.91 (0.770)						
Week 4									
Placebo	136	135	7.95 (0.776)	0.05 (0.309)	0.05 (0.024)	[0.001, 0.094]			
Imeglimin 1000 mg bid	130	129	7.67 (0.778)	-0.24 (0.226)	-0.24 (0.024)	[-0.289, -0.194]	-0.29 (0.033)	[-0.355, -0.223]	<.0001
Week 8									
Placebo	136	134	7.99 (0.859)	0.09 (0.446)	0.10 (0.036)	[0.030, 0.172]			
Imeglimin 1000 mg bid	130	126	7.43 (0.718)	-0.47 (0.361)	-0.46 (0.037)	[-0.536, -0.391]	-0.56 (0.052)	[-0.666, -0.463]	<.0001
Week 12									
Placebo	136	129	7.96 (0.829)	0.12 (0.565)	0.16 (0.046)	[0.069, 0.252]			
Imeglimin 1000 mg bid	130	124	7.30 (0.721)	-0.59 (0.444)	-0.58 (0.048)	[-0.679, -0.491]	-0.75 (0.066)	[-0.876, -0.614]	<.0001
Week 16									
Placebo	136	124	7.92 (0.813)	0.10 (0.607)	0.19 (0.053)	[0.082, 0.291]			
Imeglimin 1000 mg bid	130	122	7.23 (0.798)	-0.67 (0.495)	-0.67 (0.054)	[-0.776, -0.562]	-0.86 (0.076)	[-1.005, -0.706]	<.0001
Week 20									
Placebo	136	123	7.94 (0.855)	0.12 (0.673)	0.23 (0.060)	[0.113, 0.352]			
Imeglimin 1000 mg bid	130	120	7.19 (0.805)	-0.70 (0.555)	-0.69 (0.062)	[-0.812, -0.569]	-0.92 (0.086)	[-1.093, -0.753]	<.0001
Week 24									
Placebo	136	122	7.98 (0.927)	0.17 (0.775)	0.30 (0.067)	[0.162, 0.428]			
Imeglimin 1000 mg bid	130	116	7.19 (0.735)	-0.69 (0.571)	-0.67 (0.069)	[-0.803, -0.532]	-0.96 (0.096)	[-1.152, -0.773]	<.0001
LOCF Endpoint									
Placebo	136	136	8.20 (1.138)	0.27 (0.838)					
Imeglimin 1000 mg bid	130	129	7.26 (0.821)	-0.66 (0.576)					
Stage 3a									
Baseline									
Placebo	29	29	7.78 (0.648)						
Imeglimin 1000 mg bid	28	28	7.90 (0.570)						
Week 4									

CKD		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Placebo	29	29	7.85 (0.776)	0.07 (0.281)	0.08 (0.055)	[-0.028, 0.193]			
Imeglimin 1000 mg bid	28	28	7.59 (0.580)	-0.31 (0.302)	-0.30 (0.059)	[-0.417, -0.180]	-0.38 (0.078)	[-0.538, -0.223]	<.0001
Week 8									
Placebo	29	29	7.90 (0.895)	0.12 (0.467)	0.13 (0.086)	[-0.038, 0.306]			
Imeglimin 1000 mg bid	28	28	7.43 (0.609)	-0.47 (0.455)	-0.46 (0.089)	[-0.638, -0.281]	-0.59 (0.122)	[-0.838, -0.348]	<.0001
Week 12									
Placebo	29	27	7.86 (0.783)	0.10 (0.475)	0.15 (0.098)	[-0.047, 0.348]			
Imeglimin 1000 mg bid	28	28	7.33 (0.571)	-0.57 (0.530)	-0.56 (0.101)	[-0.761, -0.357]	-0.71 (0.139)	[-0.990, -0.430]	<.0001
Week 16									
Placebo	29	26	7.72 (0.723)	-0.02 (0.436)	0.10 (0.112)	[-0.128, 0.324]			
Imeglimin 1000 mg bid	28	28	7.23 (0.638)	-0.67 (0.591)	-0.66 (0.113)	[-0.884, -0.427]	-0.75 (0.158)	[-1.072, -0.435]	<.0001
Week 20									
Placebo	29	26	7.68 (0.671)	-0.07 (0.434)	0.04 (0.114)	[-0.185, 0.274]			
Imeglimin 1000 mg bid	28	28	7.22 (0.696)	-0.68 (0.622)	-0.67 (0.114)	[-0.897, -0.436]	-0.71 (0.160)	[-1.034, -0.388]	<.0001
Week 24									
Placebo	29	25	7.64 (0.553)	-0.03 (0.467)	0.09 (0.122)	[-0.152, 0.338]			
Imeglimin 1000 mg bid	28	28	7.32 (0.735)	-0.58 (0.672)	-0.57 (0.121)	[-0.810, -0.322]	-0.66 (0.171)	[-1.002, -0.315]	0.0004
LOCF Endpoint									
Placebo	29	29	7.87 (0.956)	0.09 (0.608)					
Imeglimin 1000 mg bid	28	28	7.32 (0.735)	-0.58 (0.672)					

- Abbreviations: MMRM, Mixed Model Repeated Measures; LOCF, Last Observation Carried Forward; bid, Twice a day; SD, standard deviation; SE, standard error; LS, least square; CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2, CKD Stage 3a includes subjects with eGFR >= 45 to < 60 mL/min/1.73m2.
- MMRM model was used with fixed effects for treatment group, visit, study, interaction of treatment-by-visit, and baseline HbA1c as a covariate, assuming an unstructured covariance matrix.

Control No:<<t-e-087-subhb-24wdb.sas, 2020-03-06T00:16:04>>

Table E-088 Subgroup and MMRM Analysis of Change from Baseline in HbA1c (%) to All Visits by Hepatic Parameter Abnormality in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Efficacy Population)

Hepatic Parameter Abnormality		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Yes									
Baseline									
Placebo	31	31	7.96 (0.839)						
Imeglimin 1000 mg bid	24	24	8.05 (0.840)						
Week 4									
Placebo	31	31	7.99 (1.000)	0.03 (0.291)	0.03 (0.044)	[-0.062, 0.115]			
Imeglimin 1000 mg bid	24	24	7.84 (0.875)	-0.21 (0.191)	-0.23 (0.050)	[-0.327, -0.125]	-0.25 (0.067)	[-0.387, -0.118]	0.0004
Week 8									
Placebo	31	31	8.00 (1.159)	0.04 (0.491)	0.03 (0.075)	[-0.118, 0.183]			
Imeglimin 1000 mg bid	24	23	7.56 (0.802)	-0.44 (0.320)	-0.44 (0.086)	[-0.609, -0.262]	-0.47 (0.114)	[-0.698, -0.239]	0.0001
Week 12									
Placebo	31	29	7.90 (0.894)	0.06 (0.531)	0.16 (0.100)	[-0.040, 0.365]			
Imeglimin 1000 mg bid	24	23	7.46 (0.811)	-0.54 (0.351)	-0.54 (0.115)	[-0.768, -0.303]	-0.70 (0.153)	[-1.007, -0.390]	<.0001
Week 16									
Placebo	31	27	7.77 (0.961)	-0.02 (0.670)	0.15 (0.117)	[-0.088, 0.382]			
Imeglimin 1000 mg bid	24	23	7.41 (0.888)	-0.59 (0.355)	-0.59 (0.132)	[-0.852, -0.319]	-0.73 (0.176)	[-1.088, -0.377]	0.0002
Week 20									
Placebo	31	27	7.74 (1.002)	-0.05 (0.741)	0.12 (0.132)	[-0.149, 0.384]			
Imeglimin 1000 mg bid	24	23	7.37 (0.846)	-0.63 (0.455)	-0.63 (0.148)	[-0.926, -0.327]	-0.74 (0.199)	[-1.145, -0.343]	0.0006
Week 24									
Placebo	31	26	7.70 (1.076)	-0.02 (0.893)	0.15 (0.146)	[-0.147, 0.443]			
Imeglimin 1000 mg bid	24	23	7.43 (0.853)	-0.57 (0.438)	-0.57 (0.162)	[-0.893, -0.237]	-0.71 (0.219)	[-1.155, -0.272]	0.0022
LOCF Endpoint									
Placebo	31	31	8.10 (1.430)	0.14 (0.915)					
Imeglimin 1000 mg bid	24	24	7.51 (0.935)	-0.54 (0.457)					
No									

Hepatic Parameter Abnormality		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Baseline									
Placebo	150	150	7.90 (0.644)						
Imeglimin 1000 mg bid	155	155	7.91 (0.702)						
Week 4									
Placebo	150	149	7.94 (0.726)	0.05 (0.299)	0.05 (0.027)	[0.001, 0.107]			
Imeglimin 1000 mg bid	155	154	7.66 (0.709)	-0.25 (0.260)	-0.25 (0.027)	[-0.299, -0.195]	-0.30 (0.037)	[-0.374, -0.227]	<.0001
Week 8									
Placebo	150	148	7.99 (0.788)	0.11 (0.420)	0.13 (0.039)	[0.051, 0.203]			
Imeglimin 1000 mg bid	155	152	7.46 (0.698)	-0.45 (0.411)	-0.45 (0.038)	[-0.522, -0.372]	-0.57 (0.054)	[-0.680, -0.468]	<.0001
Week 12									
Placebo	150	142	7.97 (0.794)	0.13 (0.529)	0.16 (0.044)	[0.073, 0.245]			
Imeglimin 1000 mg bid	155	150	7.35 (0.718)	-0.57 (0.514)	-0.56 (0.043)	[-0.643, -0.473]	-0.72 (0.061)	[-0.837, -0.596]	<.0001
Week 16									
Placebo	150	138	7.93 (0.750)	0.10 (0.547)	0.16 (0.045)	[0.074, 0.251]			
Imeglimin 1000 mg bid	155	147	7.25 (0.751)	-0.67 (0.525)	-0.65 (0.044)	[-0.737, -0.563]	-0.81 (0.063)	[-0.936, -0.689]	<.0001
Week 20									
Placebo	150	137	7.95 (0.775)	0.12 (0.593)	0.20 (0.047)	[0.103, 0.288]			
Imeglimin 1000 mg bid	155	145	7.21 (0.770)	-0.70 (0.571)	-0.68 (0.046)	[-0.766, -0.585]	-0.87 (0.066)	[-1.001, -0.743]	<.0001
Week 24									
Placebo	150	135	7.97 (0.798)	0.16 (0.666)	0.24 (0.051)	[0.142, 0.344]			
Imeglimin 1000 mg bid	155	141	7.23 (0.726)	-0.68 (0.605)	-0.64 (0.050)	[-0.743, -0.545]	-0.89 (0.072)	[-1.028, -0.746]	<.0001
LOCF Endpoint									
Placebo	150	150	8.16 (1.001)	0.25 (0.741)					
Imeglimin 1000 mg bid	155	154	7.28 (0.806)	-0.64 (0.638)					

- Abbreviations: MMRM, Mixed Model Repeated Measures; LOCF, Last Observation Carried Forward; bid, Twice a day; SD, standard deviation; SE, standard error; LS, least square; CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c)
- Hepatic parameter abnormality is defined as any one of following parameter applied: Total Bilirubin >= 1.6 mg/dL; Aspartate aminotransferase (AST) >= 1.25 x Upper Limit of Normal (ULN); AST >= 50 IU; Alanine aminotransferase (ALT) >= 1.25 x ULN; ALT >= 50 IU; Alkaline phosphatase >= 1.25 x ULN; Gamma glutamyl transferase >= 1.5 x ULN.
- MMRM model was used with fixed effects for treatment group, visit, study, interaction of treatment-by-visit, and baseline HbA1c as a covariate, assuming an unstructured covariance matrix.

Table E-089 Subgroup and MMRM Analysis of Change from Baseline in HbA1c (%) to All Visits by BMI in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Efficacy Population)

BMI at baseline		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
< 25 kg/m2									
Baseline									
Placebo	94	94	7.97 (0.744)						
Imeglimin 1000 mg bid	90	90	7.78 (0.638)						
Week 4									
Placebo	94	93	7.99 (0.843)	0.04 (0.289)	0.06 (0.047)	[-0.030, 0.156]			
Imeglimin 1000 mg bid	90	90	7.51 (0.627)	-0.27 (0.250)	-0.27 (0.048)	[-0.360, -0.173]	-0.33 (0.067)	[-0.461, -0.198]	<.0001
Week 8									
Placebo	94	92	8.04 (0.924)	0.10 (0.419)	0.14 (0.047)	[0.044, 0.230]			
Imeglimin 1000 mg bid	90	90	7.31 (0.617)	-0.47 (0.410)	-0.47 (0.048)	[-0.559, -0.372]	-0.60 (0.067)	[-0.734, -0.471]	<.0001
Week 12									
Placebo	94	86	7.96 (0.804)	0.08 (0.432)	0.14 (0.048)	[0.050, 0.238]			
Imeglimin 1000 mg bid	90	90	7.18 (0.606)	-0.60 (0.490)	-0.60 (0.048)	[-0.690, -0.503]	-0.74 (0.067)	[-0.873, -0.608]	<.0001
Week 16									
Placebo	94	84	7.91 (0.792)	0.05 (0.478)	0.13 (0.048)	[0.030, 0.220]			
Imeglimin 1000 mg bid	90	89	7.06 (0.622)	-0.72 (0.487)	-0.72 (0.048)	[-0.810, -0.622]	-0.84 (0.068)	[-0.974, -0.708]	<.0001
Week 20									
Placebo	94	84	7.97 (0.789)	0.12 (0.525)	0.18 (0.049)	[0.082, 0.274]			
Imeglimin 1000 mg bid	90	89	7.04 (0.587)	-0.74 (0.505)	-0.73 (0.048)	[-0.827, -0.639]	-0.91 (0.068)	[-1.045, -0.777]	<.0001
Week 24									
Placebo	94	81	7.95 (0.715)	0.14 (0.580)	0.22 (0.049)	[0.122, 0.316]			
Imeglimin 1000 mg bid	90	87	7.10 (0.615)	-0.69 (0.545)	-0.68 (0.048)	[-0.777, -0.588]	-0.90 (0.068)	[-1.037, -0.767]	<.0001
LOCF Endpoint									
Placebo	94	94	8.20 (1.041)	0.23 (0.639)					
Imeglimin 1000 mg bid	90	90	7.09 (0.609)	-0.69 (0.536)					
>= 25 kg/m2									

BMI at baseline		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Baseline									
Placebo	87	87	7.85 (0.598)						
Imeglimin 1000 mg bid	89	89	8.09 (0.769)						
Week 4									
Placebo	87	87	7.90 (0.702)	0.05 (0.306)	0.05 (0.030)	[-0.006, 0.114]			
Imeglimin 1000 mg bid	89	88	7.88 (0.789)	-0.22 (0.253)	-0.22 (0.031)	[-0.280, -0.159]	-0.27 (0.043)	[-0.359, -0.188]	<.0001
Week 8									
Placebo	87	87	7.94 (0.788)	0.09 (0.449)	0.10 (0.046)	[0.006, 0.186]			
Imeglimin 1000 mg bid	89	85	7.65 (0.764)	-0.43 (0.390)	-0.42 (0.046)	[-0.515, -0.333]	-0.52 (0.065)	[-0.648, -0.392]	<.0001
Week 12									
Placebo	87	85	7.97 (0.820)	0.15 (0.612)	0.18 (0.062)	[0.060, 0.304]			
Imeglimin 1000 mg bid	89	83	7.56 (0.799)	-0.52 (0.500)	-0.51 (0.062)	[-0.631, -0.385]	-0.69 (0.088)	[-0.863, -0.516]	<.0001
Week 16									
Placebo	87	81	7.89 (0.787)	0.11 (0.651)	0.21 (0.073)	[0.064, 0.353]			
Imeglimin 1000 mg bid	89	81	7.50 (0.852)	-0.59 (0.518)	-0.55 (0.074)	[-0.700, -0.409]	-0.76 (0.104)	[-0.968, -0.558]	<.0001
Week 20									
Placebo	87	80	7.86 (0.846)	0.08 (0.710)	0.21 (0.083)	[0.045, 0.375]			
Imeglimin 1000 mg bid	89	79	7.45 (0.909)	-0.63 (0.607)	-0.59 (0.084)	[-0.755, -0.423]	-0.80 (0.118)	[-1.033, -0.565]	<.0001
Week 24									
Placebo	87	80	7.91 (0.974)	0.13 (0.820)	0.27 (0.092)	[0.084, 0.447]			
Imeglimin 1000 mg bid	89	77	7.43 (0.839)	-0.63 (0.628)	-0.56 (0.093)	[-0.747, -0.381]	-0.83 (0.131)	[-1.088, -0.571]	<.0001
LOCF Endpoint									
Placebo	87	87	8.08 (1.127)	0.24 (0.898)					
Imeglimin 1000 mg bid	89	88	7.54 (0.950)	-0.55 (0.685)					
>= 25 to < 30 kg/m2									
Baseline									
Placebo	64	64	7.83 (0.599)						
Imeglimin 1000 mg bid	65	65	8.07 (0.801)						
Week 4									

BMI at baseline		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Placebo	64	64	7.88 (0.686)	0.06 (0.316)	0.06 (0.037)	[-0.013, 0.133]			
Imeglimin 1000 mg bid	65	65	7.82 (0.823)	-0.25 (0.257)	-0.24 (0.037)	[-0.316, -0.171]	-0.30 (0.052)	[-0.406, -0.201]	<.0001
Week 8									
Placebo	64	64	7.93 (0.767)	0.10 (0.452)	0.11 (0.051)	[0.003, 0.207]			
Imeglimin 1000 mg bid	65	63	7.57 (0.779)	-0.47 (0.349)	-0.47 (0.052)	[-0.571, -0.367]	-0.57 (0.073)	[-0.718, -0.430]	<.0001
Week 12									
Placebo	64	63	7.97 (0.796)	0.16 (0.584)	0.19 (0.066)	[0.055, 0.317]			
Imeglimin 1000 mg bid	65	61	7.48 (0.785)	-0.58 (0.426)	-0.56 (0.067)	[-0.695, -0.432]	-0.75 (0.094)	[-0.935, -0.564]	<.0001
Week 16									
Placebo	64	60	7.89 (0.742)	0.11 (0.576)	0.20 (0.078)	[0.047, 0.355]			
Imeglimin 1000 mg bid	65	60	7.47 (0.889)	-0.59 (0.494)	-0.58 (0.078)	[-0.740, -0.429]	-0.79 (0.110)	[-1.004, -0.567]	<.0001
Week 20									
Placebo	64	60	7.89 (0.826)	0.10 (0.679)	0.20 (0.090)	[0.025, 0.383]			
Imeglimin 1000 mg bid	65	59	7.40 (0.943)	-0.64 (0.592)	-0.62 (0.091)	[-0.804, -0.445]	-0.83 (0.128)	[-1.082, -0.575]	<.0001
Week 24									
Placebo	64	60	7.94 (0.954)	0.16 (0.790)	0.26 (0.100)	[0.060, 0.456]			
Imeglimin 1000 mg bid	65	57	7.36 (0.849)	-0.65 (0.597)	-0.61 (0.100)	[-0.806, -0.408]	-0.87 (0.141)	[-1.146, -0.585]	<.0001
LOCF Endpoint									
Placebo	64	64	8.07 (1.071)	0.24 (0.860)					
Imeglimin 1000 mg bid	65	65	7.47 (0.960)	-0.60 (0.611)					
>= 30 kg/m2									
Baseline									
Placebo	23	23	7.91 (0.605)						
Imeglimin 1000 mg bid	24	24	8.15 (0.685)						
Week 4									
Placebo	23	23	7.94 (0.758)	0.03 (0.284)	0.03 (0.073)	[-0.120, 0.177]			
Imeglimin 1000 mg bid	24	23	8.03 (0.677)	-0.15 (0.231)	-0.15 (0.074)	[-0.296, 0.005]	-0.17 (0.106)	[-0.389, 0.040]	0.1086
Week 8									
Placebo	23	23	7.98 (0.862)	0.07 (0.447)	0.06 (0.118)	[-0.174, 0.300]			

BMI at baseline		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Imeglimin 1000 mg bid	24	22	7.86 (0.695)	-0.30 (0.478)	-0.29 (0.118)	[-0.529, -0.052]	-0.35 (0.168)	[-0.692, -0.015]	0.0408
Week 12									
Placebo	23	22	7.96 (0.905)	0.12 (0.702)	0.16 (0.145)	[-0.131, 0.452]			
Imeglimin 1000 mg bid	24	22	7.80 (0.807)	-0.36 (0.648)	-0.34 (0.146)	[-0.638, -0.051]	-0.50 (0.206)	[-0.920, -0.090]	0.0182
Week 16									
Placebo	23	21	7.91 (0.925)	0.12 (0.846)	0.21 (0.152)	[-0.096, 0.515]			
Imeglimin 1000 mg bid	24	21	7.60 (0.746)	-0.58 (0.595)	-0.47 (0.153)	[-0.778, -0.163]	-0.68 (0.217)	[-1.115, -0.244]	0.0029
Week 20									
Placebo	23	20	7.77 (0.918)	-0.01 (0.806)	0.18 (0.159)	[-0.140, 0.499]			
Imeglimin 1000 mg bid	24	20	7.61 (0.802)	-0.61 (0.662)	-0.51 (0.160)	[-0.826, -0.184]	-0.68 (0.227)	[-1.139, -0.230]	0.0039
Week 24									
Placebo	23	20	7.82 (1.054)	0.04 (0.921)	0.20 (0.168)	[-0.135, 0.538]			
Imeglimin 1000 mg bid	24	20	7.65 (0.793)	-0.57 (0.723)	-0.47 (0.169)	[-0.810, -0.134]	-0.67 (0.239)	[-1.152, -0.195]	0.0066
LOCF Endpoint									
Placebo	23	23	8.13 (1.295)	0.23 (1.017)					
Imeglimin 1000 mg bid	24	23	7.76 (0.906)	-0.43 (0.864)					

- Abbreviations: MMRM, Mixed Model Repeated Measures; LOCF, Last Observation Carried Forward; bid, Twice a day; SD, standard deviation; SE, standard error; LS, least square; CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); BMI, Body Mass Index
- MMRM model was used with fixed effects for treatment group, visit, study, interaction of treatment-by-visit, and baseline HbA1c as a covariate, assuming an unstructured covariance matrix.

Control No:<<t-e-089-subhb-24wdb.sas, 2020-03-06T00:16:35>>

Table E-090 Subgroup and MMRM Analysis of Change from Baseline in HbA1c (%) to All Visits by HOMA-IR at Baseline in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Efficacy Population)

HOMA-IR at baseline		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
< 2.5									
Baseline									
Placebo	91	91	7.85 (0.622)						
Imeglimin 1000 mg bid	101	101	7.71 (0.640)						
Week 4									
Placebo	91	91	7.88 (0.676)	0.02 (0.230)	0.04 (0.026)	[-0.015, 0.086]			
Imeglimin 1000 mg bid	101	101	7.48 (0.664)	-0.23 (0.238)	-0.22 (0.024)	[-0.266, -0.171]	-0.25 (0.034)	[-0.321, -0.186]	<.0001
Week 8									
Placebo	91	91	7.93 (0.779)	0.08 (0.376)	0.09 (0.042)	[0.008, 0.174]			
Imeglimin 1000 mg bid	101	101	7.30 (0.671)	-0.41 (0.412)	-0.40 (0.040)	[-0.479, -0.322]	-0.49 (0.057)	[-0.604, -0.379]	<.0001
Week 12									
Placebo	91	88	7.93 (0.799)	0.08 (0.441)	0.10 (0.049)	[0.002, 0.197]			
Imeglimin 1000 mg bid	101	100	7.20 (0.648)	-0.52 (0.489)	-0.50 (0.047)	[-0.593, -0.409]	-0.60 (0.067)	[-0.733, -0.467]	<.0001
Week 16									
Placebo	91	85	7.83 (0.729)	0.02 (0.475)	0.07 (0.054)	[-0.037, 0.175]			
Imeglimin 1000 mg bid	101	99	7.11 (0.706)	-0.60 (0.499)	-0.59 (0.050)	[-0.687, -0.489]	-0.66 (0.073)	[-0.801, -0.513]	<.0001
Week 20									
Placebo	91	85	7.88 (0.770)	0.07 (0.556)	0.12 (0.059)	[0.003, 0.237]			
Imeglimin 1000 mg bid	101	98	7.08 (0.667)	-0.62 (0.531)	-0.60 (0.056)	[-0.713, -0.493]	-0.72 (0.081)	[-0.883, -0.564]	<.0001
Week 24									
Placebo	91	83	7.90 (0.726)	0.11 (0.617)	0.19 (0.067)	[0.055, 0.317]			
Imeglimin 1000 mg bid	101	95	7.13 (0.704)	-0.57 (0.588)	-0.56 (0.062)	[-0.682, -0.435]	-0.74 (0.091)	[-0.924, -0.565]	<.0001
LOCF Endpoint									
Placebo	91	91	8.02 (0.858)	0.16 (0.643)					
Imeglimin 1000 mg bid	101	101	7.14 (0.712)	-0.57 (0.575)					
>= 2.5 to < 4.0									

HOMA-IR at baseline		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Baseline									
Placebo	47	47	7.87 (0.715)						
Imeglimin 1000 mg bid	36	36	8.12 (0.736)						
Week 4									
Placebo	47	47	7.89 (0.869)	0.02 (0.357)	0.02 (0.049)	[-0.076, 0.117]			
Imeglimin 1000 mg bid	36	35	7.81 (0.701)	-0.33 (0.273)	-0.34 (0.056)	[-0.448, -0.224]	-0.36 (0.075)	[-0.505, -0.207]	<.0001
Week 8									
Placebo	47	47	7.95 (0.981)	0.09 (0.472)	0.09 (0.062)	[-0.037, 0.210]			
Imeglimin 1000 mg bid	36	35	7.55 (0.616)	-0.59 (0.334)	-0.59 (0.072)	[-0.731, -0.444]	-0.67 (0.095)	[-0.864, -0.484]	<.0001
Week 12									
Placebo	47	44	7.82 (0.649)	0.07 (0.444)	0.15 (0.075)	[0.001, 0.300]			
Imeglimin 1000 mg bid	36	34	7.42 (0.657)	-0.73 (0.420)	-0.72 (0.087)	[-0.892, -0.546]	-0.87 (0.115)	[-1.099, -0.641]	<.0001
Week 16									
Placebo	47	43	7.82 (0.683)	0.07 (0.527)	0.16 (0.084)	[-0.009, 0.328]			
Imeglimin 1000 mg bid	36	33	7.39 (0.723)	-0.78 (0.471)	-0.78 (0.097)	[-0.970, -0.581]	-0.94 (0.129)	[-1.193, -0.678]	<.0001
Week 20									
Placebo	47	43	7.82 (0.708)	0.07 (0.579)	0.16 (0.092)	[-0.022, 0.346]			
Imeglimin 1000 mg bid	36	33	7.31 (0.824)	-0.86 (0.528)	-0.86 (0.106)	[-1.067, -0.644]	-1.02 (0.140)	[-1.298, -0.737]	<.0001
Week 24									
Placebo	47	43	7.86 (0.758)	0.11 (0.604)	0.21 (0.096)	[0.016, 0.398]			
Imeglimin 1000 mg bid	36	33	7.34 (0.797)	-0.82 (0.549)	-0.82 (0.110)	[-1.043, -0.603]	-1.03 (0.146)	[-1.322, -0.738]	<.0001
LOCF Endpoint									
Placebo	47	47	8.06 (1.042)	0.19 (0.660)					
Imeglimin 1000 mg bid	36	35	7.33 (0.782)	-0.81 (0.540)					
>= 4.0									
Baseline									
Placebo	42	42	8.07 (0.728)						
Imeglimin 1000 mg bid	42	42	8.30 (0.715)						
Week 4									

HOMA-IR at baseline		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Placebo	42	41	8.13 (0.834)	0.11 (0.344)	0.12 (0.048)	[0.029, 0.221]			
Imeglimin 1000 mg bid	42	42	8.08 (0.753)	-0.22 (0.257)	-0.23 (0.048)	[-0.324, -0.134]	-0.35 (0.068)	[-0.489, -0.218]	<.0001
Week 8									
Placebo	42	40	8.14 (0.863)	0.15 (0.508)	0.19 (0.077)	[0.040, 0.348]			
Imeglimin 1000 mg bid	42	39	7.84 (0.755)	-0.43 (0.405)	-0.44 (0.077)	[-0.590, -0.282]	-0.63 (0.109)	[-0.848, -0.413]	<.0001
Week 12									
Placebo	42	39	8.20 (0.954)	0.25 (0.747)	0.33 (0.109)	[0.111, 0.544]			
Imeglimin 1000 mg bid	42	39	7.73 (0.849)	-0.54 (0.551)	-0.54 (0.109)	[-0.760, -0.326]	-0.87 (0.154)	[-1.177, -0.564]	<.0001
Week 16									
Placebo	42	37	8.16 (0.975)	0.23 (0.768)	0.42 (0.132)	[0.158, 0.685]			
Imeglimin 1000 mg bid	42	38	7.58 (0.872)	-0.70 (0.538)	-0.65 (0.132)	[-0.909, -0.381]	-1.07 (0.187)	[-1.440, -0.694]	<.0001
Week 20									
Placebo	42	36	8.10 (1.016)	0.18 (0.799)	0.44 (0.147)	[0.146, 0.733]			
Imeglimin 1000 mg bid	42	37	7.58 (0.908)	-0.72 (0.621)	-0.65 (0.146)	[-0.944, -0.358]	-1.09 (0.207)	[-1.505, -0.677]	<.0001
Week 24									
Placebo	42	35	8.09 (1.182)	0.21 (0.988)	0.46 (0.160)	[0.144, 0.785]			
Imeglimin 1000 mg bid	42	36	7.51 (0.745)	-0.75 (0.576)	-0.63 (0.159)	[-0.947, -0.308]	-1.09 (0.225)	[-1.544, -0.640]	<.0001
LOCF Endpoint									
Placebo	42	42	8.50 (1.444)	0.43 (1.082)					
Imeglimin 1000 mg bid	42	42	7.71 (0.985)	-0.59 (0.745)					

- Abbreviations: MMRM, Mixed Model Repeated Measures; LOCF, Last Observation Carried Forward; bid, Twice a day; SD, standard deviation; SE, standard error; LS, least square; CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); HOMA, Homeostasis model assessment; HOMA-IR, HOMA of insulin resistance
- MMRM model was used with fixed effects for treatment group, visit, study, interaction of treatment-by-visit, and baseline HbA1c as a covariate, assuming an unstructured covariance matrix.

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Table E-091 Subgroup and MMRM Analysis of Change from Baseline in HbA1c (%) to All Visits by HOMA-B at Baseline in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Efficacy Population)

HOMA-B at baseline		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
< 30.0%									
Baseline									
Placebo	112	112	8.04 (0.723)						
Imeglimin 1000 mg bid	133	133	7.96 (0.743)						
Week 4									
Placebo	112	111	8.08 (0.825)	0.05 (0.318)	0.06 (0.029)	[0.007, 0.120]			
Imeglimin 1000 mg bid	133	133	7.72 (0.750)	-0.25 (0.265)	-0.24 (0.026)	[-0.288, -0.186]	-0.30 (0.037)	[-0.374, -0.226]	<.0001
Week 8									
Placebo	112	110	8.13 (0.898)	0.11 (0.441)	0.14 (0.043)	[0.053, 0.222]			
Imeglimin 1000 mg bid	133	132	7.49 (0.720)	-0.46 (0.429)	-0.44 (0.039)	[-0.521, -0.368]	-0.58 (0.057)	[-0.695, -0.470]	<.0001
Week 12									
Placebo	112	105	8.05 (0.821)	0.10 (0.491)	0.16 (0.053)	[0.055, 0.264]			
Imeglimin 1000 mg bid	133	130	7.38 (0.731)	-0.57 (0.540)	-0.55 (0.048)	[-0.648, -0.460]	-0.71 (0.071)	[-0.853, -0.574]	<.0001
Week 16									
Placebo	112	102	7.97 (0.811)	0.04 (0.562)	0.12 (0.058)	[0.007, 0.235]			
Imeglimin 1000 mg bid	133	128	7.28 (0.780)	-0.68 (0.536)	-0.65 (0.052)	[-0.750, -0.545]	-0.77 (0.077)	[-0.920, -0.616]	<.0001
Week 20									
Placebo	112	101	7.99 (0.823)	0.07 (0.602)	0.18 (0.065)	[0.049, 0.303]			
Imeglimin 1000 mg bid	133	127	7.24 (0.798)	-0.70 (0.590)	-0.67 (0.058)	[-0.781, -0.551]	-0.84 (0.086)	[-1.012, -0.672]	<.0001
Week 24									
Placebo	112	98	7.99 (0.794)	0.11 (0.663)	0.24 (0.070)	[0.106, 0.382]			
Imeglimin 1000 mg bid	133	123	7.26 (0.742)	-0.68 (0.614)	-0.63 (0.063)	[-0.753, -0.505]	-0.87 (0.094)	[-1.057, -0.688]	<.0001
LOCF Endpoint									
Placebo	112	112	8.26 (1.081)	0.22 (0.740)					
Imeglimin 1000 mg bid	133	133	7.33 (0.848)	-0.63 (0.659)					
>= 30.0%									

HOMA-B at baseline		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Baseline									
Placebo	68	68	7.68 (0.517)						
Imeglimin 1000 mg bid	46	46	7.85 (0.655)						
Week 4									
Placebo	68	68	7.71 (0.614)	0.03 (0.258)	0.03 (0.030)	[-0.029, 0.089]			
Imeglimin 1000 mg bid	46	45	7.61 (0.684)	-0.25 (0.211)	-0.26 (0.036)	[-0.328, -0.184]	-0.29 (0.047)	[-0.379, -0.193]	<.0001
Week 8									
Placebo	68	68	7.75 (0.727)	0.07 (0.422)	0.07 (0.046)	[-0.022, 0.162]			
Imeglimin 1000 mg bid	46	43	7.41 (0.686)	-0.43 (0.295)	-0.44 (0.058)	[-0.552, -0.324]	-0.51 (0.074)	[-0.655, -0.362]	<.0001
Week 12									
Placebo	68	66	7.82 (0.775)	0.15 (0.587)	0.17 (0.062)	[0.044, 0.289]			
Imeglimin 1000 mg bid	46	43	7.30 (0.729)	-0.53 (0.328)	-0.54 (0.077)	[-0.696, -0.390]	-0.71 (0.099)	[-0.906, -0.514]	<.0001
Week 16									
Placebo	68	63	7.80 (0.741)	0.15 (0.578)	0.24 (0.075)	[0.095, 0.391]			
Imeglimin 1000 mg bid	46	42	7.25 (0.748)	-0.59 (0.394)	-0.61 (0.093)	[-0.793, -0.425]	-0.85 (0.119)	[-1.088, -0.616]	<.0001
Week 20									
Placebo	68	63	7.79 (0.797)	0.14 (0.650)	0.23 (0.081)	[0.072, 0.394]			
Imeglimin 1000 mg bid	46	41	7.21 (0.733)	-0.64 (0.435)	-0.66 (0.101)	[-0.858, -0.458]	-0.89 (0.129)	[-1.148, -0.634]	<.0001
Week 24									
Placebo	68	63	7.82 (0.931)	0.18 (0.775)	0.26 (0.092)	[0.079, 0.444]			
Imeglimin 1000 mg bid	46	41	7.25 (0.765)	-0.60 (0.486)	-0.62 (0.114)	[-0.845, -0.391]	-0.88 (0.147)	[-1.171, -0.588]	<.0001
LOCF Endpoint									
Placebo	68	68	7.93 (1.054)	0.25 (0.833)					
Imeglimin 1000 mg bid	46	45	7.26 (0.763)	-0.60 (0.476)					

- Abbreviations: MMRM, Mixed Model Repeated Measures; LOCF, Last Observation Carried Forward; bid, Twice a day; SD, standard deviation; SE, standard error; LS, least square; CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); HOMA, Homeostasis model assessment; HOMA-B, HOMA of beta-cell function
- MMRM model was used with fixed effects for treatment group, visit, study, interaction of treatment-by-visit, and baseline HbA1c as a covariate, assuming an unstructured covariance matrix.

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Table E-092 Subgroup and MMRM Analysis of Change from Baseline in HbA1c (%) to All Visits by QUICKI at Baseline in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Efficacy Population)

QUICKI at baseline		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
< 0.33									
Baseline									
Placebo	81	81	7.99 (0.731)						
Imeglimin 1000 mg bid	69	69	8.24 (0.701)						
Week 4									
Placebo	81	80	8.04 (0.869)	0.08 (0.359)	0.08 (0.036)	[0.013, 0.154]			
Imeglimin 1000 mg bid	69	68	7.99 (0.720)	-0.25 (0.263)	-0.27 (0.039)	[-0.345, -0.190]	-0.35 (0.053)	[-0.457, -0.245]	<.0001
Week 8									
Placebo	81	79	8.08 (0.940)	0.13 (0.491)	0.15 (0.051)	[0.053, 0.254]			
Imeglimin 1000 mg bid	69	65	7.74 (0.694)	-0.49 (0.369)	-0.49 (0.056)	[-0.606, -0.384]	-0.65 (0.076)	[-0.798, -0.499]	<.0001
Week 12									
Placebo	81	75	8.02 (0.826)	0.16 (0.613)	0.25 (0.069)	[0.110, 0.383]			
Imeglimin 1000 mg bid	69	64	7.64 (0.764)	-0.59 (0.496)	-0.60 (0.076)	[-0.750, -0.450]	-0.85 (0.103)	[-1.050, -0.644]	<.0001
Week 16									
Placebo	81	72	7.99 (0.852)	0.15 (0.658)	0.30 (0.082)	[0.138, 0.464]			
Imeglimin 1000 mg bid	69	62	7.52 (0.777)	-0.73 (0.494)	-0.70 (0.090)	[-0.879, -0.522]	-1.00 (0.122)	[-1.243, -0.759]	<.0001
Week 20									
Placebo	81	71	7.96 (0.872)	0.12 (0.691)	0.31 (0.091)	[0.126, 0.486]			
Imeglimin 1000 mg bid	69	61	7.49 (0.825)	-0.77 (0.567)	-0.74 (0.099)	[-0.937, -0.544]	-1.05 (0.134)	[-1.313, -0.780]	<.0001
Week 24									
Placebo	81	70	7.97 (0.986)	0.15 (0.813)	0.34 (0.098)	[0.144, 0.534]			
Imeglimin 1000 mg bid	69	60	7.47 (0.719)	-0.77 (0.548)	-0.70 (0.107)	[-0.914, -0.489]	-1.04 (0.145)	[-1.329, -0.752]	<.0001
LOCF Endpoint									
Placebo	81	81	8.30 (1.289)	0.31 (0.909)					
Imeglimin 1000 mg bid	69	68	7.58 (0.888)	-0.66 (0.666)					
>= 0.33									

QUICKI at baseline		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Baseline									
Placebo	99	99	7.84 (0.621)						
Imeglimin 1000 mg bid	110	110	7.74 (0.670)						
Week 4									
Placebo	99	99	7.85 (0.673)	0.01 (0.233)	0.03 (0.025)	[-0.023, 0.075]			
Imeglimin 1000 mg bid	110	110	7.50 (0.679)	-0.24 (0.246)	-0.23 (0.024)	[-0.279, -0.185]	-0.26 (0.033)	[-0.323, -0.192]	<.0001
Week 8									
Placebo	99	99	7.91 (0.775)	0.07 (0.381)	0.08 (0.041)	[-0.001, 0.160]			
Imeglimin 1000 mg bid	110	110	7.31 (0.675)	-0.43 (0.417)	-0.42 (0.039)	[-0.494, -0.342]	-0.50 (0.055)	[-0.607, -0.388]	<.0001
Week 12									
Placebo	99	96	7.91 (0.798)	0.08 (0.452)	0.10 (0.048)	[0.006, 0.195]			
Imeglimin 1000 mg bid	110	109	7.20 (0.658)	-0.54 (0.496)	-0.53 (0.046)	[-0.619, -0.439]	-0.63 (0.066)	[-0.759, -0.500]	<.0001
Week 16									
Placebo	99	93	7.83 (0.730)	0.03 (0.487)	0.07 (0.052)	[-0.029, 0.177]			
Imeglimin 1000 mg bid	110	108	7.13 (0.731)	-0.62 (0.509)	-0.60 (0.049)	[-0.701, -0.508]	-0.68 (0.071)	[-0.818, -0.539]	<.0001
Week 20									
Placebo	99	93	7.88 (0.775)	0.08 (0.564)	0.12 (0.058)	[0.010, 0.238]			
Imeglimin 1000 mg bid	110	107	7.09 (0.718)	-0.64 (0.546)	-0.62 (0.054)	[-0.730, -0.516]	-0.75 (0.079)	[-0.902, -0.592]	<.0001
Week 24									
Placebo	99	91	7.89 (0.736)	0.12 (0.618)	0.19 (0.064)	[0.063, 0.315]			
Imeglimin 1000 mg bid	110	104	7.13 (0.735)	-0.60 (0.598)	-0.59 (0.060)	[-0.705, -0.468]	-0.78 (0.087)	[-0.947, -0.604]	<.0001
LOCF Endpoint									
Placebo	99	99	8.01 (0.856)	0.17 (0.641)					
Imeglimin 1000 mg bid	110	110	7.14 (0.741)	-0.60 (0.586)					

- Abbreviations: MMRM, Mixed Model Repeated Measures; LOCF, Last Observation Carried Forward; bid, Twice a day; SD, standard deviation; SE, standard error; LS, least square; CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); QUICKI, Quantitative Insulin Sensitivity Check Index
- MMRM model was used with fixed effects for treatment group, visit, study, interaction of treatment-by-visit, and baseline HbA1c as a covariate, assuming an unstructured covariance matrix.

Control No:<<t-e-092-subhb-24wdb.sas, 2020-03-06T00:16:23>>

Table E-093 Subgroup Analysis of HbA1c Response at Week 24 (LOCF) by Age Group in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Efficacy Population)

Response		Age							
Study		< 65 years		>= 65 years		< 75 years		>= 75 years	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]	n/m (%)	[95% CI]	n/m (%)	[95% CI]
HbA1c < 7.0%									
Study 014									
Placebo	75	3/47 (6.4%)	[1.3, 17.5]	2/28 (7.1%)	[0.9, 23.5]	5/75 (6.7%)	[2.2, 14.9]	.	.
Imeglimin 500 mg bid	75	5/54 (9.3%)	[3.1, 20.3]	5/21 (23.8%)	[8.2, 47.2]	10/75 (13.3%)	[6.6, 23.2]	.	.
Imeglimin 1000 mg bid	73	12/43 (27.9%)	[15.3, 43.7]	16/30 (53.3%)	[34.3, 71.7]	28/71 (39.4%)	[28.0, 51.7]	0/2	.
Imeglimin 1500 mg bid	73	11/46 (23.9%)	[12.6, 38.8]	10/27 (37.0%)	[19.4, 57.6]	21/73 (28.8%)	[18.8, 40.6]	.	.
Study 018									
Placebo	106	4/58 (6.9%)	[1.9, 16.7]	4/48 (8.3%)	[2.3, 20.0]	6/93 (6.5%)	[2.4, 13.5]	2/13 (15.4%)	[1.9, 45.4]
Imeglimin 1000 mg bid	106	13/54 (24.1%)	[13.5, 37.6]	27/52 (51.9%)	[37.6, 66.0]	37/99 (37.4%)	[27.9, 47.7]	3/7 (42.9%)	[9.9, 81.6]
Pooled (Studies 014+018)									
Placebo	181	7/105 (6.7%)	[2.7, 13.3]	6/76 (7.9%)	[3.0, 16.4]	11/168 (6.5%)	[3.3, 11.4]	2/13 (15.4%)	[1.9, 45.4]
Imeglimin 1000 mg bid	179	25/97 (25.8%)	[17.4, 35.7]	43/82 (52.4%)	[41.1, 63.6]	65/170 (38.2%)	[30.9, 46.0]	3/9 (33.3%)	[7.5, 70.1]
HbA1c decrease >= 0.5%									
Study 014									
Placebo	75	6/47 (12.8%)	[4.8, 25.7]	2/28 (7.1%)	[0.9, 23.5]	8/75 (10.7%)	[4.7, 19.9]	.	.
Imeglimin 500 mg bid	75	14/54 (25.9%)	[15.0, 39.7]	9/21 (42.9%)	[21.8, 66.0]	23/75 (30.7%)	[20.5, 42.4]	.	.
Imeglimin 1000 mg bid	73	22/43 (51.2%)	[35.5, 66.7]	21/30 (70.0%)	[50.6, 85.3]	42/71 (59.2%)	[46.8, 70.7]	1/2 (50.0%)	[1.3, 98.7]
Imeglimin 1500 mg bid	73	22/46 (47.8%)	[32.9, 63.1]	17/27 (63.0%)	[42.4, 80.6]	39/73 (53.4%)	[41.4, 65.2]	.	.
Study 018									
Placebo	106	8/58 (13.8%)	[6.1, 25.4]	5/48 (10.4%)	[3.5, 22.7]	12/93 (12.9%)	[6.8, 21.5]	1/13 (7.7%)	[0.2, 36.0]
Imeglimin 1000 mg bid	106	35/54 (64.8%)	[50.6, 77.3]	37/52 (71.2%)	[56.9, 82.9]	67/99 (67.7%)	[57.5, 76.7]	5/7 (71.4%)	[29.0, 96.3]
Pooled (Studies 014+018)									
Placebo	181	14/105 (13.3%)	[7.5, 21.4]	7/76 (9.2%)	[3.8, 18.1]	20/168 (11.9%)	[7.4, 17.8]	1/13 (7.7%)	[0.2, 36.0]
Imeglimin 1000 mg bid	179	57/97 (58.8%)	[48.3, 68.7]	58/82 (70.7%)	[59.6, 80.3]	109/170 (64.1%)	[56.4, 71.3]	6/9 (66.7%)	[29.9, 92.5]
HbA1c decrease >= 1.0%									

Response		Age							
Study		< 65 years		>= 65 years		< 75 years		>= 75 years	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]	n/m (%)	[95% CI]	n/m (%)	[95% CI]
Study 014									
Placebo	75	4/47 (8.5%)	[2.4, 20.4]	0/28	.	4/75 (5.3%)	[1.5, 13.1]	.	.
Imeglimin 500 mg bid	75	2/54 (3.7%)	[0.5, 12.7]	2/21 (9.5%)	[1.2, 30.4]	4/75 (5.3%)	[1.5, 13.1]	.	.
Imeglimin 1000 mg bid	73	6/43 (14.0%)	[5.3, 27.9]	6/30 (20.0%)	[7.7, 38.6]	12/71 (16.9%)	[9.0, 27.7]	0/2	.
Imeglimin 1500 mg bid	73	11/46 (23.9%)	[12.6, 38.8]	6/27 (22.2%)	[8.6, 42.3]	17/73 (23.3%)	[14.2, 34.6]	.	.
Study 018									
Placebo	106	1/58 (1.7%)	[0.0, 9.2]	0/48	.	1/93 (1.1%)	[0.0, 5.8]	0/13	.
Imeglimin 1000 mg bid	106	18/54 (33.3%)	[21.1, 47.5]	15/52 (28.8%)	[17.1, 43.1]	31/99 (31.3%)	[22.4, 41.4]	2/7 (28.6%)	[3.7, 71.0]
Pooled (Studies 014+018)									
Placebo	181	5/105 (4.8%)	[1.6, 10.8]	0/76	.	5/168 (3.0%)	[1.0, 6.8]	0/13	.
Imeglimin 1000 mg bid	179	24/97 (24.7%)	[16.5, 34.5]	21/82 (25.6%)	[16.6, 36.4]	43/170 (25.3%)	[19.0, 32.5]	2/9 (22.2%)	[2.8, 60.0]
Percent HbA1c decrease >= 7%									
Study 014									
Placebo	75	5/47 (10.6%)	[3.5, 23.1]	2/28 (7.1%)	[0.9, 23.5]	7/75 (9.3%)	[3.8, 18.3]	.	.
Imeglimin 500 mg bid	75	11/54 (20.4%)	[10.6, 33.5]	8/21 (38.1%)	[18.1, 61.6]	19/75 (25.3%)	[16.0, 36.7]	.	.
Imeglimin 1000 mg bid	73	17/43 (39.5%)	[25.0, 55.6]	19/30 (63.3%)	[43.9, 80.1]	35/71 (49.3%)	[37.2, 61.4]	1/2 (50.0%)	[1.3, 98.7]
Imeglimin 1500 mg bid	73	17/46 (37.0%)	[23.2, 52.5]	15/27 (55.6%)	[35.3, 74.5]	32/73 (43.8%)	[32.2, 55.9]	.	.
Study 018									
Placebo	106	7/58 (12.1%)	[5.0, 23.3]	5/48 (10.4%)	[3.5, 22.7]	11/93 (11.8%)	[6.1, 20.2]	1/13 (7.7%)	[0.2, 36.0]
Imeglimin 1000 mg bid	106	31/54 (57.4%)	[43.2, 70.8]	32/52 (61.5%)	[47.0, 74.7]	59/99 (59.6%)	[49.3, 69.3]	4/7 (57.1%)	[18.4, 90.1]
Pooled (Studies 014+018)									
Placebo	181	12/105 (11.4%)	[6.0, 19.1]	7/76 (9.2%)	[3.8, 18.1]	18/168 (10.7%)	[6.5, 16.4]	1/13 (7.7%)	[0.2, 36.0]
Imeglimin 1000 mg bid	179	48/97 (49.5%)	[39.2, 59.8]	51/82 (62.2%)	[50.8, 72.7]	94/170 (55.3%)	[47.5, 62.9]	5/9 (55.6%)	[21.2, 86.3]

- Abbreviations: bid, Twice a day; CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); LOCF, Last Observation Carried Forward
- m is the total number of subjects with the corresponding category and was used as the denominator to calculate percentage.
- Confidence interval for proportion was calculated with Clopper-Pearson exact method.
- N is the number of patients in the analysis population. Patients who have no HbA1c measurement are defined as non-responders.

Control No:<<t-e-093-subrs-24wdb.sas, 2020-03-06T00:15:45>>

Table E-094 Subgroup Analysis of HbA1c Response at Week 24 (LOCF) by Sex in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Efficacy Population)

Response		Sex			
Study		Male		Female	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]
HbA1c < 7.0%					
Study 014					
Placebo	75	2/49 (4.1%)	[0.5, 14.0]	3/26 (11.5%)	[2.4, 30.2]
Imeglimin 500 mg bid	75	7/49 (14.3%)	[5.9, 27.2]	3/26 (11.5%)	[2.4, 30.2]
Imeglimin 1000 mg bid	73	17/48 (35.4%)	[22.2, 50.5]	11/25 (44.0%)	[24.4, 65.1]
Imeglimin 1500 mg bid	73	16/52 (30.8%)	[18.7, 45.1]	5/21 (23.8%)	[8.2, 47.2]
Study 018					
Placebo	106	4/77 (5.2%)	[1.4, 12.8]	4/29 (13.8%)	[3.9, 31.7]
Imeglimin 1000 mg bid	106	32/89 (36.0%)	[26.1, 46.8]	8/17 (47.1%)	[23.0, 72.2]
Pooled (Studies 014+018)					
Placebo	181	6/126 (4.8%)	[1.8, 10.1]	7/55 (12.7%)	[5.3, 24.5]
Imeglimin 1000 mg bid	179	49/137 (35.8%)	[27.8, 44.4]	19/42 (45.2%)	[29.8, 61.3]
HbA1c decrease >= 0.5%					
Study 014					
Placebo	75	4/49 (8.2%)	[2.3, 19.6]	4/26 (15.4%)	[4.4, 34.9]
Imeglimin 500 mg bid	75	18/49 (36.7%)	[23.4, 51.7]	5/26 (19.2%)	[6.6, 39.4]
Imeglimin 1000 mg bid	73	28/48 (58.3%)	[43.2, 72.4]	15/25 (60.0%)	[38.7, 78.9]
Imeglimin 1500 mg bid	73	30/52 (57.7%)	[43.2, 71.3]	9/21 (42.9%)	[21.8, 66.0]
Study 018					
Placebo	106	10/77 (13.0%)	[6.4, 22.6]	3/29 (10.3%)	[2.2, 27.4]
Imeglimin 1000 mg bid	106	61/89 (68.5%)	[57.8, 78.0]	11/17 (64.7%)	[38.3, 85.8]
Pooled (Studies 014+018)					
Placebo	181	14/126 (11.1%)	[6.2, 17.9]	7/55 (12.7%)	[5.3, 24.5]
Imeglimin 1000 mg bid	179	89/137 (65.0%)	[56.4, 72.9]	26/42 (61.9%)	[45.6, 76.4]
HbA1c decrease >= 1.0%					
Study 014					
Placebo	75	1/49 (2.0%)	[0.1, 10.9]	3/26 (11.5%)	[2.4, 30.2]
Imeglimin 500 mg bid	75	4/49 (8.2%)	[2.3, 19.6]	0/26	.
Imeglimin 1000 mg bid	73	7/48 (14.6%)	[6.1, 27.8]	5/25 (20.0%)	[6.8, 40.7]
Imeglimin 1500 mg bid	73	13/52 (25.0%)	[14.0, 38.9]	4/21 (19.0%)	[5.4, 41.9]
Study 018					
Placebo	106	0/77	.	1/29 (3.4%)	[0.1, 17.8]
Imeglimin 1000 mg bid	106	29/89 (32.6%)	[23.0, 43.3]	4/17 (23.5%)	[6.8, 49.9]
Pooled (Studies 014+018)					
Placebo	181	1/126 (0.8%)	[0.0, 4.3]	4/55 (7.3%)	[2.0, 17.6]
Imeglimin 1000 mg bid	179	36/137 (26.3%)	[19.1, 34.5]	9/42 (21.4%)	[10.3, 36.8]
Percent HbA1c decrease >= 7%					
Study 014					
Placebo	75	3/49 (6.1%)	[1.3, 16.9]	4/26 (15.4%)	[4.4, 34.9]
Imeglimin 500 mg bid	75	16/49 (32.7%)	[19.9, 47.5]	3/26 (11.5%)	[2.4, 30.2]
Imeglimin 1000 mg bid	73	22/48 (45.8%)	[31.4, 60.8]	14/25 (56.0%)	[34.9, 75.6]
Imeglimin 1500 mg bid	73	24/52 (46.2%)	[32.2, 60.5]	8/21 (38.1%)	[18.1, 61.6]
Study 018					
Placebo	106	9/77 (11.7%)	[5.5, 21.0]	3/29 (10.3%)	[2.2, 27.4]

Response		Sex			
Study		Male		Female	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]
Imeglimin 1000 mg bid	106	54/89 (60.7%)	[49.7, 70.9]	9/17 (52.9%)	[27.8, 77.0]
Pooled (Studies 014+018)					
Placebo	181	12/126 (9.5%)	[5.0, 16.0]	7/55 (12.7%)	[5.3, 24.5]
Imeglimin 1000 mg bid	179	76/137 (55.5%)	[46.7, 64.0]	23/42 (54.8%)	[38.7, 70.2]

- Abbreviations: bid, Twice a day; CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); LOCF, Last Observation Carried Forward
- m is the total number of subjects with the corresponding category and was used as the denominator to calculate percentage.
- Confidence interval for proportion was calculated with Clopper-Pearson exact method.
- N is the number of patients in the analysis population. Patients who have no HbA1c measurement are defined as non-responders.

Control No:<<t-e-094-subrs-24wdb.sas, 2020-03-06T00:16:23>>

Table E-095 Subgroup Analysis of HbA1c Response at Week 24 (LOCF) by eGFR CKD Stage in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Efficacy Population)

Response		CKD					
Study		Stage 1		Stage 2		Stage 3a	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]	n/m (%)	[95% CI]
HbA1c < 7.0%							
Study 014							
Placebo	75	0/9	.	4/55 (7.3%)	[2.0, 17.6]	1/11 (9.1%)	[0.2, 41.3]
Imeglimin 500 mg bid	75	0/9	.	9/56 (16.1%)	[7.6, 28.3]	1/10 (10.0%)	[0.3, 44.5]
Imeglimin 1000 mg bid	73	4/9 (44.4%)	[13.7, 78.8]	21/57 (36.8%)	[24.4, 50.7]	3/7 (42.9%)	[9.9, 81.6]
Imeglimin 1500 mg bid	73	3/14 (21.4%)	[4.7, 50.8]	14/51 (27.5%)	[15.9, 41.7]	4/8 (50.0%)	[15.7, 84.3]
Study 018							
Placebo	106	0/7	.	5/81 (6.2%)	[2.0, 13.8]	3/18 (16.7%)	[3.6, 41.4]
Imeglimin 1000 mg bid	106	1/12 (8.3%)	[0.2, 38.5]	32/73 (43.8%)	[32.2, 55.9]	7/21 (33.3%)	[14.6, 57.0]
Pooled (Studies 014+018)							
Placebo	181	0/16	.	9/136 (6.6%)	[3.1, 12.2]	4/29 (13.8%)	[3.9, 31.7]
Imeglimin 1000 mg bid	179	5/21 (23.8%)	[8.2, 47.2]	53/130 (40.8%)	[32.2, 49.7]	10/28 (35.7%)	[18.6, 55.9]
HbA1c decrease >= 0.5%							
Study 014							
Placebo	75	0/9	.	7/55 (12.7%)	[5.3, 24.5]	1/11 (9.1%)	[0.2, 41.3]
Imeglimin 500 mg bid	75	1/9 (11.1%)	[0.3, 48.2]	18/56 (32.1%)	[20.3, 46.0]	4/10 (40.0%)	[12.2, 73.8]
Imeglimin 1000 mg bid	73	6/9 (66.7%)	[29.9, 92.5]	33/57 (57.9%)	[44.1, 70.9]	4/7 (57.1%)	[18.4, 90.1]
Imeglimin 1500 mg bid	73	6/14 (42.9%)	[17.7, 71.1]	28/51 (54.9%)	[40.3, 68.9]	5/8 (62.5%)	[24.5, 91.5]
Study 018							
Placebo	106	0/7	.	9/81 (11.1%)	[5.2, 20.0]	4/18 (22.2%)	[6.4, 47.6]
Imeglimin 1000 mg bid	106	6/12 (50.0%)	[21.1, 78.9]	52/73 (71.2%)	[59.4, 81.2]	14/21 (66.7%)	[43.0, 85.4]
Pooled (Studies 014+018)							
Placebo	181	0/16	.	16/136 (11.8%)	[6.9, 18.4]	5/29 (17.2%)	[5.8, 35.8]
Imeglimin 1000 mg bid	179	12/21 (57.1%)	[34.0, 78.2]	85/130 (65.4%)	[56.5, 73.5]	18/28 (64.3%)	[44.1, 81.4]
HbA1c decrease >= 1.0%							

Response		CKD					
Study		Stage 1		Stage 2		Stage 3a	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]	n/m (%)	[95% CI]
Study 014							
Placebo	75	0/9	.	4/55 (7.3%)	[2.0, 17.6]	0/11	.
Imeglimin 500 mg bid	75	1/9 (11.1%)	[0.3, 48.2]	2/56 (3.6%)	[0.4, 12.3]	1/10 (10.0%)	[0.3, 44.5]
Imeglimin 1000 mg bid	73	3/9 (33.3%)	[7.5, 70.1]	8/57 (14.0%)	[6.3, 25.8]	1/7 (14.3%)	[0.4, 57.9]
Imeglimin 1500 mg bid	73	3/14 (21.4%)	[4.7, 50.8]	11/51 (21.6%)	[11.3, 35.3]	3/8 (37.5%)	[8.5, 75.5]
Study 018							
Placebo	106	0/7	.	0/81	.	1/18 (5.6%)	[0.1, 27.3]
Imeglimin 1000 mg bid	106	3/12 (25.0%)	[5.5, 57.2]	22/73 (30.1%)	[19.9, 42.0]	8/21 (38.1%)	[18.1, 61.6]
Pooled (Studies 014+018)							
Placebo	181	0/16	.	4/136 (2.9%)	[0.8, 7.4]	1/29 (3.4%)	[0.1, 17.8]
Imeglimin 1000 mg bid	179	6/21 (28.6%)	[11.3, 52.2]	30/130 (23.1%)	[16.1, 31.3]	9/28 (32.1%)	[15.9, 52.4]
Percent HbA1c decrease >= 7%							
Study 014							
Placebo	75	0/9	.	6/55 (10.9%)	[4.1, 22.2]	1/11 (9.1%)	[0.2, 41.3]
Imeglimin 500 mg bid	75	1/9 (11.1%)	[0.3, 48.2]	14/56 (25.0%)	[14.4, 38.4]	4/10 (40.0%)	[12.2, 73.8]
Imeglimin 1000 mg bid	73	6/9 (66.7%)	[29.9, 92.5]	26/57 (45.6%)	[32.4, 59.3]	4/7 (57.1%)	[18.4, 90.1]
Imeglimin 1500 mg bid	73	5/14 (35.7%)	[12.8, 64.9]	22/51 (43.1%)	[29.3, 57.8]	5/8 (62.5%)	[24.5, 91.5]
Study 018							
Placebo	106	0/7	.	8/81 (9.9%)	[4.4, 18.5]	4/18 (22.2%)	[6.4, 47.6]
Imeglimin 1000 mg bid	106	4/12 (33.3%)	[9.9, 65.1]	46/73 (63.0%)	[50.9, 74.0]	13/21 (61.9%)	[38.4, 81.9]
Pooled (Studies 014+018)							
Placebo	181	0/16	.	14/136 (10.3%)	[5.7, 16.7]	5/29 (17.2%)	[5.8, 35.8]

Response		CKD					
Study		Stage 1		Stage 2		Stage 3a	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]	n/m (%)	[95% CI]
Imeglimin 1000 mg bid	179	10/21 (47.6%)	[25.7, 70.2]	72/130 (55.4%)	[46.4, 64.1]	17/28 (60.7%)	[40.6, 78.5]

- Abbreviations: bid, Twice a day; CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); LOCF, Last Observation Carried Forward; eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2, CKD Stage 3a includes subjects with eGFR >= 45 to < 60 mL/min/1.73m2.
- m is the total number of subjects with the corresponding category and was used as the denominator to calculate percentage.
- Confidence interval for proportion was calculated with Clopper-Pearson exact method.
- N is the number of patients in the analysis population. Patients who have no HbA1c measurement are defined as non-responders.

Control No:<<t-e-095-subrs-24wdb.sas, 2020-03-06T00:16:23>>

Table E-096 Subgroup Analysis of HbA1c Response at Week 24 (LOCF) by Hepatic Parameter Abnormality in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Efficacy Population)

Response		Hepatic parameter abnormality			
Study		Yes		No	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]
HbA1c < 7.0%					
Study 014					
Placebo	75	3/14 (21.4%)	[4.7, 50.8]	2/61 (3.3%)	[0.4, 11.3]
Imeglimin 500 mg bid	75	1/14 (7.1%)	[0.2, 33.9]	9/61 (14.8%)	[7.0, 26.2]
Imeglimin 1000 mg bid	73	6/14 (42.9%)	[17.7, 71.1]	22/59 (37.3%)	[25.0, 50.9]
Imeglimin 1500 mg bid	73	2/14 (14.3%)	[1.8, 42.8]	19/59 (32.2%)	[20.6, 45.6]
Study 018					
Placebo	106	4/17 (23.5%)	[6.8, 49.9]	4/89 (4.5%)	[1.2, 11.1]
Imeglimin 1000 mg bid	106	2/10 (20.0%)	[2.5, 55.6]	38/96 (39.6%)	[29.7, 50.1]
Pooled (Studies 014+018)					
Placebo	181	7/31 (22.6%)	[9.6, 41.1]	6/150 (4.0%)	[1.5, 8.5]
Imeglimin 1000 mg bid	179	8/24 (33.3%)	[15.6, 55.3]	60/155 (38.7%)	[31.0, 46.9]
HbA1c decrease >= 0.5%					
Study 014					
Placebo	75	1/14 (7.1%)	[0.2, 33.9]	7/61 (11.5%)	[4.7, 22.2]
Imeglimin 500 mg bid	75	4/14 (28.6%)	[8.4, 58.1]	19/61 (31.1%)	[19.9, 44.3]
Imeglimin 1000 mg bid	73	10/14 (71.4%)	[41.9, 91.6]	33/59 (55.9%)	[42.4, 68.8]
Imeglimin 1500 mg bid	73	7/14 (50.0%)	[23.0, 77.0]	32/59 (54.2%)	[40.8, 67.3]
Study 018					
Placebo	106	5/17 (29.4%)	[10.3, 56.0]	8/89 (9.0%)	[4.0, 16.9]
Imeglimin 1000 mg bid	106	4/10 (40.0%)	[12.2, 73.8]	68/96 (70.8%)	[60.7, 79.7]
Pooled (Studies 014+018)					
Placebo	181	6/31 (19.4%)	[7.5, 37.5]	15/150 (10.0%)	[5.7, 16.0]
Imeglimin 1000 mg bid	179	14/24 (58.3%)	[36.6, 77.9]	101/155 (65.2%)	[57.1, 72.6]
HbA1c decrease >= 1.0%					
Study 014					
Placebo	75	1/14 (7.1%)	[0.2, 33.9]	3/61 (4.9%)	[1.0, 13.7]
Imeglimin 500 mg bid	75	1/14 (7.1%)	[0.2, 33.9]	3/61 (4.9%)	[1.0, 13.7]
Imeglimin 1000 mg bid	73	2/14 (14.3%)	[1.8, 42.8]	10/59 (16.9%)	[8.4, 29.0]
Imeglimin 1500 mg bid	73	3/14 (21.4%)	[4.7, 50.8]	14/59 (23.7%)	[13.6, 36.6]
Study 018					
Placebo	106	1/17 (5.9%)	[0.1, 28.7]	0/89	.
Imeglimin 1000 mg bid	106	1/10 (10.0%)	[0.3, 44.5]	32/96 (33.3%)	[24.0, 43.7]
Pooled (Studies 014+018)					
Placebo	181	2/31 (6.5%)	[0.8, 21.4]	3/150 (2.0%)	[0.4, 5.7]
Imeglimin 1000 mg bid	179	3/24 (12.5%)	[2.7, 32.4]	42/155 (27.1%)	[20.3, 34.8]
Percent HbA1c decrease >= 7%					
Study 014					
Placebo	75	1/14 (7.1%)	[0.2, 33.9]	6/61 (9.8%)	[3.7, 20.2]
Imeglimin 500 mg bid	75	3/14 (21.4%)	[4.7, 50.8]	16/61 (26.2%)	[15.8, 39.1]
Imeglimin 1000 mg bid	73	8/14 (57.1%)	[28.9, 82.3]	28/59 (47.5%)	[34.3, 60.9]
Imeglimin 1500 mg bid	73	4/14 (28.6%)	[8.4, 58.1]	28/59 (47.5%)	[34.3, 60.9]
Study 018					
Placebo	106	5/17 (29.4%)	[10.3, 56.0]	7/89 (7.9%)	[3.2, 15.5]

Response		Hepatic parameter abnormality			
Study		Yes		No	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]
Imeglimin 1000 mg bid	106	4/10 (40.0%)	[12.2, 73.8]	59/96 (61.5%)	[51.0, 71.2]
Pooled (Studies 014+018)					
Placebo	181	6/31 (19.4%)	[7.5, 37.5]	13/150 (8.7%)	[4.7, 14.4]
Imeglimin 1000 mg bid	179	12/24 (50.0%)	[29.1, 70.9]	87/155 (56.1%)	[47.9, 64.1]

- Abbreviations: bid, Twice a day; CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); LOCF, Last Observation Carried Forward
- Hepatic parameter abnormality is defined as any one of following parameter applied: Total Bilirubin >= 1.6 mg/dL; Aspartate aminotransferase (AST) >= 1.25 x Upper Limit of Normal (ULN); AST >= 50 IU; Alanine aminotransferase (ALT) >= 1.25 x ULN; ALT >= 50 IU; Alkaline phosphatase >= 1.25 x ULN; Gamma glutamyl transferase >= 1.5 x ULN.
- m is the total number of subjects with the corresponding category and was used as the denominator to calculate percentage.
- Confidence interval for proportion was calculated with Clopper-Pearson exact method.
- N is the number of patients in the analysis population. Patients who have no HbA1c measurement are defined as non-responders.

Control No:<<t-e-096-subrs-24wdb.sas, 2020-03-06T00:17:06>>

Table E-097 Subgroup Analysis of HbA1c Response at Week 52 (LOCF) by Age Group in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Efficacy Population)

Response		Age							
		< 65 years		>= 65 years		< 75 years		>= 75 years	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]	n/m (%)	[95% CI]	n/m (%)	[95% CI]
HbA1c < 7.0%									
Imeglimin	134	27/86 (31.4%)	[21.8, 42.3]	26/48 (54.2%)	[39.2, 68.6]	48/127 (37.8%)	[29.3, 46.8]	5/7 (71.4%)	[29.0, 96.3]
Imeglimin + SU	127	10/76 (13.2%)	[6.5, 22.9]	7/51 (13.7%)	[5.7, 26.3]	16/122 (13.1%)	[7.7, 20.4]	1/5 (20.0%)	[0.5, 71.6]
Imeglimin + GLIN	64	9/42 (21.4%)	[10.3, 36.8]	7/22 (31.8%)	[13.9, 54.9]	15/61 (24.6%)	[14.5, 37.3]	1/3 (33.3%)	[0.8, 90.6]
Imeglimin + BIG	64	11/47 (23.4%)	[12.3, 38.0]	6/17 (35.3%)	[14.2, 61.7]	15/61 (24.6%)	[14.5, 37.3]	2/3 (66.7%)	[9.4, 99.2]
Imeglimin + AGI	64	9/41 (22.0%)	[10.6, 37.6]	6/23 (26.1%)	[10.2, 48.4]	14/62 (22.6%)	[12.9, 35.0]	1/2 (50.0%)	[1.3, 98.7]
Imeglimin + TZD	65	11/44 (25.0%)	[13.2, 40.3]	2/21 (9.5%)	[1.2, 30.4]	13/61 (21.3%)	[11.9, 33.7]	0/4	.
Imeglimin + DPP4-I	63	8/28 (28.6%)	[13.2, 48.7]	14/35 (40.0%)	[23.9, 57.9]	21/58 (36.2%)	[24.0, 49.9]	1/5 (20.0%)	[0.5, 71.6]
Imeglimin + GLP1-RA	70	4/46 (8.7%)	[2.4, 20.8]	2/24 (8.3%)	[1.0, 27.0]	6/67 (9.0%)	[3.4, 18.5]	0/3	.
Imeglimin + SGLT2-I	63	3/45 (6.7%)	[1.4, 18.3]	3/18 (16.7%)	[3.6, 41.4]	6/61 (9.8%)	[3.7, 20.2]	0/2	.
HbA1c decrease >= 0.5%									
Imeglimin	134	42/86 (48.8%)	[37.9, 59.9]	34/48 (70.8%)	[55.9, 83.0]	72/127 (56.7%)	[47.6, 65.5]	4/7 (57.1%)	[18.4, 90.1]
Imeglimin + SU	127	42/76 (55.3%)	[43.4, 66.7]	38/51 (74.5%)	[60.4, 85.7]	75/122 (61.5%)	[52.2, 70.1]	5/5 (100.0%)	[47.8, 100.0]
Imeglimin + GLIN	64	23/42 (54.8%)	[38.7, 70.2]	16/22 (72.7%)	[49.8, 89.3]	37/61 (60.7%)	[47.3, 72.9]	2/3 (66.7%)	[9.4, 99.2]
Imeglimin + BIG	64	33/47 (70.2%)	[55.1, 82.7]	8/17 (47.1%)	[23.0, 72.2]	40/61 (65.6%)	[52.3, 77.3]	1/3 (33.3%)	[0.8, 90.6]
Imeglimin + AGI	64	28/41 (68.3%)	[51.9, 81.9]	18/23 (78.3%)	[56.3, 92.5]	44/62 (71.0%)	[58.1, 81.8]	2/2 (100.0%)	[15.8, 100.0]
Imeglimin + TZD	65	26/44 (59.1%)	[43.2, 73.7]	13/21 (61.9%)	[38.4, 81.9]	38/61 (62.3%)	[49.0, 74.4]	1/4 (25.0%)	[0.6, 80.6]
Imeglimin + DPP4-I	63	17/28 (60.7%)	[40.6, 78.5]	26/35 (74.3%)	[56.7, 87.5]	40/58 (69.0%)	[55.5, 80.5]	3/5 (60.0%)	[14.7, 94.7]
Imeglimin + GLP1-RA	70	12/46 (26.1%)	[14.3, 41.1]	10/24 (41.7%)	[22.1, 63.4]	22/67 (32.8%)	[21.8, 45.4]	0/3	.
Imeglimin + SGLT2-I	63	23/45 (51.1%)	[35.8, 66.3]	12/18 (66.7%)	[41.0, 86.7]	33/61 (54.1%)	[40.8, 66.9]	2/2 (100.0%)	[15.8, 100.0]
HbA1c decrease >= 1.0%									
Imeglimin	134	15/86 (17.4%)	[10.1, 27.1]	9/48 (18.8%)	[8.9, 32.6]	23/127 (18.1%)	[11.8, 25.9]	1/7 (14.3%)	[0.4, 57.9]
Imeglimin + SU	127	19/76 (25.0%)	[15.8, 36.3]	19/51 (37.3%)	[24.1, 51.9]	34/122 (27.9%)	[20.1, 36.7]	4/5 (80.0%)	[28.4, 99.5]
Imeglimin + GLIN	64	10/42 (23.8%)	[12.1, 39.5]	9/22 (40.9%)	[20.7, 63.6]	18/61 (29.5%)	[18.5, 42.6]	1/3 (33.3%)	[0.8, 90.6]
Imeglimin + BIG	64	16/47 (34.0%)	[20.9, 49.3]	2/17 (11.8%)	[1.5, 36.4]	18/61 (29.5%)	[18.5, 42.6]	0/3	.

Response		Age < 65 years		>= 65 years		< 75 years		>= 75 years	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]	n/m (%)	[95% CI]	n/m (%)	[95% CI]
Imeglimin + AGI	64	18/41 (43.9%)	[28.5, 60.3]	11/23 (47.8%)	[26.8, 69.4]	29/62 (46.8%)	[34.0, 59.9]	0/2	.
Imeglimin + TZD	65	20/44 (45.5%)	[30.4, 61.2]	9/21 (42.9%)	[21.8, 66.0]	28/61 (45.9%)	[33.1, 59.2]	1/4 (25.0%)	[0.6, 80.6]
Imeglimin + DPP4-I	63	12/28 (42.9%)	[24.5, 62.8]	15/35 (42.9%)	[26.3, 60.6]	27/58 (46.6%)	[33.3, 60.1]	0/5	.
Imeglimin + GLP1-RA	70	4/46 (8.7%)	[2.4, 20.8]	5/24 (20.8%)	[7.1, 42.2]	9/67 (13.4%)	[6.3, 24.0]	0/3	.
Imeglimin + SGLT2-I	63	7/45 (15.6%)	[6.5, 29.5]	5/18 (27.8%)	[9.7, 53.5]	11/61 (18.0%)	[9.4, 30.0]	1/2 (50.0%)	[1.3, 98.7]
Percent HbA1c decrease >= 7%									
Imeglimin	134	36/86 (41.9%)	[31.3, 53.0]	27/48 (56.3%)	[41.2, 70.5]	59/127 (46.5%)	[37.6, 55.5]	4/7 (57.1%)	[18.4, 90.1]
Imeglimin + SU	127	36/76 (47.4%)	[35.8, 59.2]	30/51 (58.8%)	[44.2, 72.4]	62/122 (50.8%)	[41.6, 60.0]	4/5 (80.0%)	[28.4, 99.5]
Imeglimin + GLIN	64	21/42 (50.0%)	[34.2, 65.8]	13/22 (59.1%)	[36.4, 79.3]	33/61 (54.1%)	[40.8, 66.9]	1/3 (33.3%)	[0.8, 90.6]
Imeglimin + BIG	64	30/47 (63.8%)	[48.5, 77.3]	6/17 (35.3%)	[14.2, 61.7]	35/61 (57.4%)	[44.1, 70.0]	1/3 (33.3%)	[0.8, 90.6]
Imeglimin + AGI	64	26/41 (63.4%)	[46.9, 77.9]	17/23 (73.9%)	[51.6, 89.8]	41/62 (66.1%)	[53.0, 77.7]	2/2 (100.0%)	[15.8, 100.0]
Imeglimin + TZD	65	26/44 (59.1%)	[43.2, 73.7]	12/21 (57.1%)	[34.0, 78.2]	37/61 (60.7%)	[47.3, 72.9]	1/4 (25.0%)	[0.6, 80.6]
Imeglimin + DPP4-I	63	15/28 (53.6%)	[33.9, 72.5]	25/35 (71.4%)	[53.7, 85.4]	37/58 (63.8%)	[50.1, 76.0]	3/5 (60.0%)	[14.7, 94.7]
Imeglimin + GLP1-RA	70	9/46 (19.6%)	[9.4, 33.9]	8/24 (33.3%)	[15.6, 55.3]	17/67 (25.4%)	[15.5, 37.5]	0/3	.
Imeglimin + SGLT2-I	63	19/45 (42.2%)	[27.7, 57.8]	10/18 (55.6%)	[30.8, 78.5]	28/61 (45.9%)	[33.1, 59.2]	1/2 (50.0%)	[1.3, 98.7]

- Abbreviations: CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); LOCF, Last Observation Carried Forward; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- m is the total number of subjects with the corresponding category and was used as the denominator to calculate percentage.
- Confidence interval for proportion was calculated with Clopper-Pearson exact method.
- N is the number of patients in the analysis population. Patients who have no HbA1c measurement are defined as non-responders.

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Table E-098 Subgroup Analysis of HbA1c Response at Week 52 (LOCF) by Sex in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Efficacy Population)

		Sex			
Response		Male		Female	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]
HbA1c < 7.0%					
Imeglimin	134	43/106 (40.6%)	[31.1, 50.5]	10/28 (35.7%)	[18.6, 55.9]
Imeglimin + SU	127	15/101 (14.9%)	[8.6, 23.3]	2/26 (7.7%)	[0.9, 25.1]
Imeglimin + GLIN	64	10/43 (23.3%)	[11.8, 38.6]	6/21 (28.6%)	[11.3, 52.2]
Imeglimin + BIG	64	11/46 (23.9%)	[12.6, 38.8]	6/18 (33.3%)	[13.3, 59.0]
Imeglimin + AGI	64	8/48 (16.7%)	[7.5, 30.2]	7/16 (43.8%)	[19.8, 70.1]
Imeglimin + TZD	65	8/54 (14.8%)	[6.6, 27.1]	5/11 (45.5%)	[16.7, 76.6]
Imeglimin + DPP4-I	63	13/39 (33.3%)	[19.1, 50.2]	9/24 (37.5%)	[18.8, 59.4]
Imeglimin + GLP1-RA	70	3/44 (6.8%)	[1.4, 18.7]	3/26 (11.5%)	[2.4, 30.2]
Imeglimin + SGLT2-I	63	5/45 (11.1%)	[3.7, 24.1]	1/18 (5.6%)	[0.1, 27.3]
HbA1c decrease >= 0.5%					
Imeglimin	134	58/106 (54.7%)	[44.8, 64.4]	18/28 (64.3%)	[44.1, 81.4]
Imeglimin + SU	127	63/101 (62.4%)	[52.2, 71.8]	17/26 (65.4%)	[44.3, 82.8]
Imeglimin + GLIN	64	28/43 (65.1%)	[49.1, 79.0]	11/21 (52.4%)	[29.8, 74.3]
Imeglimin + BIG	64	27/46 (58.7%)	[43.2, 73.0]	14/18 (77.8%)	[52.4, 93.6]
Imeglimin + AGI	64	33/48 (68.8%)	[53.7, 81.3]	13/16 (81.3%)	[54.4, 96.0]
Imeglimin + TZD	65	32/54 (59.3%)	[45.0, 72.4]	7/11 (63.6%)	[30.8, 89.1]
Imeglimin + DPP4-I	63	26/39 (66.7%)	[49.8, 80.9]	17/24 (70.8%)	[48.9, 87.4]
Imeglimin + GLP1-RA	70	14/44 (31.8%)	[18.6, 47.6]	8/26 (30.8%)	[14.3, 51.8]
Imeglimin + SGLT2-I	63	25/45 (55.6%)	[40.0, 70.4]	10/18 (55.6%)	[30.8, 78.5]
HbA1c decrease >= 1.0%					
Imeglimin	134	16/106 (15.1%)	[8.9, 23.4]	8/28 (28.6%)	[13.2, 48.7]
Imeglimin + SU	127	32/101 (31.7%)	[22.8, 41.7]	6/26 (23.1%)	[9.0, 43.6]
Imeglimin + GLIN	64	13/43 (30.2%)	[17.2, 46.1]	6/21 (28.6%)	[11.3, 52.2]
Imeglimin + BIG	64	7/46 (15.2%)	[6.3, 28.9]	11/18 (61.1%)	[35.7, 82.7]
Imeglimin + AGI	64	20/48 (41.7%)	[27.6, 56.8]	9/16 (56.3%)	[29.9, 80.2]
Imeglimin + TZD	65	23/54 (42.6%)	[29.2, 56.8]	6/11 (54.5%)	[23.4, 83.3]
Imeglimin + DPP4-I	63	18/39 (46.2%)	[30.1, 62.8]	9/24 (37.5%)	[18.8, 59.4]
Imeglimin + GLP1-RA	70	4/44 (9.1%)	[2.5, 21.7]	5/26 (19.2%)	[6.6, 39.4]
Imeglimin + SGLT2-I	63	10/45 (22.2%)	[11.2, 37.1]	2/18 (11.1%)	[1.4, 34.7]
Percent HbA1c decrease >= 7%					
Imeglimin	134	49/106 (46.2%)	[36.5, 56.2]	14/28 (50.0%)	[30.6, 69.4]
Imeglimin + SU	127	52/101 (51.5%)	[41.3, 61.6]	14/26 (53.8%)	[33.4, 73.4]
Imeglimin + GLIN	64	25/43 (58.1%)	[42.1, 73.0]	9/21 (42.9%)	[21.8, 66.0]
Imeglimin + BIG	64	23/46 (50.0%)	[34.9, 65.1]	13/18 (72.2%)	[46.5, 90.3]
Imeglimin + AGI	64	30/48 (62.5%)	[47.4, 76.0]	13/16 (81.3%)	[54.4, 96.0]
Imeglimin + TZD	65	32/54 (59.3%)	[45.0, 72.4]	6/11 (54.5%)	[23.4, 83.3]
Imeglimin + DPP4-I	63	24/39 (61.5%)	[44.6, 76.6]	16/24 (66.7%)	[44.7, 84.4]
Imeglimin + GLP1-RA	70	10/44 (22.7%)	[11.5, 37.8]	7/26 (26.9%)	[11.6, 47.8]

		Sex			
Response		Male		Female	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]
Imeglimin + SGLT2-I	63	21/45 (46.7%)	[31.7, 62.1]	8/18 (44.4%)	[21.5, 69.2]

- Abbreviations: CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); LOCF, Last Observation Carried Forward; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- m is the total number of subjects with the corresponding category and was used as the denominator to calculate percentage.
- Confidence interval for proportion was calculated with Clopper-Pearson exact method.
- N is the number of patients in the analysis population. Patients who have no HbA1c measurement are defined as non-responders.

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Table E-099 Subgroup Analysis of HbA1c Response at Week 52 (LOCF) by eGFR CKD Stage in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Efficacy Population)

Response		CKD Stage 1		Stage 2		Stage 3a	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]	n/m (%)	[95% CI]
HbA1c < 7.0%							
Imeglimin	134	6/24 (25.0%)	[9.8, 46.7]	37/91 (40.7%)	[30.5, 51.5]	10/19 (52.6%)	[28.9, 75.6]
Imeglimin + SU	127	0/22	.	14/96 (14.6%)	[8.2, 23.3]	3/9 (33.3%)	[7.5, 70.1]
Imeglimin + GLIN	64	4/12 (33.3%)	[9.9, 65.1]	12/50 (24.0%)	[13.1, 38.2]	0/2	.
Imeglimin + BIG	64	5/18 (27.8%)	[9.7, 53.5]	12/42 (28.6%)	[15.7, 44.6]	0/4	.
Imeglimin + AGI	64	5/13 (38.5%)	[13.9, 68.4]	9/49 (18.4%)	[8.8, 32.0]	1/2 (50.0%)	[1.3, 98.7]
Imeglimin + TZD	65	2/16 (12.5%)	[1.6, 38.3]	10/44 (22.7%)	[11.5, 37.8]	1/5 (20.0%)	[0.5, 71.6]
Imeglimin + DPP4-I	63	2/9 (22.2%)	[2.8, 60.0]	15/47 (31.9%)	[19.1, 47.1]	5/7 (71.4%)	[29.0, 96.3]
Imeglimin + GLP1-RA	70	3/16 (18.8%)	[4.0, 45.6]	3/51 (5.9%)	[1.2, 16.2]	0/3	.
Imeglimin + SGLT2-I	63	1/21 (4.8%)	[0.1, 23.8]	5/40 (12.5%)	[4.2, 26.8]	0/2	.
HbA1c decrease >= 0.5%							
Imeglimin	134	10/24 (41.7%)	[22.1, 63.4]	56/91 (61.5%)	[50.8, 71.6]	10/19 (52.6%)	[28.9, 75.6]
Imeglimin + SU	127	8/22 (36.4%)	[17.2, 59.3]	67/96 (69.8%)	[59.6, 78.7]	5/9 (55.6%)	[21.2, 86.3]
Imeglimin + GLIN	64	7/12 (58.3%)	[27.7, 84.8]	31/50 (62.0%)	[47.2, 75.3]	1/2 (50.0%)	[1.3, 98.7]
Imeglimin + BIG	64	12/18 (66.7%)	[41.0, 86.7]	28/42 (66.7%)	[50.5, 80.4]	1/4 (25.0%)	[0.6, 80.6]
Imeglimin + AGI	64	9/13 (69.2%)	[38.6, 90.9]	35/49 (71.4%)	[56.7, 83.4]	2/2 (100.0%)	[15.8, 100.0]
Imeglimin + TZD	65	10/16 (62.5%)	[35.4, 84.8]	26/44 (59.1%)	[43.2, 73.7]	3/5 (60.0%)	[14.7, 94.7]
Imeglimin + DPP4-I	63	5/9 (55.6%)	[21.2, 86.3]	32/47 (68.1%)	[52.9, 80.9]	6/7 (85.7%)	[42.1, 99.6]
Imeglimin + GLP1-RA	70	8/16 (50.0%)	[24.7, 75.3]	14/51 (27.5%)	[15.9, 41.7]	0/3	.
Imeglimin + SGLT2-I	63	8/21 (38.1%)	[18.1, 61.6]	25/40 (62.5%)	[45.8, 77.3]	2/2 (100.0%)	[15.8, 100.0]
HbA1c decrease >= 1.0%							
Imeglimin	134	3/24 (12.5%)	[2.7, 32.4]	17/91 (18.7%)	[11.3, 28.2]	4/19 (21.1%)	[6.1, 45.6]
Imeglimin + SU	127	4/22 (18.2%)	[5.2, 40.3]	31/96 (32.3%)	[23.1, 42.6]	3/9 (33.3%)	[7.5, 70.1]
Imeglimin + GLIN	64	3/12 (25.0%)	[5.5, 57.2]	16/50 (32.0%)	[19.5, 46.7]	0/2	.
Imeglimin + BIG	64	4/18 (22.2%)	[6.4, 47.6]	13/42 (31.0%)	[17.6, 47.1]	1/4 (25.0%)	[0.6, 80.6]

Response		CKD Stage 1		Stage 2		Stage 3a	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]	n/m (%)	[95% CI]
Imeglimin + AGI	64	8/13 (61.5%)	[31.6, 86.1]	21/49 (42.9%)	[28.8, 57.8]	0/2	.
Imeglimin + TZD	65	5/16 (31.3%)	[11.0, 58.7]	21/44 (47.7%)	[32.5, 63.3]	3/5 (60.0%)	[14.7, 94.7]
Imeglimin + DPP4-I	63	3/9 (33.3%)	[7.5, 70.1]	20/47 (42.6%)	[28.3, 57.8]	4/7 (57.1%)	[18.4, 90.1]
Imeglimin + GLP1-RA	70	3/16 (18.8%)	[4.0, 45.6]	6/51 (11.8%)	[4.4, 23.9]	0/3	.
Imeglimin + SGLT2-I	63	3/21 (14.3%)	[3.0, 36.3]	8/40 (20.0%)	[9.1, 35.6]	1/2 (50.0%)	[1.3, 98.7]
Percent HbA1c decrease >= 7%							
Imeglimin	134	8/24 (33.3%)	[15.6, 55.3]	45/91 (49.5%)	[38.8, 60.1]	10/19 (52.6%)	[28.9, 75.6]
Imeglimin + SU	127	6/22 (27.3%)	[10.7, 50.2]	56/96 (58.3%)	[47.8, 68.3]	4/9 (44.4%)	[13.7, 78.8]
Imeglimin + GLIN	64	6/12 (50.0%)	[21.1, 78.9]	28/50 (56.0%)	[41.3, 70.0]	0/2	.
Imeglimin + BIG	64	9/18 (50.0%)	[26.0, 74.0]	26/42 (61.9%)	[45.6, 76.4]	1/4 (25.0%)	[0.6, 80.6]
Imeglimin + AGI	64	8/13 (61.5%)	[31.6, 86.1]	34/49 (69.4%)	[54.6, 81.7]	1/2 (50.0%)	[1.3, 98.7]
Imeglimin + TZD	65	9/16 (56.3%)	[29.9, 80.2]	26/44 (59.1%)	[43.2, 73.7]	3/5 (60.0%)	[14.7, 94.7]
Imeglimin + DPP4-I	63	4/9 (44.4%)	[13.7, 78.8]	30/47 (63.8%)	[48.5, 77.3]	6/7 (85.7%)	[42.1, 99.6]
Imeglimin + GLP1-RA	70	7/16 (43.8%)	[19.8, 70.1]	10/51 (19.6%)	[9.8, 33.1]	0/3	.
Imeglimin + SGLT2-I	63	7/21 (33.3%)	[14.6, 57.0]	21/40 (52.5%)	[36.1, 68.5]	1/2 (50.0%)	[1.3, 98.7]

- Abbreviations: CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); LOCF, Last Observation Carried Forward; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor; eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2, CKD Stage 3a includes subjects with eGFR >= 45 to < 60 mL/min/1.73m2.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- m is the total number of subjects with the corresponding category and was used as the denominator to calculate percentage.
- Confidence interval for proportion was calculated with Clopper-Pearson exact method.
- N is the number of patients in the analysis population. Patients who have no HbA1c measurement are defined as non-responders.

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Table E-100 Subgroup Analysis of HbA1c Response at Week 52 (LOCF) by Hepatic Parameter Abnormality in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Efficacy Population)

		Hepatic parameter abnormality			
Response		Yes		No	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]
HbA1c < 7.0%					
Imeglimin	134	9/18 (50.0%)	[26.0, 74.0]	44/116 (37.9%)	[29.1, 47.4]
Imeglimin + SU	127	3/16 (18.8%)	[4.0, 45.6]	14/111 (12.6%)	[7.1, 20.3]
Imeglimin + GLIN	64	1/11 (9.1%)	[0.2, 41.3]	15/53 (28.3%)	[16.8, 42.3]
Imeglimin + BIG	64	5/10 (50.0%)	[18.7, 81.3]	12/54 (22.2%)	[12.0, 35.6]
Imeglimin + AGI	64	3/9 (33.3%)	[7.5, 70.1]	12/55 (21.8%)	[11.8, 35.0]
Imeglimin + TZD	65	1/9 (11.1%)	[0.3, 48.2]	12/56 (21.4%)	[11.6, 34.4]
Imeglimin + DPP4-I	63	5/12 (41.7%)	[15.2, 72.3]	17/51 (33.3%)	[20.8, 47.9]
Imeglimin + GLP1-RA	70	1/20 (5.0%)	[0.1, 24.9]	5/50 (10.0%)	[3.3, 21.8]
Imeglimin + SGLT2-I	63	2/13 (15.4%)	[1.9, 45.4]	4/50 (8.0%)	[2.2, 19.2]
HbA1c decrease >= 0.5%					
Imeglimin	134	11/18 (61.1%)	[35.7, 82.7]	65/116 (56.0%)	[46.5, 65.2]
Imeglimin + SU	127	13/16 (81.3%)	[54.4, 96.0]	67/111 (60.4%)	[50.6, 69.5]
Imeglimin + GLIN	64	6/11 (54.5%)	[23.4, 83.3]	33/53 (62.3%)	[47.9, 75.2]
Imeglimin + BIG	64	7/10 (70.0%)	[34.8, 93.3]	34/54 (63.0%)	[48.7, 75.7]
Imeglimin + AGI	64	6/9 (66.7%)	[29.9, 92.5]	40/55 (72.7%)	[59.0, 83.9]
Imeglimin + TZD	65	6/9 (66.7%)	[29.9, 92.5]	33/56 (58.9%)	[45.0, 71.9]
Imeglimin + DPP4-I	63	8/12 (66.7%)	[34.9, 90.1]	35/51 (68.6%)	[54.1, 80.9]
Imeglimin + GLP1-RA	70	3/20 (15.0%)	[3.2, 37.9]	19/50 (38.0%)	[24.7, 52.8]
Imeglimin + SGLT2-I	63	7/13 (53.8%)	[25.1, 80.8]	28/50 (56.0%)	[41.3, 70.0]
HbA1c decrease >= 1.0%					
Imeglimin	134	6/18 (33.3%)	[13.3, 59.0]	18/116 (15.5%)	[9.5, 23.4]
Imeglimin + SU	127	8/16 (50.0%)	[24.7, 75.3]	30/111 (27.0%)	[19.0, 36.3]
Imeglimin + GLIN	64	3/11 (27.3%)	[6.0, 61.0]	16/53 (30.2%)	[18.3, 44.3]
Imeglimin + BIG	64	5/10 (50.0%)	[18.7, 81.3]	13/54 (24.1%)	[13.5, 37.6]
Imeglimin + AGI	64	5/9 (55.6%)	[21.2, 86.3]	24/55 (43.6%)	[30.3, 57.7]
Imeglimin + TZD	65	4/9 (44.4%)	[13.7, 78.8]	25/56 (44.6%)	[31.3, 58.5]
Imeglimin + DPP4-I	63	8/12 (66.7%)	[34.9, 90.1]	19/51 (37.3%)	[24.1, 51.9]
Imeglimin + GLP1-RA	70	0/20	.	9/50 (18.0%)	[8.6, 31.4]
Imeglimin + SGLT2-I	63	5/13 (38.5%)	[13.9, 68.4]	7/50 (14.0%)	[5.8, 26.7]
Percent HbA1c decrease >= 7%					
Imeglimin	134	11/18 (61.1%)	[35.7, 82.7]	52/116 (44.8%)	[35.6, 54.3]
Imeglimin + SU	127	11/16 (68.8%)	[41.3, 89.0]	55/111 (49.5%)	[39.9, 59.2]
Imeglimin + GLIN	64	4/11 (36.4%)	[10.9, 69.2]	30/53 (56.6%)	[42.3, 70.2]
Imeglimin + BIG	64	6/10 (60.0%)	[26.2, 87.8]	30/54 (55.6%)	[41.4, 69.1]
Imeglimin + AGI	64	6/9 (66.7%)	[29.9, 92.5]	37/55 (67.3%)	[53.3, 79.3]
Imeglimin + TZD	65	6/9 (66.7%)	[29.9, 92.5]	32/56 (57.1%)	[43.2, 70.3]
Imeglimin + DPP4-I	63	8/12 (66.7%)	[34.9, 90.1]	32/51 (62.7%)	[48.1, 75.9]
Imeglimin + GLP1-RA	70	1/20 (5.0%)	[0.1, 24.9]	16/50 (32.0%)	[19.5, 46.7]

		Hepatic parameter abnormality			
Response		Yes		No	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]
Imeglimin + SGLT2-I	63	6/13 (46.2%)	[19.2, 74.9]	23/50 (46.0%)	[31.8, 60.7]

- Abbreviations: CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); LOCF, Last Observation Carried Forward; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- Hepatic parameter abnormality is defined as any one of following parameter applied: Total Bilirubin >= 1.6 mg/dL; Aspartate aminotransferase (AST) >= 1.25 x Upper Limit of Normal (ULN); AST >= 50 IU; Alanine aminotransferase (ALT) >= 1.25 x ULN; ALT >= 50 IU; Alkaline phosphatase >= 1.25 x ULN; Gamma glutamyl transferase >= 1.5 x ULN.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- m is the total number of subjects with the corresponding category and was used as the denominator to calculate percentage.
- Confidence interval for proportion was calculated with Clopper-Pearson exact method.
- N is the number of patients in the analysis population. Patients who have no HbA1c measurement are defined as non-responders.

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Table E-101 Subgroup Analysis of HbA1c Response at Week 16 (LOCF) by Age Group in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Efficacy Population)

Response		Age							
		< 65 years		>= 65 years		< 75 years		>= 75 years	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]	n/m (%)	[95% CI]	n/m (%)	[95% CI]
HbA1c < 7.0%									
Placebo + Insulin	106	1/75 (1.3%)	[0.0, 7.2]	0/31	.	1/103 (1.0%)	[0.0, 5.3]	0/3	.
Imeglimin 1000 mg bid + Insulin	108	3/68 (4.4%)	[0.9, 12.4]	5/40 (12.5%)	[4.2, 26.8]	8/101 (7.9%)	[3.5, 15.0]	0/7	.
HbA1c decrease >= 0.5%									
Placebo + Insulin	106	19/75 (25.3%)	[16.0, 36.7]	15/31 (48.4%)	[30.2, 66.9]	34/103 (33.0%)	[24.1, 43.0]	0/3	.
Imeglimin 1000 mg bid + Insulin	108	42/68 (61.8%)	[49.2, 73.3]	31/40 (77.5%)	[61.5, 89.2]	68/101 (67.3%)	[57.3, 76.3]	5/7 (71.4%)	[29.0, 96.3]
HbA1c decrease >= 1.0%									
Placebo + Insulin	106	7/75 (9.3%)	[3.8, 18.3]	1/31 (3.2%)	[0.1, 16.7]	8/103 (7.8%)	[3.4, 14.7]	0/3	.
Imeglimin 1000 mg bid + Insulin	108	17/68 (25.0%)	[15.3, 37.0]	19/40 (47.5%)	[31.5, 63.9]	33/101 (32.7%)	[23.7, 42.7]	3/7 (42.9%)	[9.9, 81.6]
Percent HbA1c decrease >= 7%									
Placebo + Insulin	106	13/75 (17.3%)	[9.6, 27.8]	9/31 (29.0%)	[14.2, 48.0]	22/103 (21.4%)	[13.9, 30.5]	0/3	.
Imeglimin 1000 mg bid + Insulin	108	30/68 (44.1%)	[32.1, 56.7]	30/40 (75.0%)	[58.8, 87.3]	55/101 (54.5%)	[44.2, 64.4]	5/7 (71.4%)	[29.0, 96.3]

- Abbreviations: bid, Twice a day; CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); LOCF, Last Observation Carried Forward
- m is the total number of subjects with the corresponding category and was used as the denominator to calculate percentage.
- Confidence interval for proportion was calculated with Clopper-Pearson exact method.
- N is the number of patients in the analysis population. Patients who have no HbA1c measurement are defined as non-responders.

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Table E-102 Subgroup Analysis of HbA1c Response at Week 16 (LOCF) by Sex in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Efficacy Population)

		Sex			
Response		Male		Female	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]
HbA1c < 7.0%					
Placebo + Insulin	106	1/68 (1.5%)	[0.0, 7.9]	0/38	.
Imeglimin 1000 mg bid + Insulin	108	6/66 (9.1%)	[3.4, 18.7]	2/42 (4.8%)	[0.6, 16.2]
HbA1c decrease >= 0.5%					
Placebo + Insulin	106	26/68 (38.2%)	[26.7, 50.8]	8/38 (21.1%)	[9.6, 37.3]
Imeglimin 1000 mg bid + Insulin	108	47/66 (71.2%)	[58.7, 81.7]	26/42 (61.9%)	[45.6, 76.4]
HbA1c decrease >= 1.0%					
Placebo + Insulin	106	7/68 (10.3%)	[4.2, 20.1]	1/38 (2.6%)	[0.1, 13.8]
Imeglimin 1000 mg bid + Insulin	108	21/66 (31.8%)	[20.9, 44.4]	15/42 (35.7%)	[21.6, 52.0]
Percent HbA1c decrease >= 7%					
Placebo + Insulin	106	17/68 (25.0%)	[15.3, 37.0]	5/38 (13.2%)	[4.4, 28.1]
Imeglimin 1000 mg bid + Insulin	108	36/66 (54.5%)	[41.8, 66.9]	24/42 (57.1%)	[41.0, 72.3]

- Abbreviations: bid, Twice a day; CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); LOCF, Last Observation Carried Forward
- m is the total number of subjects with the corresponding category and was used as the denominator to calculate percentage.
- Confidence interval for proportion was calculated with Clopper-Pearson exact method.
- N is the number of patients in the analysis population. Patients who have no HbA1c measurement are defined as non-responders.

Control No:<<t-e-102-subrs-020db.sas, 2020-03-06T00:16:41>>

Table E-103 Subgroup Analysis of HbA1c Response at Week 16 (LOCF) by eGFR CKD Stage in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Efficacy Population)

Response		CKD Stage 1		Stage 2	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]
HbA1c < 7.0%					
Placebo + Insulin	106	0/14	.	1/92 (1.1%)	[0.0, 5.9]
Imeglimin 1000 mg bid + Insulin	108	1/16 (6.3%)	[0.2, 30.2]	7/92 (7.6%)	[3.1, 15.1]
HbA1c decrease >= 0.5%					
Placebo + Insulin	106	4/14 (28.6%)	[8.4, 58.1]	30/92 (32.6%)	[23.2, 43.2]
Imeglimin 1000 mg bid + Insulin	108	10/16 (62.5%)	[35.4, 84.8]	63/92 (68.5%)	[58.0, 77.8]
HbA1c decrease >= 1.0%					
Placebo + Insulin	106	2/14 (14.3%)	[1.8, 42.8]	6/92 (6.5%)	[2.4, 13.7]
Imeglimin 1000 mg bid + Insulin	108	5/16 (31.3%)	[11.0, 58.7]	31/92 (33.7%)	[24.2, 44.3]
Percent HbA1c decrease >= 7%					
Placebo + Insulin	106	3/14 (21.4%)	[4.7, 50.8]	19/92 (20.7%)	[12.9, 30.4]
Imeglimin 1000 mg bid + Insulin	108	8/16 (50.0%)	[24.7, 75.3]	52/92 (56.5%)	[45.8, 66.8]

- Abbreviations: bid, Twice a day; CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); LOCF, Last Observation Carried Forward; eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2.
- m is the total number of subjects with the corresponding category and was used as the denominator to calculate percentage.
- Confidence interval for proportion was calculated with Clopper-Pearson exact method.
- N is the number of patients in the analysis population. Patients who have no HbA1c measurement are defined as non-responders.

Control No:<<t-e-103-subrs-020db.sas, 2020-03-06T00:17:32>>

Table E-104 Subgroup Analysis of HbA1c Response at Week 16 (LOCF) by Hepatic Parameter Abnormality in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Efficacy Population)

		Hepatic parameter abnormality			
Response		Yes		No	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]
HbA1c < 7.0%					
Placebo + Insulin	106	0/14	.	1/92 (1.1%)	[0.0, 5.9]
Imeglimin 1000 mg bid + Insulin	108	1/17 (5.9%)	[0.1, 28.7]	7/91 (7.7%)	[3.1, 15.2]
HbA1c decrease >= 0.5%					
Placebo + Insulin	106	7/14 (50.0%)	[23.0, 77.0]	27/92 (29.3%)	[20.3, 39.8]
Imeglimin 1000 mg bid + Insulin	108	11/17 (64.7%)	[38.3, 85.8]	62/91 (68.1%)	[57.5, 77.5]
HbA1c decrease >= 1.0%					
Placebo + Insulin	106	0/14	.	8/92 (8.7%)	[3.8, 16.4]
Imeglimin 1000 mg bid + Insulin	108	7/17 (41.2%)	[18.4, 67.1]	29/91 (31.9%)	[22.5, 42.5]
Percent HbA1c decrease >= 7%					
Placebo + Insulin	106	5/14 (35.7%)	[12.8, 64.9]	17/92 (18.5%)	[11.1, 27.9]
Imeglimin 1000 mg bid + Insulin	108	9/17 (52.9%)	[27.8, 77.0]	51/91 (56.0%)	[45.2, 66.4]

- Abbreviations: bid, Twice a day; CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); LOCF, Last Observation Carried Forward
- Hepatic parameter abnormality is defined as any one of following parameter applied: Total Bilirubin >= 1.6 mg/dL; Aspartate aminotransferase (AST) >= 1.25 x Upper Limit of Normal (ULN); AST >= 50 IU; Alanine aminotransferase (ALT) >= 1.25 x ULN; ALT >= 50 IU; Alkaline phosphatase >= 1.25 x ULN; Gamma glutamyl transferase >= 1.5 x ULN.
- m is the total number of subjects with the corresponding category and was used as the denominator to calculate percentage.
- Confidence interval for proportion was calculated with Clopper-Pearson exact method.
- N is the number of patients in the analysis population. Patients who have no HbA1c measurement are defined as non-responders.

Control No:<<t-e-104-subrs-020db.sas, 2020-03-06T00:17:32>>

Table E-105 Subgroup Analysis of HbA1c Response at Week 52 (LOCF) by Age Group in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Efficacy Population)

Response		Age							
		< 65 years		>= 65 years		< 75 years		>= 75 years	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]	n/m (%)	[95% CI]	n/m (%)	[95% CI]
HbA1c < 7.0%									
Placebo/Imeglimin + Insulin	101	0/72	.	1/29 (3.4%)	[0.1, 17.8]	1/98 (1.0%)	[0.0, 5.6]	0/3	.
Imeglimin/Imeglimin + Insulin	108	4/68 (5.9%)	[1.6, 14.4]	5/40 (12.5%)	[4.2, 26.8]	9/101 (8.9%)	[4.2, 16.2]	0/7	.
Imeglimin + Insulin Total	209	4/140 (2.9%)	[0.8, 7.2]	6/69 (8.7%)	[3.3, 18.0]	10/199 (5.0%)	[2.4, 9.0]	0/10	.
HbA1c decrease >= 0.5%									
Placebo/Imeglimin + Insulin	101	40/72 (55.6%)	[43.4, 67.3]	13/29 (44.8%)	[26.4, 64.3]	53/98 (54.1%)	[43.7, 64.2]	0/3	.
Imeglimin/Imeglimin + Insulin	108	42/68 (61.8%)	[49.2, 73.3]	28/40 (70.0%)	[53.5, 83.4]	67/101 (66.3%)	[56.2, 75.4]	3/7 (42.9%)	[9.9, 81.6]
Imeglimin + Insulin Total	209	82/140 (58.6%)	[49.9, 66.8]	41/69 (59.4%)	[46.9, 71.1]	120/199 (60.3%)	[53.1, 67.2]	3/10 (30.0%)	[6.7, 65.2]
HbA1c decrease >= 1.0%									
Placebo/Imeglimin + Insulin	101	21/72 (29.2%)	[19.0, 41.1]	5/29 (17.2%)	[5.8, 35.8]	26/98 (26.5%)	[18.1, 36.4]	0/3	.
Imeglimin/Imeglimin + Insulin	108	20/68 (29.4%)	[19.0, 41.7]	17/40 (42.5%)	[27.0, 59.1]	34/101 (33.7%)	[24.6, 43.8]	3/7 (42.9%)	[9.9, 81.6]
Imeglimin + Insulin Total	209	41/140 (29.3%)	[21.9, 37.6]	22/69 (31.9%)	[21.2, 44.2]	60/199 (30.2%)	[23.9, 37.0]	3/10 (30.0%)	[6.7, 65.2]
Percent HbA1c decrease >= 7%									
Placebo/Imeglimin + Insulin	101	37/72 (51.4%)	[39.3, 63.3]	12/29 (41.4%)	[23.5, 61.1]	49/98 (50.0%)	[39.7, 60.3]	0/3	.
Imeglimin/Imeglimin + Insulin	108	39/68 (57.4%)	[44.8, 69.3]	27/40 (67.5%)	[50.9, 81.4]	63/101 (62.4%)	[52.2, 71.8]	3/7 (42.9%)	[9.9, 81.6]
Imeglimin + Insulin Total	209	76/140 (54.3%)	[45.7, 62.7]	39/69 (56.5%)	[44.0, 68.4]	112/199 (56.3%)	[49.1, 63.3]	3/10 (30.0%)	[6.7, 65.2]

- Abbreviations: CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); LOCF, Last Observation Carried Forward
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- For "Placebo/Imeglimin + Insulin" group, baseline was defined as last visit with non-missing value prior to or at the day of first dose of Investigational Medicinal Product (IMP) in open-label treatment period. For "Imeglimin/Imeglimin + Insulin" group, baseline was the same as for the double-blind treatment period.
- m is the total number of subjects with the corresponding category and was used as the denominator to calculate percentage.
- Confidence interval for proportion was calculated with Clopper-Pearson exact method.
- N is the number of patients in the analysis population. Patients who have no HbA1c measurement are defined as non-responders.

Control No:<<t-e-105-subrs-020lt.sas, 2020-03-06T00:15:26>>

Table E-106 Subgroup Analysis of HbA1c Response at Week 52 (LOCF) by Sex in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Efficacy Population)

		Sex			
Response		Male		Female	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]
HbA1c < 7.0%					
Placebo/Imeglimin + Insulin	101	1/64 (1.6%)	[0.0, 8.4]	0/37	.
Imeglimin/Imeglimin + Insulin	108	6/66 (9.1%)	[3.4, 18.7]	3/42 (7.1%)	[1.5, 19.5]
Imeglimin + Insulin Total	209	7/130 (5.4%)	[2.2, 10.8]	3/79 (3.8%)	[0.8, 10.7]
HbA1c decrease >= 0.5%					
Placebo/Imeglimin + Insulin	101	26/64 (40.6%)	[28.5, 53.6]	27/37 (73.0%)	[55.9, 86.2]
Imeglimin/Imeglimin + Insulin	108	42/66 (63.6%)	[50.9, 75.1]	28/42 (66.7%)	[50.5, 80.4]
Imeglimin + Insulin Total	209	68/130 (52.3%)	[43.4, 61.1]	55/79 (69.6%)	[58.2, 79.5]
HbA1c decrease >= 1.0%					
Placebo/Imeglimin + Insulin	101	12/64 (18.8%)	[10.1, 30.5]	14/37 (37.8%)	[22.5, 55.2]
Imeglimin/Imeglimin + Insulin	108	21/66 (31.8%)	[20.9, 44.4]	16/42 (38.1%)	[23.6, 54.4]
Imeglimin + Insulin Total	209	33/130 (25.4%)	[18.2, 33.8]	30/79 (38.0%)	[27.3, 49.6]
Percent HbA1c decrease >= 7%					
Placebo/Imeglimin + Insulin	101	25/64 (39.1%)	[27.1, 52.1]	24/37 (64.9%)	[47.5, 79.8]
Imeglimin/Imeglimin + Insulin	108	41/66 (62.1%)	[49.3, 73.8]	25/42 (59.5%)	[43.3, 74.4]
Imeglimin + Insulin Total	209	66/130 (50.8%)	[41.9, 59.6]	49/79 (62.0%)	[50.4, 72.7]

- Abbreviations: CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); LOCF, Last Observation Carried Forward
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- For "Placebo/Imeglimin + Insulin" group, baseline was defined as last visit with non-missing value prior to or at the day of first dose of Investigational Medicinal Product (IMP) in open-label treatment period. For "Imeglimin/Imeglimin + Insulin" group, baseline was the same as for the double-blind treatment period.
- m is the total number of subjects with the corresponding category and was used as the denominator to calculate percentage.
- Confidence interval for proportion was calculated with Clopper-Pearson exact method.
- N is the number of patients in the analysis population. Patients who have no HbA1c measurement are defined as non-responders.

Control No:<<t-e-106-subrs-020lt.sas, 2020-03-06T00:15:32>>

Table E-107 Subgroup Analysis of HbA1c Response at Week 52 (LOCF) by eGFR CKD Stage in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Efficacy Population)

Response		CKD Stage 1		Stage 2	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]
HbA1c < 7.0%					
Placebo/Imeglimin + Insulin	101	0/13	.	1/88 (1.1%)	[0.0, 6.2]
Imeglimin/Imeglimin + Insulin	108	1/16 (6.3%)	[0.2, 30.2]	8/92 (8.7%)	[3.8, 16.4]
Imeglimin + Insulin Total	209	1/29 (3.4%)	[0.1, 17.8]	9/180 (5.0%)	[2.3, 9.3]
HbA1c decrease >= 0.5%					
Placebo/Imeglimin + Insulin	101	6/13 (46.2%)	[19.2, 74.9]	47/88 (53.4%)	[42.5, 64.1]
Imeglimin/Imeglimin + Insulin	108	11/16 (68.8%)	[41.3, 89.0]	59/92 (64.1%)	[53.5, 73.9]
Imeglimin + Insulin Total	209	17/29 (58.6%)	[38.9, 76.5]	106/180 (58.9%)	[51.3, 66.2]
HbA1c decrease >= 1.0%					
Placebo/Imeglimin + Insulin	101	4/13 (30.8%)	[9.1, 61.4]	22/88 (25.0%)	[16.4, 35.4]
Imeglimin/Imeglimin + Insulin	108	5/16 (31.3%)	[11.0, 58.7]	32/92 (34.8%)	[25.1, 45.4]
Imeglimin + Insulin Total	209	9/29 (31.0%)	[15.3, 50.8]	54/180 (30.0%)	[23.4, 37.3]
Percent HbA1c decrease >= 7%					
Placebo/Imeglimin + Insulin	101	5/13 (38.5%)	[13.9, 68.4]	44/88 (50.0%)	[39.1, 60.9]
Imeglimin/Imeglimin + Insulin	108	10/16 (62.5%)	[35.4, 84.8]	56/92 (60.9%)	[50.1, 70.9]
Imeglimin + Insulin Total	209	15/29 (51.7%)	[32.5, 70.6]	100/180 (55.6%)	[48.0, 62.9]

- Abbreviations: CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); LOCF, Last Observation Carried Forward; eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- For "Placebo/Imeglimin + Insulin" group, baseline was defined as last visit with non-missing value prior to or at the day of first dose of Investigational Medicinal Product (IMP) in open-label treatment period. For "Imeglimin/Imeglimin + Insulin" group, baseline was the same as for the double-blind treatment period.
- m is the total number of subjects with the corresponding category and was used as the denominator to calculate percentage.
- Confidence interval for proportion was calculated with Clopper-Pearson exact method.
- N is the number of patients in the analysis population. Patients who have no HbA1c measurement are defined as non-responders.

Control No:<<t-e-107-subrs-020lt.sas, 2020-03-06T00:15:43>>

Table E-108 Subgroup Analysis of HbA1c Response at Week 52 (LOCF) by Hepatic Parameter Abnormality in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Efficacy Population)

		Hepatic parameter abnormality			
Response		Yes		No	
Treatment	N	n/m (%)	[95% CI]	n/m (%)	[95% CI]
HbA1c < 7.0%					
Placebo/Imeglimin + Insulin	101	1/14 (7.1%)	[0.2, 33.9]	0/87	.
Imeglimin/Imeglimin + Insulin	108	1/17 (5.9%)	[0.1, 28.7]	8/91 (8.8%)	[3.9, 16.6]
Imeglimin + Insulin Total	209	2/31 (6.5%)	[0.8, 21.4]	8/178 (4.5%)	[2.0, 8.7]
HbA1c decrease >= 0.5%					
Placebo/Imeglimin + Insulin	101	8/14 (57.1%)	[28.9, 82.3]	45/87 (51.7%)	[40.8, 62.6]
Imeglimin/Imeglimin + Insulin	108	13/17 (76.5%)	[50.1, 93.2]	57/91 (62.6%)	[51.9, 72.6]
Imeglimin + Insulin Total	209	21/31 (67.7%)	[48.6, 83.3]	102/178 (57.3%)	[49.7, 64.7]
HbA1c decrease >= 1.0%					
Placebo/Imeglimin + Insulin	101	7/14 (50.0%)	[23.0, 77.0]	19/87 (21.8%)	[13.7, 32.0]
Imeglimin/Imeglimin + Insulin	108	5/17 (29.4%)	[10.3, 56.0]	32/91 (35.2%)	[25.4, 45.9]
Imeglimin + Insulin Total	209	12/31 (38.7%)	[21.8, 57.8]	51/178 (28.7%)	[22.1, 35.9]
Percent HbA1c decrease >= 7%					
Placebo/Imeglimin + Insulin	101	8/14 (57.1%)	[28.9, 82.3]	41/87 (47.1%)	[36.3, 58.1]
Imeglimin/Imeglimin + Insulin	108	11/17 (64.7%)	[38.3, 85.8]	55/91 (60.4%)	[49.6, 70.5]
Imeglimin + Insulin Total	209	19/31 (61.3%)	[42.2, 78.2]	96/178 (53.9%)	[46.3, 61.4]

- Abbreviations: CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); LOCF, Last Observation Carried Forward
- Hepatic parameter abnormality is defined as any one of following parameter applied: Total Bilirubin >= 1.6 mg/dL; Aspartate aminotransferase (AST) >= 1.25 x Upper Limit of Normal (ULN); AST >= 50 IU; Alanine aminotransferase (ALT) >= 1.25 x ULN; ALT >= 50 IU; Alkaline phosphatase >= 1.25 x ULN; Gamma glutamyl transferase >= 1.5 x ULN.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- For "Placebo/Imeglimin + Insulin" group, baseline was defined as last visit with non-missing value prior to or at the day of first dose of Investigational Medicinal Product (IMP) in open-label treatment period. For "Imeglimin/Imeglimin + Insulin" group, baseline was the same as for the double-blind treatment period.
- m is the total number of subjects with the corresponding category and was used as the denominator to calculate percentage.
- Confidence interval for proportion was calculated with Clopper-Pearson exact method.
- N is the number of patients in the analysis population. Patients who have no HbA1c measurement are defined as non-responders.

Control No:<<t-e-108-subrs-020lt.sas, 2020-03-06T00:16:23>>

Table E-109 Summary of Percent Change from Baseline in Lipid Parameters to All Visits in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Efficacy Population)

Parameter Treatment Visit	Observed n	 Mean (SD)	Percent change from baseline Mean (SD)	 [95% CI]	Paired t-test P-value
Total Cholesterol (mmol/L)					
Placebo/Imeglimin + Insulin (N = 101)					
Baseline	101	4.978 (0.7958)			
Week 20	98	5.181 (0.8440)	4.786 (14.0939)	[1.9606, 7.6120]	0.0011
Week 36	93	5.058 (0.8314)	1.929 (12.7593)	[-0.6989, 4.5566]	0.1483
LOCF Endpoint	98	5.054 (0.8187)	2.200 (12.7119)	[-0.3482, 4.7489]	0.0898
Imeglimin/Imeglimin + Insulin (N = 108)					
Baseline	108	4.827 (0.8942)			
Week 16	107	4.988 (0.8956)	4.329 (14.0910)	[1.6287, 7.0302]	0.0019
Week 36	105	4.938 (0.8615)	3.999 (15.2584)	[1.0465, 6.9522]	0.0084
Week 52	103	4.914 (0.9194)	3.458 (14.6085)	[0.6031, 6.3132]	0.0181
LOCF Endpoint	107	4.952 (0.9283)	3.371 (14.4611)	[0.5995, 6.1429]	0.0176
Imeglimin + Insulin Total (N = 209)					
Baseline	209	4.900 (0.8494)			
Week 16	107	4.988 (0.8956)	4.329 (14.0910)	[1.6287, 7.0302]	0.0019
Week 20	98	5.181 (0.8440)	4.786 (14.0939)	[1.9606, 7.6120]	0.0011
Week 36	198	4.994 (0.8475)	3.027 (14.1425)	[1.0448, 5.0089]	0.0029
Week 52	103	4.914 (0.9194)	3.458 (14.6085)	[0.6031, 6.3132]	0.0181
LOCF Endpoint	205	5.000 (0.8770)	2.811 (13.6324)	[0.9342, 4.6888]	0.0035
LDL-C (mmol/L)					
Placebo/Imeglimin + Insulin (N = 101)					
Baseline	101	2.945 (0.7142)			
Week 20	98	3.094 (0.7100)	7.796 (20.9863)	[3.5884, 12.0033]	0.0004
Week 36	93	2.973 (0.7301)	3.092 (20.2575)	[-1.0800, 7.2640]	0.1444
LOCF Endpoint	98	2.975 (0.7204)	3.478 (20.2103)	[-0.5737, 7.5301]	0.0916
Imeglimin/Imeglimin + Insulin (N = 108)					
Baseline	108	2.724 (0.7794)			
Week 16	107	2.934 (0.8433)	9.777 (23.5059)	[5.2719, 14.2825]	<.0001
Week 36	105	2.867 (0.7159)	9.283 (24.3610)	[4.5681, 13.9970]	0.0002
Week 52	103	2.846 (0.8057)	7.933 (23.4541)	[3.3489, 12.5166]	0.0009
LOCF Endpoint	107	2.891 (0.8358)	7.924 (23.2120)	[3.4750, 12.3728]	0.0006
Imeglimin + Insulin Total (N = 209)					
Baseline	209	2.831 (0.7549)			
Week 16	107	2.934 (0.8433)	9.777 (23.5059)	[5.2719, 14.2825]	<.0001
Week 20	98	3.094 (0.7100)	7.796 (20.9863)	[3.5884, 12.0033]	0.0004
Week 36	198	2.917 (0.7227)	6.375 (22.6834)	[3.1958, 9.5539]	0.0001
Week 52	103	2.846 (0.8057)	7.933 (23.4541)	[3.3489, 12.5166]	0.0009
LOCF Endpoint	205	2.931 (0.7820)	5.799 (21.8892)	[2.7843, 8.8129]	0.0002
HDL-C (mmol/L)					

Parameter Treatment Visit	Observed n	Mean (SD)	Percent change from baseline Mean (SD)	[95% CI]	Paired t-test P-value
Placebo/Imeglimin + Insulin (N = 101)					
Baseline	101	1.443 (0.4231)			
Week 20	98	1.450 (0.4126)	0.571 (13.4163)	[-2.1190, 3.2606]	0.6745
Week 36	93	1.379 (0.4130)	-4.486 (12.8854)	[-7.1400, -1.8326]	0.0011
LOCF Endpoint	98	1.389 (0.4084)	-3.944 (13.0223)	[-6.5545, -1.3329]	0.0035
Imeglimin/Imeglimin + Insulin (N = 108)					
Baseline	108	1.412 (0.3975)			
Week 16	107	1.403 (0.3838)	0.395 (12.0841)	[-1.9215, 2.7107]	0.7362
Week 36	105	1.437 (0.4376)	2.060 (14.4489)	[-0.7360, 4.8565]	0.1470
Week 52	103	1.401 (0.4011)	-0.256 (13.1469)	[-2.8257, 2.3131]	0.8436
LOCF Endpoint	107	1.394 (0.4054)	-0.505 (13.0562)	[-3.0078, 1.9970]	0.6897
Imeglimin + Insulin Total (N = 209)					
Baseline	209	1.427 (0.4094)			
Week 16	107	1.403 (0.3838)	0.395 (12.0841)	[-1.9215, 2.7107]	0.7362
Week 20	98	1.450 (0.4126)	0.571 (13.4163)	[-2.1190, 3.2606]	0.6745
Week 36	198	1.409 (0.4261)	-1.015 (14.0884)	[-2.9891, 0.9598]	0.3121
Week 52	103	1.401 (0.4011)	-0.256 (13.1469)	[-2.8257, 2.3131]	0.8436
LOCF Endpoint	205	1.391 (0.4058)	-2.149 (13.1214)	[-3.9560, -0.3422]	0.0200
Triglycerides (mmol/L)					
Placebo/Imeglimin + Insulin (N = 101)					
Baseline	101	1.330 (0.8662)			
Week 20	98	1.441 (1.3020)	13.031 (54.6041)	[2.0839, 23.9788]	0.0201
Week 36	93	1.600 (1.3339)	25.372 (66.8211)	[11.6101, 39.1334]	0.0004
LOCF Endpoint	98	1.563 (1.3103)	24.008 (65.6099)	[10.8541, 37.1620]	0.0005
Imeglimin/Imeglimin + Insulin (N = 108)					
Baseline	108	1.450 (0.7730)			
Week 16	107	1.433 (0.8857)	4.033 (42.0373)	[-4.0245, 12.0896]	0.3233
Week 36	105	1.422 (1.0489)	7.056 (62.6269)	[-5.0637, 19.1760]	0.2509
Week 52	103	1.461 (0.7992)	11.116 (55.7604)	[0.2178, 22.0134]	0.0457
LOCF Endpoint	107	1.459 (0.7938)	9.841 (55.1052)	[-0.7210, 20.4024]	0.0675
Imeglimin + Insulin Total (N = 209)					
Baseline	209	1.392 (0.8196)			
Week 16	107	1.433 (0.8857)	4.033 (42.0373)	[-4.0245, 12.0896]	0.3233
Week 20	98	1.441 (1.3020)	13.031 (54.6041)	[2.0839, 23.9788]	0.0201
Week 36	198	1.506 (1.1915)	15.659 (65.1134)	[6.5333, 24.7845]	0.0009
Week 52	103	1.461 (0.7992)	11.116 (55.7604)	[0.2178, 22.0134]	0.0457
LOCF Endpoint	205	1.509 (1.0708)	16.613 (60.6216)	[8.2654, 24.9614]	0.0001

- Abbreviations: LOCF, Last Observation Carried Forward; SD, standard deviation; CI, confidence interval; LDL, Low Density Lipoprotein; LDL-C, LDL Cholesterol; HDL, High Density Lipoprotein; HDL-C, HDL Cholesterol
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- For "Placebo/Imeglimin + Insulin" group, baseline was defined as last visit with non-missing value prior to or at the day of first dose of Investigational Medicinal Product (IMP) in open-label treatment period. For "Imeglimin/Imeglimin + Insulin" group, baseline was the same as for the double-blind treatment period.

Table E-501 Baseline Value of HbA1c (%) by Subgroup in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Efficacy Population)

Parameter	Study 014								Study 018				Pooled (Studies 014+018)			
	Placebo		Imeglimin 500 mg bid		Imeglimin 1000 mg bid		Imeglimin 1500 mg bid		Placebo		Imeglimin 1000 mg bid		Placebo		Imeglimin 1000 mg bid	
Subgroup	N = 75		N = 75		N = 73		N = 73		N = 106		N = 106		N = 181		N = 179	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
HbA1c (%)																
Population																
All	75	7.89 (0.676)	75	7.94 (0.679)	73	7.85 (0.650)	73	7.91 (0.618)	106	7.93 (0.684)	106	7.99 (0.764)	181	7.91 (0.679)	179	7.93 (0.721)
Age group																
< 65 years	47	7.97 (0.719)	54	8.01 (0.736)	43	7.91 (0.746)	46	8.02 (0.633)	58	7.99 (0.682)	54	8.10 (0.807)	105	7.98 (0.696)	97	8.01 (0.782)
>= 65 years	28	7.75 (0.583)	21	7.76 (0.477)	30	7.75 (0.476)	27	7.72 (0.553)	48	7.86 (0.686)	52	7.88 (0.708)	76	7.82 (0.648)	82	7.84 (0.633)
< 75 years	75	7.89 (0.676)	75	7.94 (0.679)	71	7.84 (0.657)	73	7.91 (0.618)	93	7.94 (0.658)	99	8.00 (0.771)	168	7.92 (0.664)	170	7.93 (0.728)
>= 75 years	0	.	0	.	2	8.15 (0.071)	0	.	13	7.87 (0.875)	7	7.94 (0.700)	13	7.87 (0.875)	9	7.99 (0.613)
Sex																
Male	49	7.85 (0.690)	49	7.98 (0.681)	48	7.87 (0.668)	52	7.90 (0.601)	77	7.88 (0.638)	89	8.06 (0.774)	126	7.87 (0.657)	137	8.00 (0.741)
Female	26	7.97 (0.654)	26	7.87 (0.685)	25	7.80 (0.624)	21	7.93 (0.671)	29	8.06 (0.789)	17	7.63 (0.608)	55	8.01 (0.723)	42	7.73 (0.616)
eGFR CKD Stage																
Stage 1	9	7.86 (0.505)	9	8.19 (0.914)	9	7.90 (0.456)	14	7.89 (0.552)	7	8.31 (0.958)	12	8.28 (0.607)	16	8.06 (0.747)	21	8.12 (0.569)
Stage 2	55	7.94 (0.721)	56	7.88 (0.674)	57	7.82 (0.695)	51	7.93 (0.640)	81	7.92 (0.650)	73	7.98 (0.822)	136	7.93 (0.677)	130	7.91 (0.770)
Stage 3a	11	7.68 (0.555)	10	8.04 (0.425)	7	7.97 (0.506)	8	7.84 (0.648)	18	7.84 (0.707)	21	7.88 (0.600)	29	7.78 (0.648)	28	7.90 (0.570)
Hepatic parameter abnormality																

Parameter / Subgroup / Category	Study 014 Placebo N = 75 n	Mean (SD)	Imeglimin 500 mg bid N = 75 n	Mean (SD)	Imeglimin 1000 mg bid N = 73 n	Mean (SD)	Imeglimin 1500 mg bid N = 73 n	Mean (SD)	Study 018 Placebo N = 106 n	Mean (SD)	Imeglimin 1000 mg bid N = 106 n	Mean (SD)	Pooled (Studies 014+018) Placebo N = 181 n	Mean (SD)	Imeglimin 1000 mg bid N = 179 n	Mean (SD)
Yes	14	7.86 (0.732)	14	7.86 (0.642)	14	7.99 (0.885)	14	8.08 (0.549)	17	8.05 (0.932)	10	8.14 (0.810)	31	7.96 (0.839)	24	8.05 (0.840)
No	61	7.90 (0.669)	61	7.96 (0.691)	59	7.81 (0.586)	59	7.87 (0.630)	89	7.91 (0.630)	96	7.98 (0.762)	150	7.90 (0.644)	155	7.91 (0.702)
BMI at baseline																
< 25 kg/m2	36	7.94 (0.779)	39	7.87 (0.591)	39	7.61 (0.492)	26	7.72 (0.621)	58	7.99 (0.727)	51	7.90 (0.709)	94	7.97 (0.744)	90	7.78 (0.638)
>= 25 kg/m2	39	7.84 (0.571)	36	8.01 (0.765)	34	8.11 (0.710)	47	8.02 (0.595)	48	7.85 (0.625)	55	8.07 (0.809)	87	7.85 (0.598)	89	8.09 (0.769)
>= 25 to < 30 kg/m2	25	7.82 (0.522)	22	7.88 (0.665)	26	8.13 (0.727)	33	7.97 (0.620)	39	7.83 (0.650)	39	8.02 (0.853)	64	7.83 (0.599)	65	8.07 (0.801)
>= 30 kg/m2	14	7.88 (0.669)	14	8.23 (0.884)	8	8.05 (0.695)	14	8.13 (0.538)	9	7.96 (0.525)	16	8.21 (0.697)	23	7.91 (0.605)	24	8.15 (0.685)
HbA1c at baseline																
< 8.0%	45	7.45 (0.268)	47	7.51 (0.311)	44	7.43 (0.298)	42	7.47 (0.295)	61	7.45 (0.272)	63	7.45 (0.300)	106	7.45 (0.269)	107	7.44 (0.298)
>= 8.0%	30	8.55 (0.557)	28	8.66 (0.479)	29	8.48 (0.505)	31	8.50 (0.405)	45	8.58 (0.516)	43	8.79 (0.470)	75	8.57 (0.529)	72	8.67 (0.505)
>= 8.0 to < 9.0%	23	8.30 (0.272)	20	8.42 (0.292)	24	8.30 (0.285)	28	8.42 (0.321)	36	8.36 (0.264)	26	8.47 (0.241)	59	8.34 (0.267)	50	8.39 (0.275)
>= 9.0%	7	9.39 (0.406)	8	9.29 (0.173)	5	9.38 (0.319)	3	9.27 (0.306)	9	9.44 (0.324)	17	9.28 (0.263)	16	9.42 (0.351)	22	9.30 (0.272)
Duration of type 2 diabetes																
< 5 years	39	7.92 (0.716)	32	7.76 (0.688)	36	8.03 (0.735)	41	7.93 (0.621)	50	7.80 (0.581)	40	7.98 (0.827)	89	7.85 (0.642)	76	8.00 (0.780)
>= 5 years	36	7.86 (0.639)	43	8.07 (0.649)	37	7.67 (0.506)	32	7.88 (0.622)	56	8.05 (0.750)	66	8.00 (0.729)	92	7.98 (0.710)	103	7.88 (0.674)
Complication of diabetes																
Yes	18	7.80 (0.584)	17	8.13 (0.627)	17	7.95 (0.744)	15	8.07 (0.597)	13	8.11 (0.514)	14	8.01 (0.778)	31	7.93 (0.568)	31	7.98 (0.747)

Parameter / Subgroup / Category	Study 014 Placebo N = 75 n	Mean (SD)	Imeglimin 500 mg bid N = 75 n	Mean (SD)	Imeglimin 1000 mg bid N = 73 n	Mean (SD)	Imeglimin 1500 mg bid N = 73 n	Mean (SD)	Study 018 Placebo N = 106 n	Mean (SD)	Imeglimin 1000 mg bid N = 106 n	Mean (SD)	Pooled (Studies 014+018) Placebo N = 181 n	Mean (SD)	Imeglimin 1000 mg bid N = 179 n	Mean (SD)
No	57	7.92 (0.705)	58	7.88 (0.689)	56	7.81 (0.622)	58	7.87 (0.621)	93	7.90 (0.703)	92	7.99 (0.766)	150	7.91 (0.701)	148	7.92 (0.718)
Metabolic syndrome at baseline																
Yes	41	7.96 (0.725)	35	7.93 (0.736)	24	8.04 (0.623)	44	7.93 (0.650)	43	7.99 (0.711)	53	8.18 (0.810)	84	7.98 (0.713)	77	8.14 (0.755)
No	34	7.81 (0.611)	40	7.95 (0.635)	49	7.75 (0.648)	29	7.88 (0.574)	63	7.89 (0.667)	53	7.81 (0.671)	97	7.86 (0.646)	102	7.78 (0.657)
Previous treatment status																
Treatment naive	34	7.75 (0.638)	33	7.75 (0.686)	33	7.65 (0.548)	29	7.82 (0.666)	77	7.85 (0.614)	76	7.94 (0.765)	111	7.82 (0.621)	109	7.85 (0.717)
Previously treated	41	8.01 (0.690)	42	8.08 (0.646)	40	8.01 (0.687)	44	7.97 (0.584)	29	8.13 (0.817)	30	8.14 (0.753)	70	8.06 (0.742)	70	8.07 (0.713)
FPG at baseline																
< 160 mg/dL	44	7.71 (0.611)	40	7.64 (0.563)	38	7.54 (0.469)	39	7.65 (0.498)	61	7.66 (0.500)	50	7.48 (0.443)	105	7.68 (0.547)	88	7.50 (0.453)
>= 160 mg/dL	31	8.15 (0.688)	35	8.28 (0.645)	35	8.18 (0.657)	34	8.21 (0.614)	45	8.30 (0.728)	56	8.45 (0.693)	76	8.24 (0.711)	91	8.35 (0.689)
HOMA-IR at baseline																
< 2.5	27	7.77 (0.658)	32	7.79 (0.663)	34	7.56 (0.437)	22	7.66 (0.499)	64	7.89 (0.608)	67	7.79 (0.711)	91	7.85 (0.622)	101	7.71 (0.640)
>= 2.5 to < 4.0	20	7.79 (0.534)	16	7.89 (0.555)	16	7.84 (0.507)	13	7.68 (0.419)	27	7.92 (0.830)	20	8.35 (0.823)	47	7.87 (0.715)	36	8.12 (0.736)
>= 4.0	27	8.04 (0.745)	27	8.15 (0.732)	23	8.27 (0.776)	38	8.13 (0.660)	15	8.12 (0.718)	19	8.33 (0.654)	42	8.07 (0.728)	42	8.30 (0.715)
Missing	1	9.10 (.)	0	.	0	.	0	.	0	.	0	.	1	9.10 (.)	0	.
HOMA-B at baseline																
< 30.0%	34	8.08 (0.762)	43	7.93 (0.692)	48	7.84 (0.647)	32	7.92 (0.626)	78	8.03 (0.710)	85	8.03 (0.788)	112	8.04 (0.723)	133	7.96 (0.743)

Parameter Subgroup	Study 014 Placebo N = 75		Imeglimin 500 mg bid N = 75		Imeglimin 1000 mg bid N = 73		Imeglimin 1500 mg bid N = 73		Study 018 Placebo N = 106		Imeglimin 1000 mg bid N = 106		Pooled (Studies 014+018) Placebo N = 181		Imeglimin 1000 mg bid N = 179	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
>= 30.0%	40	7.71 (0.522)	32	7.95 (0.672)	25	7.85 (0.669)	41	7.90 (0.619)	28	7.65 (0.517)	21	7.85 (0.655)	68	7.68 (0.517)	46	7.85 (0.655)
Missing	1	9.10 (.)	0	.	0	.	0	.	0	.	0	.	1	9.10 (.)	0	.
QUICKI at baseline																
< 0.33	44	7.96 (0.671)	41	8.06 (0.685)	38	8.10 (0.714)	47	8.06 (0.634)	37	8.03 (0.804)	31	8.40 (0.658)	81	7.99 (0.731)	69	8.24 (0.701)
>= 0.33	30	7.75 (0.648)	34	7.79 (0.652)	35	7.57 (0.437)	26	7.63 (0.487)	69	7.88 (0.609)	75	7.82 (0.743)	99	7.84 (0.621)	110	7.74 (0.670)
Missing	1	9.10 (.)	0	.	0	.	0	.	0	.	0	.	1	9.10 (.)	0	.
HOMA-B x HOMA-IR at baseline																
< 30.0%, < 2.5	24	7.86 (0.639)	30	7.82 (0.669)	32	7.58 (0.443)	20	7.71 (0.500)	61	7.91 (0.615)	62	7.81 (0.733)	85	7.90 (0.618)	94	7.73 (0.656)
< 30.0%, >= 2.5 to < 4.0	7	8.20 (0.523)	9	7.86 (0.403)	9	8.06 (0.442)	7	7.83 (0.355)	14	8.41 (0.889)	15	8.68 (0.619)	21	8.34 (0.778)	24	8.45 (0.630)
< 30.0%, >= 4.0	3	9.50 (0.656)	4	8.88 (0.793)	7	8.79 (0.724)	5	8.90 (0.464)	3	8.73 (0.874)	8	8.46 (0.686)	6	9.12 (0.808)	15	8.61 (0.699)
>= 30.0%, < 2.5	3	7.03 (0.115)	2	7.25 (0.212)	2	7.25 (0.071)	2	7.20 (0.141)	3	7.47 (0.115)	5	7.52 (0.259)	6	7.25 (0.259)	7	7.44 (0.251)
>= 30.0%, >= 2.5 to < 4.0	13	7.57 (0.405)	7	7.93 (0.741)	7	7.57 (0.479)	6	7.50 (0.447)	13	7.40 (0.258)	5	7.34 (0.439)	26	7.48 (0.344)	12	7.48 (0.458)
>= 30.0%, >= 4.0	24	7.86 (0.529)	23	8.02 (0.660)	16	8.05 (0.705)	33	8.02 (0.610)	12	7.97 (0.624)	11	8.23 (0.644)	36	7.90 (0.556)	27	8.12 (0.674)
Missing	1	9.10 (.)	0	.	0	.	0	.	0	.	0	.	1	9.10 (.)	0	.
HOMA-B x QUICKI at baseline																
< 30.0%, < 0.33	9	8.62 (0.863)	12	8.16 (0.742)	15	8.40 (0.690)	9	8.48 (0.632)	14	8.57 (0.877)	18	8.61 (0.608)	23	8.59 (0.852)	33	8.51 (0.645)
< 30.0%, >= 0.33	25	7.88 (0.632)	31	7.84 (0.663)	33	7.59 (0.443)	23	7.70 (0.479)	64	7.91 (0.615)	67	7.87 (0.761)	89	7.90 (0.616)	100	7.78 (0.683)

Parameter Subgroup	Study 014 Placebo N = 75		Imeglimin 500 mg bid N = 75		Imeglimin 1000 mg bid N = 73		Imeglimin 1500 mg bid N = 73		Study 018 Placebo N = 106		Imeglimin 1000 mg bid N = 106		Pooled (Studies 014+018) Placebo N = 181		Imeglimin 1000 mg bid N = 179	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
>= 30.0%, < 0.33	35	7.79 (0.498)	29	8.02 (0.669)	23	7.90 (0.672)	38	7.96 (0.601)	23	7.70 (0.548)	13	8.12 (0.641)	58	7.75 (0.516)	36	7.98 (0.661)
>= 30.0%, >= 0.33	5	7.10 (0.141)	3	7.30 (0.173)	2	7.25 (0.071)	3	7.13 (0.153)	5	7.44 (0.297)	8	7.40 (0.393)	10	7.27 (0.283)	10	7.37 (0.353)
Missing	1	9.10 (.)	0	.	0	.	0	.	0	.	0	.	1	9.10 (.)	0	.

- Abbreviations: bid, Twice a day; SD, standard deviation; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); BMI, body mass index; eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease; FPG, Fasting Plasma Glucose; HOMA, Homeostasis model assessment; HOMA-IR, HOMA of insulin resistance; HOMA-B, HOMA of beta-cell function; QUICKI, Quantitative Insulin Sensitivity Check Index
- Complication of diabetes is defined as any MedDRA Preferred Term (PT) of medical history which are included in High-Level Group Term (HLGT) of diabetic complication.
- Metabolic Syndrome is defined as an excessive waist circumference (>= 85 cm in men and >= 90 cm in women) as well as the presence of two or more of the following symptoms: (1) Hypertension: systolic blood pressure >= 130 mmHg, or diastolic blood pressure >= 85 mmHg; (2) Glucose intolerance: fasting glucose >= 110 mg/dL; (3) Dyslipidemia: triglyceride >= 150 mg/dL, or HDL cholesterol < 40 mg/dL.
- Hepatic parameter abnormality is defined as any one of following parameter applied: Total Bilirubin >= 1.6 mg/dL; Aspartate aminotransferase (AST) >= 1.25 x Upper Limit of Normal (ULN); AST >= 50 IU; Alanine aminotransferase (ALT) >= 1.25 x ULN; ALT >= 50 IU; Alkaline phosphatase >= 1.25 x ULN; Gamma glutamyl transferase >= 1.5 x ULN.
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2, CKD Stage 3a includes subjects with eGFR >= 45 to < 60 mL/min/1.73m2.

Control No:<<t-e-501-subhb-24wdb.sas, 2020-03-09T15:51:47>>

Table E-502 Baseline Value of Fasting Plasma Glucose (mg/dL) by Subgroup in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Efficacy Population)

Parameter	Study 014								Study 018				Pooled (Studies 014+018)			
	Placebo		Imeglimin 500 mg bid		Imeglimin 1000 mg bid		Imeglimin 1500 mg bid		Placebo		Imeglimin 1000 mg bid		Placebo		Imeglimin 1000 mg bid	
Subgroup	N = 75		N = 75		N = 73		N = 73		N = 106		N = 106		N = 181		N = 179	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Fasting Plasma Glucose (mg/dL)																
Population																
All	75	160.44 (30.385)	75	164.51 (31.747)	73	163.44 (31.001)	73	164.79 (31.465)	106	159.49 (24.684)	106	163.72 (28.590)	181	159.88 (27.115)	179	163.61 (29.511)
Age group																
< 65 years	47	167.47 (33.041)	54	166.93 (33.969)	43	167.91 (35.301)	46	166.87 (34.318)	58	162.82 (23.699)	54	169.15 (29.303)	105	164.90 (28.215)	97	168.60 (31.932)
>= 65 years	28	148.64 (20.977)	21	158.29 (24.793)	30	157.03 (22.566)	27	161.26 (26.128)	48	155.46 (25.491)	52	158.09 (26.963)	76	152.95 (24.012)	82	157.70 (25.304)
< 75 years	75	160.44 (30.385)	75	164.51 (31.747)	71	163.10 (31.216)	73	164.79 (31.465)	93	160.47 (24.552)	99	164.23 (29.124)	168	160.46 (27.224)	170	163.76 (29.930)
>= 75 years	0	.	0	.	2	175.50 (26.163)	0	.	13	152.44 (25.473)	7	156.48 (19.609)	13	152.44 (25.473)	9	160.71 (21.079)
Sex																
Male	49	162.82 (32.734)	49	166.65 (30.876)	48	166.42 (34.003)	52	166.48 (25.100)	77	159.54 (23.726)	89	167.16 (27.910)	126	160.82 (27.500)	137	166.90 (30.062)
Female	26	155.96 (25.368)	26	160.46 (33.567)	25	157.72 (23.814)	21	160.62 (43.953)	29	159.34 (27.515)	17	145.71 (25.872)	55	157.75 (26.332)	42	152.86 (25.075)
eGFR CKD Stage																
Stage 1	9	165.22 (26.475)	9	163.33 (31.129)	9	177.56 (31.381)	14	152.00 (22.278)	7	161.37 (21.057)	12	166.34 (27.797)	16	163.54 (23.561)	21	171.15 (29.175)
Stage 2	55	160.75 (31.863)	56	164.73 (32.815)	57	162.30 (32.306)	51	167.43 (30.359)	81	159.00 (24.429)	73	165.97 (28.787)	136	159.71 (27.577)	130	164.36 (30.314)
Stage 3a	11	155.00 (27.111)	10	164.30 (29.037)	7	154.57 (8.696)	8	170.38 (47.584)	18	160.94 (28.175)	21	154.42 (27.741)	29	158.69 (27.442)	28	154.46 (24.225)
Hepatic parameter abnormality																

Parameter Subgroup Category	Study 014 Placebo N = 75 n	Mean (SD)	Imeglimin 500 mg bid N = 75 n	Mean (SD)	Imeglimin 1000 mg bid N = 73 n	Mean (SD)	Imeglimin 1500 mg bid N = 73 n	Mean (SD)	Study 018 Placebo N = 106 n	Mean (SD)	Imeglimin 1000 mg bid N = 106 n	Mean (SD)	Pooled (Studies 014+018) Placebo N = 181 n	Mean (SD)	Imeglimin 1000 mg bid N = 179 n	Mean (SD)
Yes	14	150.64 (14.431)	14	168.14 (34.977)	14	170.36 (32.818)	14	171.64 (27.171)	17	165.64 (28.673)	10	168.45 (28.978)	31	158.87 (24.213)	24	169.56 (30.631)
No	61	162.69 (32.649)	61	163.67 (31.211)	59	161.80 (30.616)	59	163.17 (32.396)	89	158.31 (23.851)	96	163.23 (28.658)	150	160.09 (27.747)	155	162.68 (29.328)
BMI at baseline																
< 25 kg/m2	36	161.14 (35.805)	39	153.38 (19.965)	39	154.59 (25.737)	26	155.31 (28.836)	58	158.10 (25.708)	51	161.75 (29.199)	94	159.27 (29.828)	90	158.65 (27.831)
>= 25 kg/m2	39	159.79 (24.823)	36	176.56 (37.562)	34	173.59 (33.696)	47	170.04 (31.917)	48	161.16 (23.548)	55	165.55 (28.158)	87	160.55 (23.995)	89	168.62 (30.459)
>= 25 to < 30 kg/m2	25	159.68 (27.146)	22	171.23 (36.879)	26	173.42 (32.426)	33	175.09 (33.544)	39	157.43 (22.873)	39	158.31 (27.475)	64	158.31 (24.444)	65	164.35 (30.243)
>= 30 kg/m2	14	160.00 (20.991)	14	184.93 (38.446)	8	174.13 (39.962)	14	158.14 (24.853)	9	177.35 (20.245)	16	183.20 (21.756)	23	166.79 (22.009)	24	180.17 (28.527)
HbA1c at baseline																
< 8.0%	45	148.91 (18.267)	47	150.98 (19.928)	44	150.68 (20.030)	42	151.67 (19.904)	61	147.67 (19.381)	63	151.02 (23.544)	106	148.20 (18.837)	107	150.88 (22.068)
>= 8.0%	30	177.73 (36.523)	28	187.21 (35.106)	29	182.79 (34.806)	31	182.58 (35.587)	45	175.51 (22.036)	43	182.33 (25.067)	75	176.40 (28.508)	72	182.52 (29.146)
>= 8.0 to < 9.0%	23	168.70 (22.922)	20	179.80 (29.839)	24	172.38 (26.231)	28	180.96 (31.788)	36	171.00 (19.807)	26	174.13 (22.986)	59	170.10 (20.912)	50	173.29 (24.358)
>= 9.0%	7	207.43 (56.382)	8	205.75 (42.274)	5	232.80 (27.326)	3	197.67 (70.550)	9	193.57 (22.268)	17	194.89 (23.388)	16	199.63 (39.831)	22	203.50 (28.696)
Duration of type 2 diabetes																
< 5 years	39	162.97 (34.622)	32	161.50 (30.430)	36	166.53 (34.911)	41	165.61 (31.109)	50	157.78 (22.490)	40	162.95 (29.631)	89	160.06 (28.389)	76	164.65 (32.071)
>= 5 years	36	157.69 (25.212)	43	166.74 (32.867)	37	160.43 (26.802)	32	163.75 (32.383)	56	161.01 (26.601)	66	164.19 (28.161)	92	159.72 (25.977)	103	162.84 (27.607)
Complication of diabetes																
Yes	18	158.72 (31.406)	17	171.29 (37.108)	17	169.24 (39.372)	15	183.00 (42.829)	13	164.77 (19.921)	14	164.20 (25.319)	31	161.26 (26.961)	31	166.96 (33.332)

Parameter Subgroup Category	Study 014 Placebo N = 75 n	Mean (SD)	Imeglimin 500 mg bid N = 75 n	Mean (SD)	Imeglimin 1000 mg bid N = 73 n	Mean (SD)	Imeglimin 1500 mg bid N = 73 n	Mean (SD)	Study 018 Placebo N = 106 n	Mean (SD)	Imeglimin 1000 mg bid N = 106 n	Mean (SD)	Pooled (Studies 014+018) Placebo N = 181 n	Mean (SD)	Imeglimin 1000 mg bid N = 179 n	Mean (SD)
No	57	160.98 (30.320)	58	162.52 (30.069)	56	161.68 (28.171)	58	160.09 (26.273)	93	158.75 (25.282)	92	163.65 (29.181)	150	159.60 (27.228)	148	162.90 (28.722)
Metabolic syndrome at baseline																
Yes	41	162.98 (29.555)	35	170.17 (36.773)	24	168.04 (30.766)	44	170.41 (31.309)	43	164.44 (24.448)	53	173.46 (29.709)	84	163.73 (26.907)	77	171.77 (29.945)
No	34	157.38 (31.525)	40	159.55 (26.066)	49	161.18 (31.181)	29	156.28 (30.261)	63	156.11 (24.461)	53	153.98 (23.970)	97	156.55 (26.990)	102	157.44 (27.766)
Previous treatment status																
Treatment naive	34	155.44 (27.348)	33	156.06 (27.113)	33	151.70 (20.731)	29	162.41 (30.625)	77	158.00 (24.096)	76	162.24 (28.175)	111	157.22 (25.039)	109	159.04 (26.500)
Previously treated	41	164.59 (32.436)	42	171.14 (33.805)	40	173.13 (34.767)	44	166.36 (32.259)	29	163.44 (26.204)	30	167.48 (29.767)	70	164.11 (29.814)	70	170.71 (32.611)
FPG at baseline																
< 160 mg/dL	44	142.09 (11.018)	40	141.53 (10.682)	38	141.92 (13.461)	39	143.23 (11.524)	61	142.47 (12.795)	50	138.79 (11.236)	105	142.31 (12.028)	88	140.14 (12.272)
>= 160 mg/dL	31	186.48 (30.143)	35	190.77 (27.040)	35	186.80 (27.544)	34	189.53 (28.762)	45	182.56 (16.883)	56	185.98 (19.458)	76	184.16 (23.118)	91	186.29 (22.763)
HOMA-IR at baseline																
< 2.5	27	150.30 (23.360)	32	148.63 (16.482)	34	148.82 (21.138)	22	153.14 (27.975)	64	153.58 (21.535)	67	152.78 (23.184)	91	152.61 (22.013)	101	151.45 (22.489)
>= 2.5 to < 4.0	20	155.45 (27.192)	16	160.69 (26.199)	16	169.06 (24.428)	13	154.54 (21.896)	27	164.34 (25.748)	20	173.85 (30.103)	47	160.56 (26.455)	36	171.72 (27.450)
>= 4.0	27	172.22 (33.952)	27	185.59 (36.979)	23	181.13 (37.254)	38	175.05 (33.182)	15	175.95 (27.505)	19	191.63 (21.428)	42	173.55 (31.505)	42	185.88 (31.213)
Missing	1	216.00 (.)	0	.	0	.	0	.	0	.	0	.	1	216.00 (.)	0	.
HOMA-B at baseline																
< 30.0%	34	166.85 (35.887)	43	163.84 (31.466)	48	168.31 (34.269)	32	171.41 (37.722)	78	161.77 (25.689)	85	164.54 (27.845)	112	163.31 (29.089)	133	165.90 (30.247)

Parameter Subgroup Category	Study 014 Placebo N = 75 n	Mean (SD)	Imeglimin 500 mg bid N = 75 n	Mean (SD)	Imeglimin 1000 mg bid N = 73 n	Mean (SD)	Imeglimin 1500 mg bid N = 73 n	Mean (SD)	Study 018 Placebo N = 106 n	Mean (SD)	Imeglimin 1000 mg bid N = 106 n	Mean (SD)	Pooled (Studies 014+018) Placebo N = 181 n	Mean (SD)	Imeglimin 1000 mg bid N = 179 n	Mean (SD)
>= 30.0%	40	153.60 (22.339)	32	165.41 (32.602)	25	154.08 (21.085)	41	159.63 (24.839)	28	153.13 (20.751)	21	160.42 (31.946)	68	153.41 (21.542)	46	156.98 (26.475)
Missing	1	216.00 (.)	0	.	0	.	0	.	0	.	0	.	1	216.00 (.)	0	.
QUICKI at baseline																
< 0.33	44	166.52 (32.588)	41	176.54 (34.944)	38	176.53 (33.158)	47	171.81 (32.241)	37	171.20 (25.915)	31	188.99 (24.145)	81	168.66 (29.640)	69	182.13 (29.907)
>= 0.33	30	149.67 (22.327)	34	150.00 (19.579)	35	149.23 (20.962)	26	152.12 (26.056)	69	153.21 (21.697)	75	153.28 (23.354)	99	152.14 (21.837)	110	151.99 (22.604)
Missing	1	216.00 (.)	0	.	0	.	0	.	0	.	0	.	1	216.00 (.)	0	.
HOMA-B x HOMA-IR at baseline																
< 30.0%, < 2.5	24	154.42 (21.256)	30	149.73 (16.415)	32	151.00 (19.708)	20	156.90 (26.475)	61	154.67 (21.440)	62	154.90 (22.721)	85	154.60 (21.262)	94	153.58 (21.715)
< 30.0%, >= 2.5 to < 4.0	7	178.57 (34.141)	9	179.56 (16.637)	9	185.00 (19.281)	7	168.14 (19.583)	14	181.44 (21.519)	15	184.84 (25.211)	21	180.49 (25.546)	24	184.90 (22.720)
< 30.0%, >= 4.0	3	239.00 (49.122)	4	234.25 (34.326)	7	226.00 (28.255)	5	234.00 (33.985)	3	214.39 (14.412)	8	201.10 (17.359)	6	226.69 (35.072)	15	212.72 (25.655)
>= 30.0%, < 2.5	3	117.33 (8.021)	2	132.00 (4.243)	2	114.00 (11.314)	2	115.50 (0.707)	3	131.51 (7.206)	5	126.47 (7.791)	6	124.42 (10.336)	7	122.91 (9.941)
>= 30.0%, >= 2.5 to < 4.0	13	143.00 (10.400)	7	136.43 (11.238)	7	148.57 (11.193)	6	138.67 (11.361)	13	145.93 (15.037)	5	140.88 (16.383)	26	144.46 (12.755)	12	145.37 (13.477)
>= 30.0%, >= 4.0	24	163.88 (20.950)	23	177.13 (30.824)	16	161.50 (19.121)	33	166.12 (22.438)	12	166.34 (20.531)	11	184.74 (22.173)	36	164.70 (20.550)	27	170.97 (23.139)
Missing	1	216.00 (.)	0	.	0	.	0	.	0	.	0	.	1	216.00 (.)	0	.
HOMA-B x QUICKI at baseline																
< 30.0%, < 0.33	9	201.56 (46.592)	12	195.08 (35.380)	15	205.60 (30.097)	9	210.11 (38.644)	14	192.12 (22.773)	18	195.27 (23.352)	23	195.81 (33.436)	33	199.96 (26.707)
< 30.0%, >= 0.33	25	154.36 (20.810)	31	151.74 (19.635)	33	151.36 (19.509)	23	156.26 (24.686)	64	155.13 (21.215)	67	156.28 (22.793)	89	154.91 (20.987)	100	154.66 (21.789)

Parameter Subgroup	Study 014 Placebo N = 75		Imeglimin 500 mg bid N = 75		Imeglimin 1000 mg bid N = 73		Imeglimin 1500 mg bid N = 73		Study 018 Placebo N = 106		Imeglimin 1000 mg bid N = 106		Pooled (Studies 014+018) Placebo N = 181		Imeglimin 1000 mg bid N = 179	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
>= 30.0%, < 0.33	35	157.51 (20.589)	29	168.86 (32.314)	23	157.57 (17.901)	38	162.74 (22.980)	23	158.46 (18.552)	13	180.29 (23.321)	58	157.89 (19.645)	36	165.77 (22.594)
>= 30.0%, >= 0.33	5	126.20 (13.773)	3	132.00 (3.000)	2	114.00 (11.314)	3	120.33 (8.386)	5	128.63 (9.998)	8	128.14 (7.670)	10	127.42 (11.418)	10	125.31 (9.772)
Missing	1	216.00 (.)	0	.	0	.	0	.	0	.	0	.	1	216.00 (.)	0	.

- Abbreviations: bid, Twice a day; SD, standard deviation; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); BMI, body mass index; eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease; FPG, Fasting Plasma Glucose; HOMA, Homeostasis model assessment; HOMA-IR, HOMA of insulin resistance; HOMA-B, HOMA of beta-cell function; QUICKI, Quantitative Insulin Sensitivity Check Index
- Complication of diabetes is defined as any MedDRA Preferred Term (PT) of medical history which are included in High-Level Group Term (HLGT) of diabetic complication.
- Metabolic Syndrome is defined as an excessive waist circumference (>= 85 cm in men and >= 90 cm in women) as well as the presence of two or more of the following symptoms: (1) Hypertension: systolic blood pressure >= 130 mmHg, or diastolic blood pressure >= 85 mmHg; (2) Glucose intolerance: fasting glucose >= 110 mg/dL; (3) Dyslipidemia: triglyceride >= 150 mg/dL, or HDL cholesterol < 40 mg/dL.
- Hepatic parameter abnormality is defined as any one of following parameter applied: Total Bilirubin >= 1.6 mg/dL; Aspartate aminotransferase (AST) >= 1.25 x Upper Limit of Normal (ULN); AST >= 50 IU; Alanine aminotransferase (ALT) >= 1.25 x ULN; ALT >= 50 IU; Alkaline phosphatase >= 1.25 x ULN; Gamma glutamyl transferase >= 1.5 x ULN.
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2, CKD Stage 3a includes subjects with eGFR >= 45 to < 60 mL/min/1.73m2.

Control No:<<t-e-502-subgl-24wdb.sas, 2020-03-09T15:51:57>>

Table E-503 Baseline Value of HbA1c (%) by Subgroup in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Efficacy Population)

Parameter Subgroup	Imeglimin N = 134		Imeglimin + SU N = 127		Imeglimin + GLIN N = 64		Imeglimin + BIG N = 64		Imeglimin + AGI N = 64		Imeglimin + TZD N = 65		Imeglimin + DPP4-I N = 63		Imeglimin + GLP1-RA N = 70		Imeglimin + SGLT2-I N = 63	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
HbA1c (%)																		
Population																		
All	134	7.83 (0.730)	127	8.63 (0.903)	64	8.48 (0.837)	64	8.16 (0.607)	64	8.37 (0.771)	65	8.72 (0.942)	63	8.23 (0.750)	70	8.66 (0.848)	63	8.50 (0.748)
Age group																		
< 65 years	86	7.88 (0.775)	76	8.71 (0.922)	42	8.54 (0.829)	47	8.28 (0.600)	41	8.45 (0.862)	44	8.63 (0.918)	28	8.54 (0.720)	46	8.73 (0.854)	45	8.58 (0.787)
>= 65 years	48	7.74 (0.641)	51	8.52 (0.871)	22	8.37 (0.860)	17	7.83 (0.507)	23	8.23 (0.564)	21	8.92 (0.985)	35	7.98 (0.685)	24	8.54 (0.840)	18	8.31 (0.620)
< 75 years	127	7.85 (0.736)	122	8.62 (0.898)	61	8.51 (0.846)	61	8.20 (0.595)	62	8.39 (0.775)	61	8.67 (0.913)	58	8.28 (0.763)	67	8.66 (0.855)	61	8.51 (0.753)
>= 75 years	7	7.47 (0.538)	5	8.98 (1.057)	3	7.90 (0.265)	3	7.40 (0.300)	2	7.80 (0.424)	4	9.48 (1.212)	5	7.72 (0.249)	3	8.77 (0.802)	2	8.15 (0.636)
Sex																		
Male	106	7.82 (0.760)	101	8.62 (0.883)	43	8.41 (0.831)	46	8.12 (0.632)	48	8.40 (0.819)	54	8.74 (0.976)	39	8.33 (0.804)	44	8.56 (0.836)	45	8.52 (0.788)
Female	28	7.85 (0.614)	26	8.67 (0.992)	21	8.61 (0.852)	18	8.27 (0.540)	16	8.26 (0.615)	11	8.65 (0.790)	24	8.08 (0.637)	26	8.84 (0.855)	18	8.46 (0.655)
eGFR CKD Stage																		
Stage 1	24	8.08 (0.916)	22	8.81 (1.101)	12	8.50 (0.975)	18	8.06 (0.619)	13	8.68 (0.977)	16	8.71 (0.818)	9	8.44 (0.720)	16	8.65 (0.855)	21	8.41 (0.679)
Stage 2	91	7.76 (0.657)	96	8.60 (0.860)	50	8.50 (0.804)	42	8.18 (0.616)	49	8.31 (0.702)	44	8.73 (0.898)	47	8.23 (0.785)	51	8.68 (0.876)	40	8.54 (0.778)
Stage 3a	19	7.86 (0.772)	9	8.54 (0.879)	2	7.90 (1.131)	4	8.48 (0.427)	2	7.75 (0.354)	5	8.70 (1.739)	7	7.99 (0.505)	3	8.43 (0.252)	2	8.60 (1.273)
Hepatic parameter abnormality																		

Parameter Subgroup	Imeglimin N = 134		Imeglimin + SU N = 127		Imeglimin + GLIN N = 64		Imeglimin + BIG N = 64		Imeglimin + AGI N = 64		Imeglimin + TZD N = 65		Imeglimin + DPP4-I N = 63		Imeglimin + GLP1-RA N = 70		Imeglimin + SGLT2-I N = 63	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Yes	18	8.05 (0.748)	16	8.89 (0.999)	11	8.89 (0.776)	10	8.46 (0.664)	9	8.50 (1.006)	9	9.01 (0.968)	12	8.31 (0.663)	20	8.48 (0.982)	13	8.75 (0.782)
No	116	7.79 (0.725)	111	8.59 (0.887)	53	8.39 (0.830)	54	8.11 (0.586)	55	8.35 (0.735)	56	8.67 (0.939)	51	8.21 (0.774)	50	8.74 (0.787)	50	8.43 (0.732)
BMI at baseline																		
< 25 kg/m2	67	7.86 (0.748)	65	8.48 (0.835)	35	8.29 (0.824)	22	8.09 (0.681)	31	8.22 (0.749)	24	8.64 (0.930)	38	8.10 (0.708)	27	8.54 (0.765)	32	8.41 (0.766)
>= 25 kg/m2	67	7.80 (0.717)	62	8.79 (0.948)	29	8.71 (0.806)	42	8.20 (0.569)	33	8.51 (0.777)	41	8.77 (0.958)	25	8.43 (0.783)	43	8.74 (0.897)	31	8.60 (0.728)
>= 25 to < 30 kg/m2	51	7.80 (0.663)	43	8.80 (0.957)	18	8.71 (0.718)	29	8.09 (0.482)	26	8.55 (0.716)	25	9.01 (1.022)	23	8.43 (0.814)	31	8.83 (0.869)	24	8.69 (0.756)
>= 30 kg/m2	16	7.80 (0.891)	19	8.77 (0.955)	11	8.71 (0.972)	13	8.46 (0.679)	7	8.36 (1.026)	16	8.38 (0.720)	2	8.35 (0.354)	12	8.50 (0.963)	7	8.29 (0.558)
HbA1c at baseline																		
< 8.0%	89	7.41 (0.311)	33	7.60 (0.226)	23	7.60 (0.243)	26	7.59 (0.190)	20	7.66 (0.190)	16	7.73 (0.154)	24	7.59 (0.255)	17	7.58 (0.194)	16	7.71 (0.124)
>= 8.0%	45	8.66 (0.605)	94	8.99 (0.759)	41	8.97 (0.613)	38	8.55 (0.468)	44	8.69 (0.719)	49	9.04 (0.863)	39	8.63 (0.678)	53	9.01 (0.662)	47	8.77 (0.674)
>= 8.0 to < 9.0%	34	8.36 (0.291)	52	8.41 (0.277)	22	8.50 (0.314)	32	8.39 (0.254)	31	8.29 (0.245)	24	8.35 (0.278)	28	8.27 (0.282)	26	8.44 (0.289)	31	8.37 (0.289)
>= 9.0%	11	9.55 (0.393)	42	9.71 (0.507)	19	9.52 (0.375)	6	9.43 (0.339)	13	9.64 (0.559)	25	9.71 (0.680)	11	9.54 (0.510)	27	9.56 (0.407)	16	9.55 (0.494)
Duration of type 2 diabetes																		
< 5 years	72	7.77 (0.726)	23	8.18 (0.574)	18	8.31 (0.751)	22	8.10 (0.599)	26	8.38 (0.770)	20	8.39 (0.677)	20	8.16 (0.749)	15	8.56 (0.821)	12	8.03 (0.439)
>= 5 years	62	7.90 (0.735)	104	8.73 (0.933)	46	8.55 (0.866)	42	8.19 (0.617)	38	8.36 (0.782)	45	8.87 (1.010)	43	8.27 (0.756)	55	8.69 (0.861)	51	8.61 (0.764)
Complication of diabetes																		
Yes	23	8.00 (0.672)	46	8.48 (0.799)	24	8.33 (0.734)	24	8.25 (0.559)	16	8.36 (0.748)	10	8.52 (0.636)	22	8.31 (0.648)	32	8.71 (0.950)	16	8.60 (0.681)

Parameter Subgroup	Imeglimin N = 134		Imeglimin + SU N = 127		Imeglimin + GLIN N = 64		Imeglimin + BIG N = 64		Imeglimin + AGI N = 64		Imeglimin + TZD N = 65		Imeglimin + DPP4-I N = 63		Imeglimin + GLP1-RA N = 70		Imeglimin + SGLT2-I N = 63	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
No	111	7.79 (0.739)	81	8.72 (0.950)	40	8.57 (0.890)	40	8.11 (0.635)	48	8.37 (0.786)	55	8.76 (0.988)	41	8.19 (0.803)	38	8.62 (0.762)	47	8.47 (0.773)
Metabolic syndrome at baseline																		
Yes	62	7.76 (0.714)	64	8.68 (0.941)	28	8.42 (0.852)	36	8.27 (0.626)	32	8.43 (0.769)	32	8.76 (1.024)	25	8.38 (0.773)	39	8.68 (0.845)	31	8.43 (0.713)
No	72	7.89 (0.744)	63	8.58 (0.867)	36	8.53 (0.834)	28	8.03 (0.566)	32	8.30 (0.779)	33	8.68 (0.871)	38	8.14 (0.729)	31	8.64 (0.865)	32	8.57 (0.785)
Previous treatment status																		
Treatment naive	134	7.83 (0.730)	0	.	0	.	0	.	0	.	0	.	0	.	0	.	0	.
Previously treated	0	.	127	8.63 (0.903)	64	8.48 (0.837)	64	8.16 (0.607)	64	8.37 (0.771)	65	8.72 (0.942)	63	8.23 (0.750)	70	8.66 (0.848)	63	8.50 (0.748)
FPG at baseline																		
< 160 mg/dL	63	7.42 (0.359)	29	7.96 (0.478)	20	7.96 (0.760)	18	7.89 (0.490)	20	7.85 (0.375)	26	8.14 (0.543)	20	7.76 (0.379)	14	8.19 (0.729)	33	8.20 (0.563)
>= 160 mg/dL	71	8.19 (0.786)	98	8.83 (0.905)	44	8.72 (0.764)	46	8.27 (0.621)	44	8.60 (0.792)	39	9.11 (0.957)	43	8.45 (0.778)	56	8.78 (0.839)	30	8.83 (0.794)
HOMA-IR at baseline																		
< 2.5	89	7.79 (0.732)	80	8.46 (0.822)	42	8.38 (0.882)	41	8.11 (0.617)	39	8.27 (0.722)	48	8.65 (0.904)	38	8.01 (0.649)	36	8.54 (0.663)	42	8.52 (0.830)
>= 2.5 to < 4.0	25	7.86 (0.715)	17	8.99 (0.854)	10	8.73 (0.776)	14	8.24 (0.464)	17	8.32 (0.732)	11	8.97 (1.201)	14	8.40 (0.874)	20	8.60 (1.008)	12	8.52 (0.554)
>= 4.0	20	7.96 (0.761)	30	8.89 (1.036)	12	8.61 (0.712)	9	8.26 (0.784)	7	8.97 (1.005)	6	8.78 (0.783)	11	8.80 (0.585)	14	9.07 (0.960)	9	8.39 (0.603)
Missing	0	.	0	.	0	.	0	.	1	8.60 (.)	0	.	0	.	0	.	0	.
HOMA-B at baseline																		
< 30.0%	108	7.88 (0.739)	108	8.69 (0.903)	53	8.57 (0.869)	53	8.20 (0.642)	53	8.42 (0.773)	57	8.81 (0.955)	52	8.25 (0.797)	59	8.77 (0.811)	55	8.54 (0.756)

Parameter Subgroup	Imeglimin N = 134		Imeglimin + SU N = 127		Imeglimin + GLIN N = 64		Imeglimin + BIG N = 64		Imeglimin + AGI N = 64		Imeglimin + TZD N = 65		Imeglimin + DPP4-I N = 63		Imeglimin + GLP1-RA N = 70		Imeglimin + SGLT2-I N = 63	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
>= 30.0%	26	7.61 (0.659)	19	8.32 (0.860)	11	8.06 (0.507)	11	7.98 (0.368)	10	8.07 (0.767)	8	8.11 (0.584)	11	8.15 (0.480)	11	8.11 (0.864)	8	8.20 (0.652)
Missing	0	.	0	.	0	.	0	.	1	8.60 (.)	0	.	0	.	0	.	0	.
QUICKI at baseline																		
< 0.33	42	7.85 (0.672)	45	8.91 (0.978)	19	8.71 (0.754)	22	8.25 (0.606)	22	8.53 (0.883)	13	8.77 (0.718)	24	8.55 (0.774)	28	8.73 (1.010)	17	8.49 (0.615)
>= 0.33	92	7.82 (0.758)	82	8.48 (0.826)	45	8.38 (0.858)	42	8.12 (0.611)	41	8.27 (0.708)	52	8.71 (0.996)	39	8.04 (0.673)	42	8.62 (0.730)	46	8.50 (0.797)
Missing	0	.	0	.	0	.	0	.	1	8.60 (.)	0	.	0	.	0	.	0	.
HOMA-B x HOMA-IR at baseline																		
< 30.0%, < 2.5	86	7.80 (0.741)	79	8.46 (0.827)	40	8.42 (0.888)	40	8.12 (0.624)	38	8.29 (0.723)	45	8.71 (0.908)	36	8.02 (0.653)	35	8.52 (0.659)	40	8.51 (0.830)
< 30.0%, >= 2.5 to < 4.0	15	8.17 (0.745)	14	9.18 (0.758)	8	8.93 (0.707)	11	8.25 (0.505)	12	8.53 (0.761)	9	9.19 (1.229)	9	8.60 (1.023)	15	8.97 (0.871)	10	8.63 (0.533)
< 30.0%, >= 4.0	7	8.24 (0.461)	15	9.42 (0.882)	5	9.16 (0.586)	2	9.50 (0.141)	3	9.60 (0.458)	3	9.13 (0.551)	7	8.97 (0.650)	9	9.38 (0.909)	5	8.64 (0.555)
>= 30.0%, < 2.5	3	7.57 (0.404)	1	8.30 (.)	2	7.65 (0.212)	1	7.90 (.)	1	7.60 (.)	3	7.87 (0.252)	2	7.70 (0.707)	1	9.30 (.)	2	8.70 (1.131)
>= 30.0%, >= 2.5 to < 4.0	10	7.38 (0.282)	3	8.10 (0.819)	2	7.95 (0.636)	3	8.20 (0.346)	5	7.82 (0.342)	2	8.00 (0.141)	5	8.04 (0.365)	5	7.46 (0.152)	2	7.95 (0.212)
>= 30.0%, >= 4.0	13	7.80 (0.857)	15	8.36 (0.919)	7	8.21 (0.515)	7	7.90 (0.392)	4	8.50 (1.089)	3	8.43 (0.929)	4	8.50 (0.327)	5	8.52 (0.867)	4	8.08 (0.568)
Missing	0	.	0	.	0	.	0	.	1	8.60 (.)	0	.	0	.	0	.	0	.
HOMA-B x QUICKI at baseline																		
< 30.0%, < 0.33	20	8.11 (0.545)	27	9.30 (0.838)	10	9.21 (0.565)	12	8.46 (0.686)	13	8.82 (0.854)	8	9.09 (0.549)	15	8.73 (0.892)	18	9.14 (0.877)	11	8.75 (0.552)
< 30.0%, >= 0.33	88	7.83 (0.770)	81	8.48 (0.831)	43	8.42 (0.863)	41	8.12 (0.617)	40	8.29 (0.709)	49	8.76 (1.002)	37	8.06 (0.677)	41	8.60 (0.731)	44	8.49 (0.796)

Parameter Subgroup	Imeglimin N = 134		Imeglimin + SU N = 127		Imeglimin + GLIN N = 64		Imeglimin + BIG N = 64		Imeglimin + AGI N = 64		Imeglimin + TZD N = 65		Imeglimin + DPP4-I N = 63		Imeglimin + GLP1-RA N = 70		Imeglimin + SGLT2-I N = 63	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
>= 30.0%, < 0.33	22	7.63 (0.707)	18	8.32 (0.885)	9	8.16 (0.513)	10	7.99 (0.387)	9	8.12 (0.795)	5	8.26 (0.702)	9	8.24 (0.407)	10	7.99 (0.810)	6	8.03 (0.455)
>= 30.0%, >= 0.33	4	7.53 (0.340)	1	8.30 (.)	2	7.65 (0.212)	1	7.90 (.)	1	7.60 (.)	3	7.87 (0.252)	2	7.70 (0.707)	1	9.30 (.)	2	8.70 (1.131)
Missing	0	.	0	.	0	.	0	.	1	8.60 (.)	0	.	0	.	0	.	0	.

- Abbreviations: SD, standard deviation; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); BMI, body mass index; eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease; FPG, Fasting Plasma Glucose; HOMA, Homeostasis model assessment; HOMA-IR, HOMA of insulin resistance; HOMA-B, HOMA of beta-cell function; QUICKI, Quantitative Insulin Sensitivity Check Index; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- Complication of diabetes is defined as any MedDRA Preferred Term (PT) of medical history which are included in High-Level Group Term (HLGT) of diabetic complication.
- Metabolic Syndrome is defined as an excessive waist circumference (>= 85 cm in men and >= 90 cm in women) as well as the presence of two or more of the following symptoms: (1) Hypertension: systolic blood pressure >= 130 mmHg, or diastolic blood pressure >= 85 mmHg; (2) Glucose intolerance: fasting glucose >= 110 mg/dL; (3) Dyslipidemia: triglyceride >= 150 mg/dL, or HDL cholesterol < 40 mg/dL.
- Hepatic parameter abnormality is defined as any one of following parameter applied: Total Bilirubin >= 1.6 mg/dL; Aspartate aminotransferase (AST) >= 1.25 x Upper Limit of Normal (ULN); AST >= 50 IU; Alanine aminotransferase (ALT) >= 1.25 x ULN; ALT >= 50 IU; Alkaline phosphatase >= 1.25 x ULN; Gamma glutamyl transferase >= 1.5 x ULN.
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2, CKD Stage 3a includes subjects with eGFR >= 45 to < 60 mL/min/1.73m2.

Control No:<<t-e-503-subhb-019lt.sas, 2020-03-09T15:52:08>>

Table E-504 Baseline Value of Fasting Plasma Glucose (mg/dL) by Subgroup in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Efficacy Population)

Parameter Subgroup	Imeglimin N = 134		Imeglimin + SU N = 127		Imeglimin + GLIN N = 64		Imeglimin + BIG N = 64		Imeglimin + AGI N = 64		Imeglimin + TZD N = 65		Imeglimin + DPP4-I N = 63		Imeglimin + GLP1-RA N = 70		Imeglimin + SGLT2-I N = 63	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Fasting Plasma Glucose (mg/dL)																		
Population																		
All	134	163.19 (25.578)	127	185.13 (37.679)	64	179.76 (33.493)	64	174.86 (30.714)	64	173.93 (31.336)	65	171.62 (32.202)	63	180.10 (32.963)	70	191.04 (39.655)	63	165.57 (27.745)
Age group																		
< 65 years	86	167.25 (27.394)	76	186.65 (39.400)	42	187.06 (33.617)	47	175.63 (30.106)	41	173.78 (33.793)	44	166.85 (28.459)	28	192.19 (34.598)	46	188.50 (39.185)	45	165.50 (27.821)
>= 65 years	48	155.91 (20.243)	51	182.88 (35.219)	22	165.83 (29.137)	17	172.74 (33.200)	23	174.20 (27.118)	21	181.61 (37.711)	35	170.43 (28.533)	24	195.92 (40.935)	18	165.74 (28.358)
< 75 years	127	163.76 (26.004)	122	183.97 (37.419)	61	182.05 (32.544)	61	175.49 (30.971)	62	174.23 (31.791)	61	170.88 (32.761)	58	181.93 (33.629)	67	188.25 (38.033)	61	165.27 (27.117)
>= 75 years	7	152.88 (13.051)	5	213.66 (36.135)	3	133.32 (12.991)	3	162.14 (26.169)	2	164.84 (6.369)	4	182.86 (21.843)	5	158.90 (10.764)	3	253.42 (20.488)	2	174.75 (58.599)
Sex																		
Male	106	164.26 (26.187)	101	185.70 (37.968)	43	179.86 (33.277)	46	177.92 (31.570)	48	175.73 (29.352)	54	172.98 (33.579)	39	189.39 (34.887)	44	190.64 (37.459)	45	166.38 (28.335)
Female	28	159.12 (23.108)	26	182.93 (37.185)	21	179.56 (34.758)	18	167.04 (27.709)	16	168.56 (37.195)	11	164.92 (24.522)	24	164.99 (23.095)	26	191.73 (43.885)	18	163.54 (26.896)
eGFR CKD Stage																		
Stage 1	24	179.18 (29.397)	22	202.43 (40.922)	12	184.21 (38.001)	18	164.44 (23.325)	13	171.01 (38.192)	16	169.68 (29.837)	9	184.56 (31.270)	16	186.69 (36.383)	21	167.03 (27.730)
Stage 2	91	160.02 (23.381)	96	181.66 (35.995)	50	178.68 (33.298)	42	178.27 (32.087)	49	175.19 (30.237)	44	173.60 (31.211)	47	180.12 (34.065)	51	193.33 (41.786)	40	162.91 (27.181)
Stage 3a	19	158.16 (24.040)	9	179.96 (39.761)	2	180.16 (12.739)	4	186.01 (40.960)	2	162.14 (2.548)	5	160.34 (50.636)	7	174.24 (30.938)	3	175.35 (4.161)	2	203.58 (17.835)

Parameter Subgroup	Imeglimin N = 134		Imeglimin + SU N = 127		Imeglimin + GLIN N = 64		Imeglimin + BIG N = 64		Imeglimin + AGI N = 64		Imeglimin + TZD N = 65		Imeglimin + DPP4-I N = 63		Imeglimin + GLP1-RA N = 70		Imeglimin + SGLT2-I N = 63	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Hepatic parameter abnormality																		
Yes	18	175.95 (30.032)	16	199.75 (37.783)	11	184.74 (26.944)	10	187.36 (27.611)	9	179.96 (41.567)	9	184.56 (50.717)	12	189.91 (34.082)	20	186.37 (43.405)	13	179.74 (30.353)
No	116	161.21 (24.369)	111	183.03 (37.363)	53	178.73 (34.830)	54	172.55 (30.935)	55	172.95 (29.708)	56	169.54 (28.297)	51	177.79 (32.607)	50	192.91 (38.358)	50	161.89 (26.102)
BMI at baseline																		
< 25 kg/m2	67	164.02 (25.378)	65	185.31 (36.645)	35	164.56 (27.772)	22	173.93 (29.959)	31	171.61 (29.886)	24	173.70 (35.984)	38	175.18 (31.875)	27	192.57 (33.434)	32	162.03 (27.490)
>= 25 kg/m2	67	162.36 (25.940)	62	184.95 (39.032)	29	198.11 (30.821)	42	175.35 (31.451)	33	176.12 (32.949)	41	170.40 (30.175)	25	187.58 (33.822)	43	190.09 (43.463)	31	169.23 (27.979)
>= 25 to < 30 kg/m2	51	161.72 (24.121)	43	184.39 (37.438)	18	202.27 (33.016)	29	175.00 (31.868)	26	178.70 (31.477)	25	169.78 (34.772)	23	186.58 (34.903)	31	191.20 (44.737)	24	171.37 (29.133)
>= 30 kg/m2	16	164.39 (31.866)	19	186.22 (43.475)	11	191.29 (26.913)	13	176.14 (31.764)	7	166.52 (39.055)	16	171.37 (22.181)	2	199.07 (19.108)	12	187.21 (41.734)	7	161.88 (24.068)
HbA1c at baseline																		
< 8.0%	89	153.64 (21.150)	33	161.92 (26.774)	23	156.42 (28.638)	26	160.55 (25.768)	20	151.42 (20.294)	16	144.24 (14.374)	24	157.94 (14.399)	17	164.05 (30.297)	16	155.72 (21.638)
>= 8.0%	45	182.08 (23.098)	94	193.28 (37.663)	41	192.85 (28.754)	38	184.66 (30.250)	44	184.17 (30.228)	49	180.56 (31.410)	39	193.74 (33.855)	53	199.70 (38.594)	47	168.92 (28.977)
>= 8.0 to < 9.0%	34	177.40 (23.293)	52	178.18 (31.608)	22	187.03 (20.281)	32	178.35 (27.729)	31	175.04 (23.742)	24	167.24 (25.376)	28	179.58 (26.162)	26	184.45 (34.387)	31	160.45 (23.351)
>= 9.0%	11	196.53 (15.900)	42	211.98 (36.432)	19	199.59 (35.611)	6	218.29 (19.814)	13	205.93 (33.715)	25	193.34 (31.757)	11	229.78 (22.736)	27	214.39 (37.224)	16	185.34 (32.387)
Duration of type 2 diabetes																		
< 5 years	72	161.11 (26.051)	23	175.46 (37.797)	18	181.16 (35.756)	22	170.17 (27.591)	26	174.89 (31.120)	20	162.05 (21.599)	20	182.32 (29.415)	15	178.47 (40.073)	12	166.34 (26.325)
>= 5 years	62	165.60 (25.011)	104	187.28 (37.497)	46	179.22 (32.961)	42	177.32 (32.274)	38	173.28 (31.882)	45	175.87 (35.310)	43	179.07 (34.772)	55	194.47 (39.206)	51	165.39 (28.318)
Complication of diabetes																		

Parameter Subgroup	Imeglimin N = 134		Imeglimin + SU N = 127		Imeglimin + GLIN N = 64		Imeglimin + BIG N = 64		Imeglimin + AGI N = 64		Imeglimin + TZD N = 65		Imeglimin + DPP4-I N = 63		Imeglimin + GLP1-RA N = 70		Imeglimin + SGLT2-I N = 63	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Yes	23	164.26 (20.073)	46	178.55 (33.178)	24	178.80 (34.092)	24	175.50 (27.383)	16	177.45 (34.666)	10	167.36 (32.798)	22	185.89 (30.798)	32	194.17 (35.293)	16	174.30 (31.900)
No	111	162.97 (26.648)	81	188.87 (39.721)	40	180.34 (33.553)	40	174.48 (32.883)	48	172.76 (30.447)	55	172.39 (32.339)	41	176.99 (34.027)	38	188.41 (43.281)	47	162.60 (25.888)
Metabolic syndrome at baseline																		
Yes	62	165.69 (25.430)	64	187.33 (41.209)	28	189.03 (29.214)	36	182.16 (28.863)	32	176.21 (31.359)	32	175.60 (29.687)	25	187.79 (33.929)	39	194.52 (42.298)	31	168.59 (30.991)
No	72	161.04 (25.686)	63	182.90 (33.905)	36	172.55 (35.193)	28	165.49 (30.971)	32	171.65 (31.644)	33	167.76 (34.483)	38	175.04 (31.743)	31	186.66 (36.264)	32	162.65 (24.335)
Previous treatment status																		
Treatment naive	134	163.19 (25.578)	0	.	0	.	0	.	0	.	0	.	0	.	0	.	0	.
Previously treated	0	.	127	185.13 (37.679)	64	179.76 (33.493)	64	174.86 (30.714)	64	173.93 (31.336)	65	171.62 (32.202)	63	180.10 (32.963)	70	191.04 (39.655)	63	165.57 (27.745)
FPG at baseline																		
< 160 mg/dL	63	141.87 (12.894)	29	140.02 (12.218)	20	141.60 (13.282)	18	139.22 (15.520)	20	141.96 (13.104)	26	142.39 (10.911)	20	145.84 (11.281)	14	139.75 (10.522)	33	143.85 (11.079)
>= 160 mg/dL	71	182.11 (17.984)	98	198.48 (31.822)	44	197.11 (24.093)	46	188.81 (22.863)	44	188.47 (25.907)	39	191.10 (26.346)	43	196.03 (26.970)	56	203.87 (33.309)	30	189.46 (19.570)
HOMA-IR at baseline																		
< 2.5	89	158.54 (23.752)	80	175.47 (32.282)	42	168.27 (29.496)	41	169.08 (31.549)	39	169.02 (28.019)	48	168.18 (33.028)	38	169.39 (30.226)	36	177.85 (31.867)	42	158.37 (26.327)
>= 2.5 to < 4.0	25	164.73 (21.991)	17	197.85 (41.127)	10	196.91 (34.393)	14	189.03 (29.708)	17	178.46 (32.281)	11	180.48 (31.523)	14	190.97 (35.718)	20	184.93 (36.056)	12	175.35 (25.666)
>= 4.0	20	181.96 (29.672)	30	203.70 (41.079)	12	205.68 (26.653)	9	179.15 (21.789)	7	193.80 (42.248)	6	182.86 (24.378)	11	203.25 (22.528)	14	233.69 (34.851)	9	186.16 (24.800)
Missing	0	.	0	.	0	.	0	.	1	149.53 (.)	0	.	0	.	0	.	0	.
HOMA-B at baseline																		

Parameter Subgroup	Imeglimin N = 134		Imeglimin + SU N = 127		Imeglimin + GLIN N = 64		Imeglimin + BIG N = 64		Imeglimin + AGI N = 64		Imeglimin + TZD N = 65		Imeglimin + DPP4-I N = 63		Imeglimin + GLP1-RA N = 70		Imeglimin + SGLT2-I N = 63	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
< 30.0%	108	165.26 (24.818)	108	188.58 (37.827)	53	181.82 (34.037)	53	178.29 (31.753)	53	178.32 (30.180)	57	175.16 (32.179)	52	183.34 (33.944)	59	194.02 (37.703)	55	167.51 (27.226)
>= 30.0%	26	154.59 (27.365)	19	165.55 (30.925)	11	169.84 (30.201)	11	158.37 (18.416)	10	153.13 (30.832)	8	146.38 (19.157)	11	164.76 (23.384)	11	175.08 (47.677)	8	152.23 (29.446)
Missing	0	.	0	.	0	.	0	.	1	149.53 (.)	0	.	0	.	0	.	0	.
QUICKI at baseline																		
< 0.33	42	172.43 (26.841)	45	201.17 (41.606)	19	202.82 (31.721)	22	184.41 (27.183)	22	182.94 (36.744)	13	176.69 (24.398)	24	194.87 (30.387)	28	208.34 (45.288)	17	180.37 (27.484)
>= 0.33	92	158.97 (23.961)	82	176.33 (32.353)	45	170.03 (29.463)	42	169.86 (31.568)	41	169.70 (27.565)	52	170.35 (33.957)	39	171.01 (31.486)	42	179.51 (30.908)	46	160.10 (26.053)
Missing	0	.	0	.	0	.	0	.	1	149.53 (.)	0	.	0	.	0	.	0	.
HOMA-B x HOMA-IR at baseline																		
< 30.0%, < 2.5	86	159.77 (23.067)	79	176.30 (31.617)	40	170.43 (28.525)	40	170.25 (31.046)	38	170.48 (26.847)	45	170.75 (32.437)	36	171.45 (29.682)	35	179.07 (31.466)	40	159.89 (26.001)
< 30.0%, >= 2.5 to < 4.0	15	178.23 (13.745)	14	207.69 (38.396)	8	209.43 (24.958)	11	200.79 (19.856)	12	191.72 (28.737)	9	188.96 (28.003)	9	209.58 (31.100)	15	199.13 (29.279)	10	182.86 (20.685)
< 30.0%, >= 4.0	7	204.86 (17.977)	15	235.40 (20.795)	5	228.80 (21.354)	2	215.29 (1.274)	3	223.99 (20.803)	3	199.97 (22.138)	7	210.78 (24.592)	9	243.61 (28.368)	5	197.81 (11.634)
>= 30.0%, < 2.5	3	123.11 (16.147)	1	109.90 (.)	2	125.21 (6.369)	1	122.51 (.)	1	113.50 (.)	3	129.71 (10.958)	2	132.41 (8.917)	1	135.12 (.)	2	127.91 (10.191)
>= 30.0%, >= 2.5 to < 4.0	10	144.48 (15.376)	3	151.93 (10.401)	2	146.83 (3.822)	3	145.93 (14.746)	5	146.65 (10.239)	2	142.32 (10.191)	5	157.46 (5.344)	5	142.32 (12.219)	2	137.82 (3.822)
>= 30.0%, >= 4.0	13	169.62 (27.596)	15	171.99 (30.145)	7	189.16 (15.322)	7	168.83 (8.559)	4	171.15 (41.056)	3	165.74 (10.809)	4	190.06 (10.859)	5	215.83 (41.444)	4	171.60 (30.833)
Missing	0	.	0	.	0	.	0	.	1	149.53 (.)	0	.	0	.	0	.	0	.
HOMA-B x QUICKI at baseline																		
< 30.0%, < 0.33	20	186.37 (20.344)	27	222.86 (34.240)	10	223.57 (23.109)	12	203.13 (19.767)	13	200.53 (31.242)	8	189.39 (19.979)	15	208.62 (27.828)	18	224.59 (35.217)	11	191.29 (19.945)

Parameter Subgroup	Imeglimin N = 134		Imeglimin + SU N = 127		Imeglimin + GLIN N = 64		Imeglimin + BIG N = 64		Imeglimin + AGI N = 64		Imeglimin + TZD N = 65		Imeglimin + DPP4-I N = 63		Imeglimin + GLP1-RA N = 70		Imeglimin + SGLT2-I N = 63	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
< 30.0%, >= 0.33	88	160.46 (23.267)	81	177.15 (31.685)	43	172.11 (28.432)	41	171.02 (31.049)	40	171.10 (26.388)	49	172.84 (33.326)	37	173.10 (30.935)	41	180.60 (30.475)	44	161.57 (25.643)
>= 30.0%, < 0.33	22	159.77 (26.056)	18	168.65 (28.640)	9	179.76 (22.944)	10	161.96 (14.818)	9	157.54 (29.176)	5	156.38 (15.778)	9	171.95 (18.811)	10	179.07 (48.275)	6	160.34 (29.625)
>= 30.0%, >= 0.33	4	126.11 (14.487)	1	109.90 (.)	2	125.21 (6.369)	1	122.51 (.)	1	113.50 (.)	3	129.71 (10.958)	2	132.41 (8.917)	1	135.12 (.)	2	127.91 (10.191)
Missing	0	.	0	.	0	.	0	.	1	149.53 (.)	0	.	0	.	0	.	0	.

- Abbreviations: SD, standard deviation; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); BMI, body mass index; eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease; FPG, Fasting Plasma Glucose; HOMA, Homeostasis model assessment; HOMA-IR, HOMA of insulin resistance; HOMA-B, HOMA of beta-cell function; QUICKI, Quantitative Insulin Sensitivity Check Index; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- Complication of diabetes is defined as any MedDRA Preferred Term (PT) of medical history which are included in High-Level Group Term (HLGT) of diabetic complication.
- Metabolic Syndrome is defined as an excessive waist circumference (>= 85 cm in men and >= 90 cm in women) as well as the presence of two or more of the following symptoms: (1) Hypertension: systolic blood pressure >= 130 mmHg, or diastolic blood pressure >= 85 mmHg; (2) Glucose intolerance: fasting glucose >= 110 mg/dL; (3) Dyslipidemia: triglyceride >= 150 mg/dL, or HDL cholesterol < 40 mg/dL.
- Hepatic parameter abnormality is defined as any one of following parameter applied: Total Bilirubin >= 1.6 mg/dL; Aspartate aminotransferase (AST) >= 1.25 x Upper Limit of Normal (ULN); AST >= 50 IU; Alanine aminotransferase (ALT) >= 1.25 x ULN; ALT >= 50 IU; Alkaline phosphatase >= 1.25 x ULN; Gamma glutamyl transferase >= 1.5 x ULN.
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2, CKD Stage 3a includes subjects with eGFR >= 45 to < 60 mL/min/1.73m2.

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Table E-505 Baseline Value of HbA1c (%) by Subgroup in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Efficacy Population)

Parameter Subgroup Category	Placebo + Insulin N = 106 n	 Mean (SD)	Imeglimin 1000 mg bid + Insulin N = 108 n	 Mean (SD)
HbA1c (%)				
Population				
All	106	8.82 (0.813)	108	8.74 (0.721)
Age group				
< 65 years	75	8.90 (0.811)	68	8.77 (0.710)
>= 65 years	31	8.65 (0.805)	40	8.69 (0.745)
< 75 years	103	8.85 (0.809)	101	8.74 (0.713)
>= 75 years	3	8.00 (0.557)	7	8.80 (0.894)
Sex				
Male	68	8.68 (0.734)	66	8.64 (0.617)
Female	38	9.08 (0.893)	42	8.90 (0.844)
eGFR CKD Stage				
Stage 1	14	9.04 (0.941)	16	8.77 (0.525)
Stage 2	92	8.79 (0.792)	92	8.74 (0.752)
Hepatic parameter abnormality				
Yes	14	9.19 (0.807)	17	8.98 (0.713)
No	92	8.77 (0.804)	91	8.70 (0.717)
BMI at baseline				
< 25 kg/m2	60	8.64 (0.790)	56	8.73 (0.699)
>= 25 kg/m2	46	9.07 (0.785)	52	8.75 (0.751)
>= 25 to < 30 kg/m2	35	9.00 (0.809)	44	8.73 (0.746)
>= 30 kg/m2	11	9.29 (0.691)	8	8.83 (0.826)
HbA1c at baseline				
< 8.0%	16	7.71 (0.157)	16	7.73 (0.148)
>= 8.0%	90	9.02 (0.715)	92	8.92 (0.628)
>= 8.0 to < 9.0%	44	8.42 (0.283)	53	8.48 (0.277)
>= 9.0%	46	9.60 (0.492)	39	9.52 (0.451)
Duration of type 2 diabetes				
< 5 years	12	9.09 (0.502)	16	8.52 (0.819)
>= 5 years	94	8.79 (0.840)	92	8.78 (0.700)
Complication of diabetes				
Yes	52	8.84 (0.845)	45	8.71 (0.678)
No	54	8.81 (0.789)	63	8.76 (0.755)
Metabolic syndrome at baseline				
Yes	49	9.12 (0.776)	39	8.85 (0.803)
No	57	8.56 (0.760)	69	8.68 (0.668)
Previous treatment status				
Insulin monotherapy	85	8.79 (0.828)	87	8.66 (0.691)
Insulin in combination with 1 OHA	21	8.97 (0.748)	21	9.08 (0.759)
FPG at baseline				
< 160 mg/dL	68	8.60 (0.765)	61	8.51 (0.638)

Parameter Subgroup	Placebo + Insulin N = 106		Imeglimin 1000 mg bid + Insulin N = 108	
Category	n	Mean (SD)	n	Mean (SD)
>= 160 mg/dL	38	9.22 (0.752)	47	9.04 (0.720)

- Abbreviations: bid, Twice a day; SD, standard deviation; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); BMI, body mass index; eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease; FPG, Fasting Plasma Glucose; 1 OHA, Patients on insulin in combination with one oral hypoglycemic agent
- Complication of diabetes is defined as any MedDRA Preferred Term (PT) of medical history which are included in High-Level Group Term (HLGT) of diabetic complication.
- Metabolic Syndrome is defined as an excessive waist circumference (>= 85 cm in men and >= 90 cm in women) as well as the presence of two or more of the following symptoms: (1) Hypertension: systolic blood pressure >= 130 mmHg, or diastolic blood pressure >= 85 mmHg; (2) Glucose intolerance: fasting glucose >= 110 mg/dL; (3) Dyslipidemia: triglyceride >= 150 mg/dL, or HDL cholesterol < 40 mg/dL.
- Hepatic parameter abnormality is defined as any one of following parameter applied: Total Bilirubin >= 1.6 mg/dL; Aspartate aminotransferase (AST) >= 1.25 x Upper Limit of Normal (ULN); AST >= 50 IU; Alanine aminotransferase (ALT) >= 1.25 x ULN; ALT >= 50 IU; Alkaline phosphatase >= 1.25 x ULN; Gamma glutamyl transferase >= 1.5 x ULN.
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2, CKD Stage 3a includes subjects with eGFR >= 45 to < 60 mL/min/1.73m2.

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Table E-506 Baseline Value of Fasting Plasma Glucose (mg/dL) by Subgroup in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Efficacy Population)

Parameter Subgroup	Placebo + Insulin N = 106		Imeglimin 1000 mg bid + Insulin N = 108	
Category	n	Mean (SD)	n	Mean (SD)
Fasting Plasma Glucose (mg/dL)				
Population				
All	106	146.78 (37.934)	108	153.03 (37.690)
Age group				
< 65 years	75	145.95 (38.258)	68	159.28 (40.907)
>= 65 years	31	148.77 (37.686)	40	142.41 (28.963)
< 75 years	103	146.84 (37.756)	101	155.40 (36.930)
>= 75 years	3	144.73 (53.270)	7	118.90 (33.896)
Sex				
Male	68	150.22 (35.868)	66	154.50 (37.703)
Female	38	140.62 (41.148)	42	150.73 (38.011)
eGFR CKD Stage				
Stage 1	14	155.06 (35.735)	16	154.71 (46.464)
Stage 2	92	145.51 (38.285)	92	152.74 (36.247)
Hepatic parameter abnormality				
Yes	14	165.61 (32.814)	17	165.32 (38.841)
No	92	143.91 (37.995)	91	150.74 (37.240)
BMI at baseline				
< 25 kg/m2	60	138.39 (38.912)	56	144.38 (35.118)
>= 25 kg/m2	46	157.71 (34.004)	52	162.35 (38.467)
>= 25 to < 30 kg/m2	35	152.36 (33.990)	44	160.26 (36.489)
>= 30 kg/m2	11	174.75 (29.250)	8	173.85 (49.225)
HbA1c at baseline				
< 8.0%	16	122.51 (28.591)	16	135.57 (27.500)
>= 8.0%	90	151.09 (37.883)	92	156.07 (38.506)
>= 8.0 to < 9.0%	44	141.55 (33.908)	53	143.75 (33.433)
>= 9.0%	46	160.22 (39.566)	39	172.81 (39.010)
Duration of type 2 diabetes				
< 5 years	12	170.40 (31.733)	16	151.78 (45.905)
>= 5 years	94	143.76 (37.740)	92	153.25 (36.368)
Complication of diabetes				
Yes	52	144.09 (37.537)	45	149.17 (39.141)
No	54	149.36 (38.484)	63	155.79 (36.685)
Metabolic syndrome at baseline				
Yes	49	157.62 (34.263)	39	171.75 (29.973)
No	57	137.46 (38.736)	69	142.45 (37.666)
Previous treatment status				
Insulin monotherapy	85	144.61 (37.521)	87	154.56 (37.878)
Insulin in combination with 1 OHA	21	155.53 (39.257)	21	146.70 (37.125)
FPG at baseline				
< 160 mg/dL	68	123.41 (24.003)	61	127.11 (22.931)

Parameter Subgroup	Placebo + Insulin N = 106		Imeglimin 1000 mg bid + Insulin N = 108	
Category	n	Mean (SD)	n	Mean (SD)
>= 160 mg/dL	38	188.59 (15.509)	47	186.67 (23.902)

- Abbreviations: bid, Twice a day; SD, standard deviation; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); BMI, body mass index; eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease; FPG, Fasting Plasma Glucose; 1 OHA, Patients on insulin in combination with one oral hypoglycemic agent
- Complication of diabetes is defined as any MedDRA Preferred Term (PT) of medical history which are included in High-Level Group Term (HLGT) of diabetic complication.
- Metabolic Syndrome is defined as an excessive waist circumference (>= 85 cm in men and >= 90 cm in women) as well as the presence of two or more of the following symptoms: (1) Hypertension: systolic blood pressure >= 130 mmHg, or diastolic blood pressure >= 85 mmHg; (2) Glucose intolerance: fasting glucose >= 110 mg/dL; (3) Dyslipidemia: triglyceride >= 150 mg/dL, or HDL cholesterol < 40 mg/dL.
- Hepatic parameter abnormality is defined as any one of following parameter applied: Total Bilirubin >= 1.6 mg/dL; Aspartate aminotransferase (AST) >= 1.25 x Upper Limit of Normal (ULN); AST >= 50 IU; Alanine aminotransferase (ALT) >= 1.25 x ULN; ALT >= 50 IU; Alkaline phosphatase >= 1.25 x ULN; Gamma glutamyl transferase >= 1.5 x ULN.
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2, CKD Stage 3a includes subjects with eGFR >= 45 to < 60 mL/min/1.73m2.

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Table E-507 Baseline Value of HbA1c (%) by Subgroup in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Efficacy Population)

Parameter Subgroup Category	Placebo/Imeglimin + Insulin N = 101 n	Mean (SD)	Imeglimin/Imeglimin + Insulin N = 108 n	Mean (SD)	Imeglimin + Insulin Total N = 209 n	Mean (SD)
HbA1c (%)						
Population						
All	101	8.72 (0.987)	108	8.74 (0.721)	209	8.73 (0.858)
Age group						
< 65 years	72	8.85 (0.982)	68	8.77 (0.710)	140	8.81 (0.859)
>= 65 years	29	8.41 (0.944)	40	8.69 (0.745)	69	8.57 (0.839)
< 75 years	98	8.75 (0.990)	101	8.74 (0.713)	199	8.74 (0.859)
>= 75 years	3	7.90 (0.346)	7	8.80 (0.894)	10	8.53 (0.865)
Sex						
Male	64	8.50 (0.927)	66	8.64 (0.617)	130	8.57 (0.786)
Female	37	9.12 (0.976)	42	8.90 (0.844)	79	9.00 (0.909)
eGFR CKD Stage						
Stage 1	13	8.98 (0.912)	16	8.77 (0.525)	29	8.86 (0.718)
Stage 2	88	8.69 (0.997)	92	8.74 (0.752)	180	8.71 (0.879)
Hepatic parameter abnormality						
Yes	14	8.99 (0.803)	17	8.98 (0.713)	31	8.99 (0.742)
No	87	8.68 (1.011)	91	8.70 (0.717)	178	8.69 (0.871)
BMI at baseline						
< 25 kg/m2	58	8.46 (0.958)	56	8.73 (0.699)	114	8.60 (0.848)
>= 25 kg/m2	43	9.07 (0.925)	52	8.75 (0.751)	95	8.90 (0.846)
>= 25 to < 30 kg/m2	33	9.03 (0.905)	44	8.73 (0.746)	77	8.86 (0.826)
>= 30 kg/m2	10	9.22 (1.025)	8	8.83 (0.826)	18	9.04 (0.937)
HbA1c at baseline						
< 8.0%	16	7.78 (0.480)	16	7.73 (0.148)	32	7.75 (0.350)
>= 8.0%	85	8.90 (0.957)	92	8.92 (0.628)	177	8.91 (0.801)
>= 8.0 to < 9.0%	41	8.31 (0.763)	53	8.48 (0.277)	94	8.40 (0.548)
>= 9.0%	44	9.45 (0.777)	39	9.52 (0.451)	83	9.48 (0.642)
Duration of type 2 diabetes						
< 5 years	11	9.31 (0.883)	16	8.52 (0.819)	27	8.84 (0.918)
>= 5 years	90	8.65 (0.980)	92	8.78 (0.700)	182	8.72 (0.850)
Complication of diabetes						
Yes	48	8.74 (0.952)	45	8.71 (0.678)	93	8.73 (0.826)
No	53	8.71 (1.027)	63	8.76 (0.755)	116	8.74 (0.886)
Metabolic syndrome at baseline						
Yes	46	9.05 (0.819)	39	8.85 (0.803)	85	8.96 (0.813)
No	55	8.45 (1.037)	69	8.68 (0.668)	124	8.58 (0.856)
Previous treatment status						
Insulin monotherapy	83	8.69 (0.999)	87	8.66 (0.691)	170	8.67 (0.853)
Insulin in combination with 1 OHA	18	8.88 (0.943)	21	9.08 (0.759)	39	8.99 (0.844)
FPG at baseline						
< 160 mg/dL	65	8.50 (0.911)	61	8.51 (0.638)	126	8.50 (0.787)

Parameter Subgroup	Placebo/Imeglimin + Insulin N = 101		Imeglimin/Imeglimin + Insulin N = 108		Imeglimin + Insulin Total N = 209	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
>= 160 mg/dL	36	9.13 (1.003)	47	9.04 (0.720)	83	9.08 (0.850)

- Abbreviations: SD, standard deviation; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); BMI, body mass index; eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease; FPG, Fasting Plasma Glucose; 1 OHA, Patients on insulin in combination with one oral hypoglycemic agent
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- For "Placebo/Imeglimin + Insulin" group, baseline was defined as last visit with non-missing value prior to or at the day of first dose of Investigational Medicinal Product (IMP) in open-label treatment period. For "Imeglimin/Imeglimin + Insulin" group, baseline was the same as for the double-blind treatment period.
- Complication of diabetes is defined as any MedDRA Preferred Term (PT) of medical history which are included in High-Level Group Term (HLGT) of diabetic complication.
- Metabolic Syndrome is defined as an excessive waist circumference (>= 85 cm in men and >= 90 cm in women) as well as the presence of two or more of the following symptoms: (1) Hypertension: systolic blood pressure >= 130 mmHg, or diastolic blood pressure >= 85 mmHg; (2) Glucose intolerance: fasting glucose >= 110 mg/dL; (3) Dyslipidemia: triglyceride >= 150 mg/dL, or HDL cholesterol < 40 mg/dL.
- Hepatic parameter abnormality is defined as any one of following parameter applied: Total Bilirubin >= 1.6 mg/dL; Aspartate aminotransferase (AST) >= 1.25 x Upper Limit of Normal (ULN); AST >= 50 IU; Alanine aminotransferase (ALT) >= 1.25 x ULN; ALT >= 50 IU; Alkaline phosphatase >= 1.25 x ULN; Gamma glutamyl transferase >= 1.5 x ULN.
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2, CKD Stage 3a includes subjects with eGFR >= 45 to < 60 mL/min/1.73m2.

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Table E-508 Baseline Value of Fasting Plasma Glucose (mg/dL) by Subgroup in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Efficacy Population)

Parameter Subgroup Category	Placebo/Imeglimin + Insulin N = 101 n	Mean (SD)	Imeglimin/Imeglimin + Insulin N = 108 n	Mean (SD)	Imeglimin + Insulin Total N = 209 n	Mean (SD)
Fasting Plasma Glucose (mg/dL)						
Population						
All	101	147.09 (40.389)	108	153.03 (37.690)	209	150.16 (39.037)
Age group						
< 65 years	72	145.23 (40.219)	68	159.28 (40.907)	140	152.05 (41.019)
>= 65 years	29	151.70 (41.151)	40	142.41 (28.963)	69	146.32 (34.637)
< 75 years	98	146.62 (40.915)	101	155.40 (36.930)	199	151.08 (39.093)
>= 75 years	3	162.14 (4.766)	7	118.90 (33.896)	10	131.87 (34.745)
Sex						
Male	64	150.74 (38.060)	66	154.50 (37.703)	130	152.65 (37.779)
Female	37	140.76 (43.949)	42	150.73 (38.011)	79	146.06 (40.939)
eGFR CKD Stage						
Stage 1	13	153.13 (45.237)	16	154.71 (46.464)	29	154.00 (45.102)
Stage 2	88	146.19 (39.831)	92	152.74 (36.247)	180	149.54 (38.076)
Hepatic parameter abnormality						
Yes	14	146.83 (36.257)	17	165.32 (38.841)	31	156.97 (38.233)
No	87	147.13 (41.208)	91	150.74 (37.240)	178	148.97 (39.160)
BMI at baseline						
< 25 kg/m2	58	138.07 (41.126)	56	144.38 (35.118)	114	141.17 (38.255)
>= 25 kg/m2	43	159.25 (36.398)	52	162.35 (38.467)	95	160.95 (37.379)
>= 25 to < 30 kg/m2	33	158.81 (38.143)	44	160.26 (36.489)	77	159.64 (36.965)
>= 30 kg/m2	10	160.70 (31.729)	8	173.85 (49.225)	18	166.54 (39.698)
HbA1c at baseline						
< 8.0%	16	127.35 (40.406)	16	135.57 (27.500)	32	131.46 (34.254)
>= 8.0%	85	150.80 (39.526)	92	156.07 (38.506)	177	153.54 (38.977)
>= 8.0 to < 9.0%	41	140.83 (39.661)	53	143.75 (33.433)	94	142.48 (36.106)
>= 9.0%	44	160.09 (37.490)	39	172.81 (39.010)	83	166.07 (38.510)
Duration of type 2 diabetes						
< 5 years	11	154.61 (41.277)	16	151.78 (45.905)	27	152.93 (43.279)
>= 5 years	90	146.17 (40.418)	92	153.25 (36.368)	182	149.75 (38.482)
Complication of diabetes						
Yes	48	146.71 (41.176)	45	149.17 (39.141)	93	147.90 (40.005)
No	53	147.42 (40.055)	63	155.79 (36.685)	116	151.97 (38.322)
Metabolic syndrome at baseline						
Yes	46	161.16 (36.395)	39	171.75 (29.973)	85	166.02 (33.826)
No	55	135.31 (40.089)	69	142.45 (37.666)	124	139.29 (38.763)
Previous treatment status						
Insulin monotherapy	83	146.30 (38.541)	87	154.56 (37.878)	170	150.53 (38.315)
Insulin in combination with 1 OHA	18	150.73 (49.128)	21	146.70 (37.125)	39	148.56 (42.536)
FPG at baseline						
< 160 mg/dL	65	133.07 (34.639)	61	127.11 (22.931)	126	130.18 (29.591)

Parameter Subgroup	Placebo/Imeglimin + Insulin N = 101		Imeglimin/Imeglimin + Insulin N = 108		Imeglimin + Insulin Total N = 209	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
>= 160 mg/dL	36	172.40 (37.983)	47	186.67 (23.902)	83	180.48 (31.415)

- Abbreviations: SD, standard deviation; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); BMI, body mass index; eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease; FPG, Fasting Plasma Glucose; 1 OHA, Patients on insulin in combination with one oral hypoglycemic agent
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- For "Placebo/Imeglimin + Insulin" group, baseline was defined as last visit with non-missing value prior to or at the day of first dose of Investigational Medicinal Product (IMP) in open-label treatment period. For "Imeglimin/Imeglimin + Insulin" group, baseline was the same as for the double-blind treatment period.
- Complication of diabetes is defined as any MedDRA Preferred Term (PT) of medical history which are included in High-Level Group Term (HLGT) of diabetic complication.
- Metabolic Syndrome is defined as an excessive waist circumference (>= 85 cm in men and >= 90 cm in women) as well as the presence of two or more of the following symptoms: (1) Hypertension: systolic blood pressure >= 130 mmHg, or diastolic blood pressure >= 85 mmHg; (2) Glucose intolerance: fasting glucose >= 110 mg/dL; (3) Dyslipidemia: triglyceride >= 150 mg/dL, or HDL cholesterol < 40 mg/dL.
- Hepatic parameter abnormality is defined as any one of following parameter applied: Total Bilirubin >= 1.6 mg/dL; Aspartate aminotransferase (AST) >= 1.25 x Upper Limit of Normal (ULN); AST >= 50 IU; Alanine aminotransferase (ALT) >= 1.25 x ULN; ALT >= 50 IU; Alkaline phosphatase >= 1.25 x ULN; Gamma glutamyl transferase >= 1.5 x ULN.
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2, CKD Stage 3a includes subjects with eGFR >= 45 to < 60 mL/min/1.73m2.

Control No:<<t-e-508-subgl-020lt.sas, 2020-03-09T15:53:07>>

Table E-509 Analysis of Change from Baseline in HbA1c (%) to Week 24 (LOCF) in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Efficacy Population)

Parameter Study Treatment	N	n	Mean (SD)
HbA1c (%)			
Study 014			
Placebo	75	75	0.37 (0.913)
Imeglimin 500 mg bid	75	75	-0.10 (0.627)
Imeglimin 1000 mg bid	73	73	-0.49 (0.571)
Imeglimin 1500 mg bid	73	73	-0.54 (0.708)
Study 018			
Placebo	106	106	0.14 (0.643)
Imeglimin 1000 mg bid	106	105	-0.71 (0.633)
Pooled (Studies 014+018)			
Placebo	181	181	0.23 (0.772)
Imeglimin 1000 mg bid	179	178	-0.62 (0.617)

- Abbreviations: bid, Twice a day; SD, standard deviation; LOCF, Last Observation Carried Forward; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c)

Control No:<<t-e-509-hba1c-24wdb.sas, 2020-03-09T15:53:17>>

Table E-510 Analysis of Change from Baseline in Fasting Plasma Glucose (mg/dL) to Week 24 (LOCF) in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Efficacy Population)

Parameter Study Treatment	N	n	Mean (SD)
Fasting Plasma Glucose (mg/dL)			
Study 014			
Placebo	75	75	13.47 (34.193)
Imeglimin 500 mg bid	75	75	4.01 (26.297)
Imeglimin 1000 mg bid	73	73	-11.70 (21.571)
Imeglimin 1500 mg bid	73	73	-12.52 (27.429)
Study 018			
Placebo	106	106	5.37 (25.704)
Imeglimin 1000 mg bid	106	105	-12.95 (25.236)
Pooled (Studies 014+018)			
Placebo	181	181	8.73 (29.699)
Imeglimin 1000 mg bid	179	178	-12.44 (23.745)

- Abbreviations: bid, Twice a day; SD, standard deviation; LOCF, Last Observation Carried Forward

Control No:<<t-e-510-gluco-24wdb.sas, 2020-03-09T15:53:28>>

Table E-511 MMRM Analysis of Change from Baseline in HbA1c (%) to All Visits in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Efficacy Population)

Population		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
All									
Baseline									
Placebo	181	181	7.91 (0.679)						
Imeglimin 1000 mg bid	179	179	7.93 (0.721)						
Week 4									
Placebo	181	180	7.95 (0.777)	0.05 (0.297)	0.05 (0.021)	[0.008, 0.089]			
Imeglimin 1000 mg bid	179	178	7.69 (0.734)	-0.25 (0.252)	-0.24 (0.021)	[-0.286, -0.204]	-0.29 (0.029)	[-0.350, -0.236]	<.0001
Week 8									
Placebo	181	179	7.99 (0.860)	0.10 (0.432)	0.11 (0.032)	[0.047, 0.172]			
Imeglimin 1000 mg bid	179	175	7.47 (0.711)	-0.45 (0.400)	-0.45 (0.032)	[-0.509, -0.383]	-0.56 (0.045)	[-0.644, -0.467]	<.0001
Week 12									
Placebo	181	171	7.96 (0.810)	0.12 (0.529)	0.16 (0.040)	[0.081, 0.239]			
Imeglimin 1000 mg bid	179	173	7.36 (0.729)	-0.56 (0.495)	-0.55 (0.040)	[-0.634, -0.475]	-0.71 (0.057)	[-0.826, -0.603]	<.0001
Week 16									
Placebo	181	165	7.90 (0.787)	0.08 (0.569)	0.16 (0.045)	[0.075, 0.253]			
Imeglimin 1000 mg bid	179	170	7.27 (0.770)	-0.66 (0.505)	-0.64 (0.045)	[-0.730, -0.552]	-0.80 (0.064)	[-0.930, -0.679]	<.0001
Week 20									
Placebo	181	164	7.91 (0.817)	0.10 (0.620)	0.20 (0.050)	[0.098, 0.295]			
Imeglimin 1000 mg bid	179	168	7.23 (0.780)	-0.69 (0.556)	-0.67 (0.050)	[-0.766, -0.569]	-0.86 (0.071)	[-1.002, -0.724]	<.0001
Week 24									
Placebo	181	161	7.93 (0.851)	0.13 (0.707)	0.25 (0.055)	[0.143, 0.360]			
Imeglimin 1000 mg bid	179	164	7.26 (0.745)	-0.66 (0.584)	-0.63 (0.055)	[-0.738, -0.521]	-0.88 (0.078)	[-1.034, -0.727]	<.0001
LOCF Endpoint									
Placebo	181	181	8.15 (1.082)	0.23 (0.772)					

Population		Observed		Change from baseline			Difference vs Placebo		
Visit									
Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Imeglimin 1000 mg bid	179	178	7.31 (0.826)	-0.62 (0.617)					

- Abbreviations: MMRM, Mixed Model Repeated Measures; LOCF, Last Observation Carried Forward; bid, Twice a day; SD, standard deviation; SE, standard error; LS, least square; CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c)
- MMRM model was used with fixed effects for treatment group, visit, study, interaction of treatment-by-visit, and baseline HbA1c as a covariate, assuming an unstructured covariance matrix.

Control No:<<t-e-511-hba1c-24wdb.sas, 2020-03-09T15:53:43>>

Table E-512 Analysis of HbA1c Response at Week 24 (LOCF) in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Efficacy Population)

Response Study Treatment	N	n (%)	[95% CI]
HbA1c < 7.0%			
Study 014			
Placebo	75	5 (6.7%)	[2.2, 14.9]
Imeglimin 500 mg bid	75	10 (13.3%)	[6.6, 23.2]
Imeglimin 1000 mg bid	73	28 (38.4%)	[27.2, 50.5]
Imeglimin 1500 mg bid	73	21 (28.8%)	[18.8, 40.6]
Study 018			
Placebo	106	8 (7.5%)	[3.3, 14.3]
Imeglimin 1000 mg bid	106	40 (37.7%)	[28.5, 47.7]
Pooled (Studies 014+018)			
Placebo	181	13 (7.2%)	[3.9, 12.0]
Imeglimin 1000 mg bid	179	68 (38.0%)	[30.9, 45.5]
HbA1c decrease >= 0.5%			
Study 014			
Placebo	75	8 (10.7%)	[4.7, 19.9]
Imeglimin 500 mg bid	75	23 (30.7%)	[20.5, 42.4]
Imeglimin 1000 mg bid	73	43 (58.9%)	[46.8, 70.3]
Imeglimin 1500 mg bid	73	39 (53.4%)	[41.4, 65.2]
Study 018			
Placebo	106	13 (12.3%)	[6.7, 20.1]
Imeglimin 1000 mg bid	106	72 (67.9%)	[58.2, 76.7]
Pooled (Studies 014+018)			
Placebo	181	21 (11.6%)	[7.3, 17.2]
Imeglimin 1000 mg bid	179	115 (64.2%)	[56.8, 71.3]
HbA1c decrease >= 1.0%			
Study 014			

Response			
Study			
Treatment	N	n (%)	[95% CI]
Placebo	75	4 (5.3%)	[1.5, 13.1]
Imeglimin 500 mg bid	75	4 (5.3%)	[1.5, 13.1]
Imeglimin 1000 mg bid	73	12 (16.4%)	[8.8, 27.0]
Imeglimin 1500 mg bid	73	17 (23.3%)	[14.2, 34.6]
Study 018			
Placebo	106	1 (0.9%)	[0.0, 5.1]
Imeglimin 1000 mg bid	106	33 (31.1%)	[22.5, 40.9]
Pooled (Studies 014+018)			
Placebo	181	5 (2.8%)	[0.9, 6.3]
Imeglimin 1000 mg bid	179	45 (25.1%)	[19.0, 32.2]
Percent HbA1c decrease >= 7%			
Study 014			
Placebo	75	7 (9.3%)	[3.8, 18.3]
Imeglimin 500 mg bid	75	19 (25.3%)	[16.0, 36.7]
Imeglimin 1000 mg bid	73	36 (49.3%)	[37.4, 61.3]
Imeglimin 1500 mg bid	73	32 (43.8%)	[32.2, 55.9]
Study 018			
Placebo	106	12 (11.3%)	[6.0, 18.9]
Imeglimin 1000 mg bid	106	63 (59.4%)	[49.5, 68.9]
Pooled (Studies 014+018)			
Placebo	181	19 (10.5%)	[6.4, 15.9]

Response Study Treatment	N	n (%)	[95% CI]
Imeglimin 1000 mg bid	179	99 (55.3%)	[47.7, 62.7]

- Abbreviations: bid, Twice a day; CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); LOCF, Last Observation Carried Forward
- Confidence interval for proportion was calculated with Clopper-Pearson exact method.
- N is the number of patients in the analysis population and was used as the denominator to calculate percentage.
- Patients who have no HbA1c measurement are defined as non-responders.

Control No:<<t-e-512-respo-24wdb.sas, 2020-03-09T15:53:54>>

Table E-513 Subgroup Analysis of Change from Baseline in HbA1c (%) to Week 24 (LOCF) by HOMA-B, HOMA-IR and QUICKI in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Efficacy Population)

Parameter	Study 014								Study 018				Pooled (Studies 014+018)			
	Placebo		Imeglimin 500 mg bid		Imeglimin 1000 mg bid		Imeglimin 1500 mg bid		Placebo		Imeglimin 1000 mg bid		Placebo		Imeglimin 1000 mg bid	
Subgroup	N = 75		N = 75		N = 73		N = 73		N = 106		N = 106		N = 181		N = 179	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
HbA1c (%)																
HOMA-B x HOMA-IR at baseline																
< 30.0%, < 2.5	24	0.34 (0.822)	30	-0.27 (0.597)	32	-0.45 (0.626)	20	-0.51 (0.518)	61	0.07 (0.528)	62	-0.67 (0.544)	85	0.15 (0.631)	94	-0.59 (0.579)
< 30.0%, >= 2.5 to < 4.0	7	0.00 (1.042)	9	0.02 (0.587)	9	-0.52 (0.432)	7	-0.49 (0.402)	14	0.36 (0.817)	15	-1.09 (0.610)	21	0.24 (0.889)	24	-0.88 (0.608)
< 30.0%, >= 4.0	3	1.60 (0.400)	4	0.63 (0.427)	7	-0.23 (0.699)	5	-1.12 (0.356)	3	0.77 (1.436)	8	-0.73 (1.300)	6	1.18 (1.048)	15	-0.49 (1.059)
>= 30.0%, < 2.5	3	0.03 (0.351)	2	0.25 (0.354)	2	-0.10 (0.707)	2	-0.50 (0.141)	3	0.70 (1.136)	5	-0.36 (0.391)	6	0.37 (0.836)	7	-0.29 (0.449)
>= 30.0%, >= 2.5 to < 4.0	13	0.33 (0.379)	7	0.17 (0.613)	7	-0.60 (0.342)	6	-0.72 (0.527)	13	-0.02 (0.368)	4	-0.80 (0.316)	26	0.15 (0.408)	11	-0.67 (0.332)
>= 30.0%, >= 4.0	24	0.41 (1.168)	23	-0.17 (0.644)	16	-0.68 (0.529)	33	-0.45 (0.900)	12	0.08 (0.748)	11	-0.59 (0.509)	36	0.30 (1.048)	27	-0.64 (0.513)
Missing	1	0.40 (.)	0	.	0	.	0	.	0	.	0	.	1	0.40 (.)	0	.
HOMA-B x QUICKI at baseline																
< 30.0%, < 0.33	9	0.54 (1.217)	12	0.21 (0.626)	15	-0.34 (0.540)	9	-0.89 (0.426)	14	0.44 (1.001)	18	-0.97 (0.929)	23	0.48 (1.064)	33	-0.68 (0.829)
< 30.0%, >= 0.33	25	0.32 (0.810)	31	-0.25 (0.593)	33	-0.47 (0.630)	23	-0.48 (0.508)	64	0.09 (0.522)	67	-0.69 (0.570)	89	0.15 (0.621)	100	-0.62 (0.596)
>= 30.0%, < 0.33	35	0.35 (0.974)	29	-0.09 (0.654)	23	-0.66 (0.474)	38	-0.48 (0.864)	23	0.08 (0.563)	12	-0.63 (0.499)	58	0.24 (0.840)	35	-0.65 (0.475)
>= 30.0%, >= 0.33	5	0.40 (0.612)	3	0.20 (0.265)	2	-0.10 (0.707)	3	-0.53 (0.115)	5	0.18 (1.076)	8	-0.50 (0.400)	10	0.29 (0.833)	10	-0.42 (0.457)

Parameter Subgroup Category	Study 014 Placebo N = 75 n	Mean (SD)	Imeglimin 500 mg bid N = 75 n	Mean (SD)	Imeglimin 1000 mg bid N = 73 n	Mean (SD)	Imeglimin 1500 mg bid N = 73 n	Mean (SD)	Study 018 Placebo N = 106 n	Mean (SD)	Imeglimin 1000 mg bid N = 106 n	Mean (SD)	Pooled (Studies 014+018) Placebo N = 181 n	Mean (SD)	Imeglimin 1000 mg bid N = 179 n	Mean (SD)
Missing	1	0.40 (.)	0	.	0	.	0	.	0	.	0	.	1	0.40 (.)	0	.

- Abbreviations: LOCF, Last Observation Carried Forward; bid, Twice a day; SD, standard deviation; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); HOMA, Homeostasis model assessment; HOMA-IR, HOMA of insulin resistance; HOMA-B, HOMA of beta-cell function; QUICKI, Quantitative Insulin Sensitivity Check Index

Control No:<<t-e-513-subhb-24wdb.sas, 2020-03-09T15:54:06>>

Table E-514 Subgroup and MMRM Analysis of Change from Baseline in HbA1c (%) to All Visits by HOMA-B x HOMA-IR in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Efficacy Population)

HOMA-B x HOMA-IR at baseline		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
< 30.0%, < 2.5									
Baseline									
Placebo	85	85	7.90 (0.618)						
Imeglimin 1000 mg bid	94	94	7.73 (0.656)						
Week 4									
Placebo	85	85	7.92 (0.674)	0.03 (0.236)	0.04 (0.027)	[-0.015, 0.092]			
Imeglimin 1000 mg bid	94	94	7.50 (0.679)	-0.23 (0.242)	-0.22 (0.026)	[-0.270, -0.169]	-0.26 (0.036)	[-0.329, -0.187]	<.0001
Week 8									
Placebo	85	85	7.98 (0.779)	0.09 (0.386)	0.10 (0.045)	[0.009, 0.185]			
Imeglimin 1000 mg bid	94	94	7.32 (0.687)	-0.42 (0.421)	-0.41 (0.042)	[-0.491, -0.325]	-0.51 (0.061)	[-0.625, -0.385]	<.0001
Week 12									
Placebo	85	83	7.96 (0.805)	0.08 (0.449)	0.10 (0.052)	[-0.003, 0.203]			
Imeglimin 1000 mg bid	94	93	7.21 (0.660)	-0.53 (0.500)	-0.51 (0.049)	[-0.607, -0.412]	-0.61 (0.071)	[-0.750, -0.469]	<.0001
Week 16									
Placebo	85	80	7.84 (0.734)	0.00 (0.468)	0.05 (0.056)	[-0.060, 0.159]			
Imeglimin 1000 mg bid	94	92	7.12 (0.722)	-0.62 (0.506)	-0.61 (0.052)	[-0.710, -0.503]	-0.66 (0.076)	[-0.805, -0.507]	<.0001
Week 20									
Placebo	85	80	7.90 (0.767)	0.06 (0.547)	0.11 (0.061)	[-0.016, 0.227]			
Imeglimin 1000 mg bid	94	91	7.08 (0.682)	-0.64 (0.538)	-0.62 (0.058)	[-0.737, -0.509]	-0.73 (0.084)	[-0.894, -0.563]	<.0001
Week 24									
Placebo	85	78	7.90 (0.708)	0.09 (0.596)	0.17 (0.068)	[0.034, 0.303]			
Imeglimin 1000 mg bid	94	88	7.13 (0.720)	-0.59 (0.594)	-0.58 (0.064)	[-0.708, -0.455]	-0.75 (0.093)	[-0.934, -0.566]	<.0001
LOCF Endpoint									
Placebo	85	85	8.04 (0.845)	0.15 (0.631)					
Imeglimin 1000 mg bid	94	94	7.14 (0.727)	-0.59 (0.579)					

HOMA-B x HOMA-IR at baseline Visit Treatment	N	Observed n	Mean (SD)	Change from baseline Mean (SD)	LS Mean (SE)	[95% CI]	Difference vs Placebo LS Mean (SE)	[95% CI]	P-value
< 30.0%, >= 2.5 to < 4.0									
Baseline									
Placebo	21	21	8.34 (0.778)						
Imeglimin 1000 mg bid	24	24	8.45 (0.630)						
Week 4									
Placebo	21	21	8.37 (1.027)	0.03 (0.458)	0.05 (0.086)	[-0.122, 0.226]			
Imeglimin 1000 mg bid	24	24	8.10 (0.611)	-0.35 (0.298)	-0.34 (0.080)	[-0.505, -0.184]	-0.40 (0.115)	[-0.628, -0.165]	0.0013
Week 8									
Placebo	21	21	8.49 (1.147)	0.15 (0.594)	0.17 (0.109)	[-0.048, 0.390]			
Imeglimin 1000 mg bid	24	24	7.82 (0.515)	-0.63 (0.357)	-0.62 (0.101)	[-0.827, -0.420]	-0.79 (0.146)	[-1.089, -0.500]	<.0001
Week 12									
Placebo	21	18	8.14 (0.598)	0.01 (0.463)	0.23 (0.135)	[-0.047, 0.499]			
Imeglimin 1000 mg bid	24	23	7.68 (0.575)	-0.79 (0.468)	-0.77 (0.125)	[-1.022, -0.517]	-1.00 (0.182)	[-1.364, -0.627]	<.0001
Week 16									
Placebo	21	18	8.14 (0.663)	0.01 (0.666)	0.24 (0.161)	[-0.085, 0.568]			
Imeglimin 1000 mg bid	24	23	7.63 (0.675)	-0.84 (0.504)	-0.82 (0.147)	[-1.120, -0.522]	-1.06 (0.216)	[-1.502, -0.623]	<.0001
Week 20									
Placebo	21	18	8.17 (0.803)	0.04 (0.793)	0.28 (0.184)	[-0.097, 0.652]			
Imeglimin 1000 mg bid	24	23	7.57 (0.810)	-0.91 (0.598)	-0.89 (0.168)	[-1.227, -0.544]	-1.16 (0.248)	[-1.667, -0.658]	<.0001
Week 24									
Placebo	21	18	8.22 (0.858)	0.08 (0.821)	0.33 (0.190)	[-0.053, 0.718]			
Imeglimin 1000 mg bid	24	23	7.57 (0.763)	-0.90 (0.609)	-0.88 (0.173)	[-1.228, -0.524]	-1.21 (0.255)	[-1.727, -0.689]	<.0001
LOCF Endpoint									
Placebo	21	21	8.58 (1.253)	0.24 (0.889)					
Imeglimin 1000 mg bid	24	24	7.57 (0.747)	-0.88 (0.608)					
< 30.0%, >= 4.0									
Baseline									
Placebo	6	6	9.12 (0.808)						

HOMA-B x HOMA-IR at baseline		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Imeglimin 1000 mg bid	15	15	8.61 (0.699)						
Week 4									
Placebo	6	5	9.46 (0.730)	0.56 (0.483)	0.62 (0.176)	[0.242, 0.989]			
Imeglimin 1000 mg bid	15	15	8.43 (0.726)	-0.18 (0.321)	-0.18 (0.097)	[-0.383, 0.030]	-0.79 (0.201)	[-1.218, -0.366]	0.0012
Week 8									
Placebo	6	4	9.30 (0.408)	0.53 (0.532)	0.74 (0.260)	[0.186, 1.289]			
Imeglimin 1000 mg bid	15	14	8.14 (0.723)	-0.43 (0.541)	-0.40 (0.140)	[-0.699, -0.099]	-1.14 (0.295)	[-1.764, -0.508]	0.0015
Week 12									
Placebo	6	4	9.58 (0.519)	0.80 (0.956)	1.05 (0.410)	[0.182, 1.918]			
Imeglimin 1000 mg bid	15	14	8.04 (0.907)	-0.53 (0.807)	-0.49 (0.220)	[-0.962, -0.022]	-1.54 (0.465)	[-2.529, -0.555]	0.0044
Week 16									
Placebo	6	4	9.65 (1.054)	0.88 (1.170)	1.11 (0.493)	[0.052, 2.177]			
Imeglimin 1000 mg bid	15	13	7.80 (0.959)	-0.82 (0.730)	-0.61 (0.265)	[-1.182, -0.033]	-1.72 (0.560)	[-2.930, -0.514]	0.0087
Week 20									
Placebo	6	3	9.47 (1.115)	0.43 (0.874)	1.18 (0.547)	[-0.017, 2.381]			
Imeglimin 1000 mg bid	15	13	7.83 (1.100)	-0.78 (0.841)	-0.58 (0.291)	[-1.217, 0.066]	-1.76 (0.620)	[-3.118, -0.397]	0.0159
Week 24									
Placebo	6	2	9.55 (1.909)	0.85 (1.626)	1.69 (0.523)	[0.538, 2.842]			
Imeglimin 1000 mg bid	15	12	7.63 (0.584)	-0.88 (0.670)	-0.58 (0.277)	[-1.196, 0.029]	-2.27 (0.592)	[-3.579, -0.968]	0.0028
LOCF Endpoint									
Placebo	6	6	10.30 (1.207)	1.18 (1.048)					
Imeglimin 1000 mg bid	15	15	8.12 (1.160)	-0.49 (1.059)					
>= 30.0%, < 2.5									
Baseline									
Placebo	6	6	7.25 (0.259)						
Imeglimin 1000 mg bid	7	7	7.44 (0.251)						
Week 4									
Placebo	6	6	7.22 (0.194)	-0.03 (0.103)	0.02 (0.075)	[-0.147, 0.196]			

HOMA-B x HOMA-IR at baseline		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Imeglimin 1000 mg bid	7	7	7.21 (0.334)	-0.23 (0.180)	-0.21 (0.062)	[-0.350, -0.063]	-0.23 (0.096)	[-0.452, -0.011]	0.0417
Week 8									
Placebo	6	6	7.23 (0.339)	-0.02 (0.160)	0.04 (0.115)	[-0.216, 0.299]			
Imeglimin 1000 mg bid	7	7	7.11 (0.380)	-0.33 (0.269)	-0.31 (0.102)	[-0.537, -0.077]	-0.35 (0.153)	[-0.691, -0.005]	0.0475
Week 12									
Placebo	6	5	7.40 (0.495)	0.08 (0.311)	0.14 (0.142)	[-0.178, 0.451]			
Imeglimin 1000 mg bid	7	7	7.03 (0.457)	-0.41 (0.313)	-0.39 (0.121)	[-0.664, -0.121]	-0.53 (0.186)	[-0.942, -0.116]	0.0170
Week 16									
Placebo	6	5	7.68 (0.712)	0.36 (0.518)	0.41 (0.182)	[0.011, 0.810]			
Imeglimin 1000 mg bid	7	7	7.07 (0.486)	-0.37 (0.350)	-0.35 (0.158)	[-0.701, 0.002]	-0.76 (0.239)	[-1.289, -0.230]	0.0093
Week 20									
Placebo	6	5	7.66 (0.868)	0.34 (0.699)	0.39 (0.222)	[-0.103, 0.875]			
Imeglimin 1000 mg bid	7	7	7.07 (0.464)	-0.37 (0.359)	-0.35 (0.188)	[-0.766, 0.067]	-0.74 (0.289)	[-1.375, -0.096]	0.0281
Week 24									
Placebo	6	5	7.76 (1.074)	0.44 (0.913)	0.49 (0.288)	[-0.145, 1.118]			
Imeglimin 1000 mg bid	7	7	7.16 (0.500)	-0.29 (0.449)	-0.26 (0.247)	[-0.810, 0.282]	-0.75 (0.378)	[-1.583, 0.082]	0.0728
LOCF Endpoint									
Placebo	6	6	7.62 (1.023)	0.37 (0.836)					
Imeglimin 1000 mg bid	7	7	7.16 (0.500)	-0.29 (0.449)					
>= 30.0%, >= 2.5 to < 4.0									
Baseline									
Placebo	26	26	7.48 (0.344)						
Imeglimin 1000 mg bid	12	12	7.48 (0.458)						
Week 4									
Placebo	26	26	7.49 (0.431)	0.01 (0.259)	0.01 (0.050)	[-0.093, 0.109]			
Imeglimin 1000 mg bid	12	11	7.17 (0.410)	-0.30 (0.219)	-0.30 (0.077)	[-0.459, -0.145]	-0.31 (0.092)	[-0.497, -0.123]	0.0020
Week 8									
Placebo	26	26	7.52 (0.527)	0.03 (0.348)	0.03 (0.065)	[-0.101, 0.163]			

HOMA-B x HOMA-IR at baseline		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Imeglimin 1000 mg bid	12	11	6.98 (0.392)	-0.49 (0.266)	-0.49 (0.101)	[-0.697, -0.289]	-0.52 (0.120)	[-0.767, -0.281]	0.0001
Week 12									
Placebo	26	26	7.60 (0.594)	0.11 (0.436)	0.11 (0.078)	[-0.047, 0.271]			
Imeglimin 1000 mg bid	12	11	6.88 (0.471)	-0.59 (0.266)	-0.59 (0.121)	[-0.839, -0.347]	-0.71 (0.144)	[-0.998, -0.412]	<.0001
Week 16									
Placebo	26	25	7.58 (0.606)	0.10 (0.410)	0.13 (0.081)	[-0.035, 0.296]			
Imeglimin 1000 mg bid	12	10	6.84 (0.510)	-0.62 (0.358)	-0.65 (0.126)	[-0.903, -0.388]	-0.78 (0.150)	[-1.082, -0.470]	<.0001
Week 20									
Placebo	26	25	7.56 (0.509)	0.09 (0.375)	0.11 (0.072)	[-0.040, 0.254]			
Imeglimin 1000 mg bid	12	10	6.72 (0.507)	-0.74 (0.310)	-0.76 (0.112)	[-0.994, -0.535]	-0.87 (0.133)	[-1.144, -0.599]	<.0001
Week 24									
Placebo	26	25	7.61 (0.568)	0.13 (0.401)	0.14 (0.077)	[-0.016, 0.300]			
Imeglimin 1000 mg bid	12	10	6.81 (0.619)	-0.65 (0.341)	-0.67 (0.122)	[-0.923, -0.426]	-0.82 (0.144)	[-1.111, -0.522]	<.0001
LOCF Endpoint									
Placebo	26	26	7.64 (0.578)	0.15 (0.408)					
Imeglimin 1000 mg bid	12	11	6.80 (0.588)	-0.67 (0.332)					
>= 30.0%, >= 4.0									
Baseline									
Placebo	36	36	7.90 (0.556)						
Imeglimin 1000 mg bid	27	27	8.12 (0.674)						
Week 4									
Placebo	36	36	7.95 (0.669)	0.05 (0.276)	0.06 (0.044)	[-0.031, 0.145]			
Imeglimin 1000 mg bid	27	27	7.89 (0.707)	-0.24 (0.219)	-0.25 (0.050)	[-0.347, -0.145]	-0.30 (0.066)	[-0.435, -0.170]	<.0001
Week 8									
Placebo	36	36	8.01 (0.802)	0.11 (0.496)	0.11 (0.074)	[-0.035, 0.260]			
Imeglimin 1000 mg bid	27	25	7.68 (0.736)	-0.43 (0.317)	-0.45 (0.087)	[-0.622, -0.276]	-0.56 (0.113)	[-0.788, -0.335]	<.0001
Week 12									
Placebo	36	35	8.04 (0.863)	0.19 (0.710)	0.22 (0.101)	[0.020, 0.425]			

HOMA-B x HOMA-IR at baseline		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Imeglimin 1000 mg bid	27	25	7.56 (0.783)	-0.54 (0.358)	-0.56 (0.120)	[-0.802, -0.323]	-0.78 (0.156)	[-1.098, -0.472]	<.0001
Week 16									
Placebo	36	33	7.98 (0.809)	0.15 (0.692)	0.32 (0.128)	[0.067, 0.582]			
Imeglimin 1000 mg bid	27	25	7.46 (0.820)	-0.64 (0.411)	-0.66 (0.151)	[-0.967, -0.361]	-0.99 (0.198)	[-1.386, -0.591]	<.0001
Week 20									
Placebo	36	33	7.98 (0.928)	0.16 (0.802)	0.33 (0.143)	[0.045, 0.621]			
Imeglimin 1000 mg bid	27	24	7.45 (0.779)	-0.68 (0.480)	-0.69 (0.168)	[-1.034, -0.356]	-1.03 (0.221)	[-1.472, -0.584]	<.0001
Week 24									
Placebo	36	33	8.00 (1.108)	0.18 (0.963)	0.34 (0.159)	[0.023, 0.664]			
Imeglimin 1000 mg bid	27	24	7.45 (0.819)	-0.68 (0.525)	-0.69 (0.187)	[-1.063, -0.310]	-1.03 (0.245)	[-1.524, -0.536]	0.0001
LOCF Endpoint									
Placebo	36	36	8.20 (1.259)	0.30 (1.048)					
Imeglimin 1000 mg bid	27	27	7.48 (0.807)	-0.64 (0.513)					

- Abbreviations: MMRM, Mixed Model Repeated Measures; LOCF, Last Observation Carried Forward; bid, Twice a day; SD, standard deviation; SE, standard error; LS, least square; CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); HOMA, Homeostasis model assessment; HOMA-B, HOMA of beta-cell function; HOMA-IR, HOMA of insulin resistance
- MMRM model was used with fixed effects for treatment group, visit, study, interaction of treatment-by-visit, and baseline HbA1c as a covariate, assuming an unstructured covariance matrix.
- MMRM was not performed if the number of subjects at baseline in any group was less than 5.

Control No:<<t-e-514-subhb-24wdb.sas, 2020-03-09T15:54:19>>

Table E-515 Subgroup and MMRM Analysis of Change from Baseline in HbA1c (%) to All Visits by HOMA-B x QUICKI in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Efficacy Population)

HOMA-B x QUICKI at baseline		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
< 30.0%, < 0.33									
Baseline									
Placebo	23	23	8.59 (0.852)						
Imeglimin 1000 mg bid	33	33	8.51 (0.645)						
Week 4									
Placebo	23	22	8.69 (1.094)	0.17 (0.533)	0.18 (0.090)	[0.004, 0.364]			
Imeglimin 1000 mg bid	33	33	8.27 (0.624)	-0.24 (0.308)	-0.24 (0.072)	[-0.382, -0.091]	-0.42 (0.115)	[-0.651, -0.191]	0.0006
Week 8									
Placebo	23	21	8.74 (1.143)	0.26 (0.630)	0.32 (0.117)	[0.090, 0.558]			
Imeglimin 1000 mg bid	33	32	7.97 (0.590)	-0.52 (0.429)	-0.50 (0.094)	[-0.688, -0.310]	-0.82 (0.149)	[-1.122, -0.523]	<.0001
Week 12									
Placebo	23	18	8.45 (0.840)	0.16 (0.686)	0.43 (0.165)	[0.097, 0.758]			
Imeglimin 1000 mg bid	33	31	7.88 (0.707)	-0.63 (0.622)	-0.61 (0.132)	[-0.872, -0.340]	-1.03 (0.211)	[-1.457, -0.610]	<.0001
Week 16									
Placebo	23	18	8.48 (1.000)	0.18 (0.892)	0.48 (0.196)	[0.081, 0.870]			
Imeglimin 1000 mg bid	33	30	7.71 (0.723)	-0.82 (0.566)	-0.71 (0.156)	[-1.027, -0.395]	-1.19 (0.250)	[-1.692, -0.682]	<.0001
Week 20									
Placebo	23	17	8.38 (1.004)	0.07 (0.867)	0.53 (0.223)	[0.073, 0.977]			
Imeglimin 1000 mg bid	33	30	7.67 (0.853)	-0.86 (0.667)	-0.74 (0.177)	[-1.103, -0.384]	-1.27 (0.285)	[-1.846, -0.691]	<.0001
Week 24									
Placebo	23	16	8.36 (1.094)	0.14 (0.993)	0.62 (0.236)	[0.144, 1.100]			
Imeglimin 1000 mg bid	33	29	7.61 (0.597)	-0.88 (0.596)	-0.70 (0.187)	[-1.075, -0.317]	-1.32 (0.300)	[-1.928, -0.708]	0.0001
LOCF Endpoint									
Placebo	23	23	9.07 (1.494)	0.48 (1.064)					
Imeglimin 1000 mg bid	33	33	7.83 (0.925)	-0.68 (0.829)					

HOMA-B x QUICKI at baseline		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
< 30.0%, >= 0.33									
Baseline									
Placebo	89	89	7.90 (0.616)						
Imeglimin 1000 mg bid	100	100	7.78 (0.683)						
Week 4									
Placebo	89	89	7.92 (0.668)	0.02 (0.233)	0.03 (0.027)	[-0.021, 0.086]			
Imeglimin 1000 mg bid	100	100	7.53 (0.698)	-0.25 (0.251)	-0.24 (0.025)	[-0.289, -0.189]	-0.27 (0.036)	[-0.342, -0.202]	<.0001
Week 8									
Placebo	89	89	7.98 (0.769)	0.08 (0.380)	0.09 (0.044)	[0.004, 0.177]			
Imeglimin 1000 mg bid	100	100	7.34 (0.693)	-0.44 (0.429)	-0.43 (0.041)	[-0.511, -0.349]	-0.52 (0.059)	[-0.637, -0.403]	<.0001
Week 12									
Placebo	89	87	7.97 (0.797)	0.09 (0.444)	0.10 (0.052)	[0.000, 0.204]			
Imeglimin 1000 mg bid	100	99	7.23 (0.670)	-0.55 (0.514)	-0.54 (0.049)	[-0.636, -0.444]	-0.64 (0.070)	[-0.780, -0.503]	<.0001
Week 16									
Placebo	89	84	7.86 (0.726)	0.01 (0.464)	0.05 (0.055)	[-0.057, 0.160]			
Imeglimin 1000 mg bid	100	98	7.14 (0.751)	-0.64 (0.522)	-0.63 (0.051)	[-0.727, -0.524]	-0.68 (0.075)	[-0.825, -0.530]	<.0001
Week 20									
Placebo	89	84	7.91 (0.765)	0.06 (0.541)	0.11 (0.061)	[-0.010, 0.230]			
Imeglimin 1000 mg bid	100	97	7.11 (0.734)	-0.65 (0.559)	-0.64 (0.057)	[-0.752, -0.528]	-0.75 (0.083)	[-0.913, -0.586]	<.0001
Week 24									
Placebo	89	82	7.92 (0.708)	0.10 (0.586)	0.17 (0.067)	[0.040, 0.303]			
Imeglimin 1000 mg bid	100	94	7.15 (0.751)	-0.62 (0.610)	-0.61 (0.062)	[-0.729, -0.483]	-0.78 (0.091)	[-0.957, -0.598]	<.0001
LOCF Endpoint									
Placebo	89	89	8.06 (0.837)	0.15 (0.621)					
Imeglimin 1000 mg bid	100	100	7.16 (0.756)	-0.62 (0.596)					
>= 30.0%, < 0.33									
Baseline									
Placebo	58	58	7.75 (0.516)						

HOMA-B x QUICKI at baseline		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Imeglimin 1000 mg bid	36	36	7.98 (0.661)						
Week 4									
Placebo	58	58	7.80 (0.618)	0.04 (0.262)	0.05 (0.033)	[-0.016, 0.115]			
Imeglimin 1000 mg bid	36	35	7.73 (0.713)	-0.27 (0.217)	-0.28 (0.043)	[-0.364, -0.192]	-0.33 (0.054)	[-0.435, -0.221]	<.0001
Week 8									
Placebo	58	58	7.84 (0.730)	0.09 (0.427)	0.09 (0.052)	[-0.010, 0.195]			
Imeglimin 1000 mg bid	36	33	7.52 (0.722)	-0.46 (0.305)	-0.47 (0.068)	[-0.608, -0.339]	-0.57 (0.085)	[-0.735, -0.398]	<.0001
Week 12									
Placebo	58	57	7.89 (0.781)	0.16 (0.595)	0.19 (0.069)	[0.050, 0.326]			
Imeglimin 1000 mg bid	36	33	7.42 (0.758)	-0.56 (0.345)	-0.57 (0.092)	[-0.755, -0.392]	-0.76 (0.115)	[-0.989, -0.533]	<.0001
Week 16									
Placebo	58	54	7.83 (0.739)	0.13 (0.569)	0.25 (0.084)	[0.080, 0.413]			
Imeglimin 1000 mg bid	36	32	7.35 (0.796)	-0.64 (0.406)	-0.67 (0.110)	[-0.886, -0.447]	-0.91 (0.138)	[-1.188, -0.638]	<.0001
Week 20									
Placebo	58	54	7.83 (0.790)	0.13 (0.635)	0.24 (0.090)	[0.057, 0.416]			
Imeglimin 1000 mg bid	36	31	7.31 (0.769)	-0.69 (0.447)	-0.71 (0.118)	[-0.947, -0.475]	-0.95 (0.148)	[-1.243, -0.651]	<.0001
Week 24									
Placebo	58	54	7.86 (0.931)	0.16 (0.763)	0.25 (0.101)	[0.051, 0.452]			
Imeglimin 1000 mg bid	36	31	7.34 (0.804)	-0.66 (0.488)	-0.68 (0.132)	[-0.944, -0.415]	-0.93 (0.166)	[-1.263, -0.600]	<.0001
LOCF Endpoint									
Placebo	58	58	8.00 (1.066)	0.24 (0.840)					
Imeglimin 1000 mg bid	36	35	7.35 (0.795)	-0.65 (0.475)					
>= 30.0%, >= 0.33									
Baseline									
Placebo	10	10	7.27 (0.283)						
Imeglimin 1000 mg bid	10	10	7.37 (0.353)						
Week 4									
Placebo	10	10	7.21 (0.247)	-0.06 (0.222)	-0.08 (0.057)	[-0.200, 0.042]			

HOMA-B x QUICKI at baseline		Observed		Change from baseline			Difference vs Placebo		
Visit Treatment	N	n	Mean (SD)	Mean (SD)	LS Mean (SE)	[95% CI]	LS Mean (SE)	[95% CI]	P-value
Imeglimin 1000 mg bid	10	10	7.18 (0.326)	-0.19 (0.185)	-0.14 (0.064)	[-0.276, -0.005]	-0.06 (0.085)	[-0.242, 0.118]	0.4785
Week 8									
Placebo	10	10	7.23 (0.455)	-0.04 (0.389)	-0.06 (0.104)	[-0.278, 0.160]			
Imeglimin 1000 mg bid	10	10	7.04 (0.386)	-0.33 (0.250)	-0.28 (0.108)	[-0.507, -0.054]	-0.22 (0.149)	[-0.535, 0.092]	0.1550
Week 12									
Placebo	10	9	7.38 (0.604)	0.07 (0.557)	0.05 (0.138)	[-0.243, 0.338]			
Imeglimin 1000 mg bid	10	10	6.92 (0.476)	-0.45 (0.264)	-0.40 (0.139)	[-0.693, -0.108]	-0.45 (0.196)	[-0.860, -0.036]	0.0347
Week 16									
Placebo	10	9	7.57 (0.757)	0.26 (0.654)	0.24 (0.166)	[-0.113, 0.583]			
Imeglimin 1000 mg bid	10	10	6.94 (0.479)	-0.43 (0.316)	-0.38 (0.165)	[-0.728, -0.033]	-0.62 (0.234)	[-1.108, -0.124]	0.0170
Week 20									
Placebo	10	9	7.54 (0.838)	0.23 (0.768)	0.21 (0.191)	[-0.187, 0.614]			
Imeglimin 1000 mg bid	10	10	6.88 (0.509)	-0.49 (0.375)	-0.44 (0.188)	[-0.835, -0.046]	-0.65 (0.268)	[-1.216, -0.092]	0.0251
Week 24									
Placebo	10	9	7.63 (0.970)	0.32 (0.877)	0.30 (0.222)	[-0.162, 0.769]			
Imeglimin 1000 mg bid	10	10	6.95 (0.560)	-0.42 (0.457)	-0.37 (0.218)	[-0.829, 0.088]	-0.67 (0.311)	[-1.327, -0.021]	0.0438
LOCF Endpoint									
Placebo	10	10	7.56 (0.943)	0.29 (0.833)					
Imeglimin 1000 mg bid	10	10	6.95 (0.560)	-0.42 (0.457)					

- Abbreviations: MMRM, Mixed Model Repeated Measures; LOCF, Last Observation Carried Forward; bid, Twice a day; SD, standard deviation; SE, standard error; LS, least square; CI, confidence interval; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); HOMA, Homeostasis model assessment; HOMA-B, HOMA of beta-cell function; QUICKI, Quantitative Insulin Sensitivity Check Index
- MMRM model was used with fixed effects for treatment group, visit, study, interaction of treatment-by-visit, and baseline HbA1c as a covariate, assuming an unstructured covariance matrix.
- MMRM was not performed if the number of subjects at baseline in any group was less than 5.

Control No:<<t-e-515-subhb-24wdb.sas, 2020-03-09T15:54:34>>

Table E-516 Subgroup Analysis of Change from Baseline in HbA1c (%) to Week 52 (LOCF) by HOMA-B, HOMA-IR and QUICKI in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Efficacy Population)

Parameter Subgroup	Imeglimin N = 134		Imeglimin + SU N = 127		Imeglimin + GLIN N = 64		Imeglimin + BIG N = 64		Imeglimin + AGI N = 64		Imeglimin + TZD N = 65		Imeglimin + DPP4-I N = 63		Imeglimin + GLP1-RA N = 70		Imeglimin + SGLT2-I N = 63	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
HbA1c (%)																		
HOMA-B x HOMA-IR at baseline																		
< 30.0%, < 2.5	86	-0.47 (0.658)	79	-0.63 (0.828)	39	-0.60 (0.836)	39	-0.57 (0.749)	38	-0.74 (0.654)	44	-0.75 (1.007)	35	-0.78 (0.503)	35	-0.15 (0.961)	40	-0.62 (0.592)
< 30.0%, >= 2.5 to < 4.0	15	-0.53 (0.625)	14	-0.54 (1.201)	8	-0.85 (0.715)	11	-0.53 (0.417)	12	-0.96 (0.637)	9	-0.99 (1.003)	9	-0.10 (0.600)	15	-0.58 (0.974)	10	-0.53 (0.673)
< 30.0%, >= 4.0	7	-0.13 (1.883)	15	-0.67 (0.511)	5	-0.20 (0.982)	2	-2.10 (0.566)	3	-1.43 (1.553)	3	-1.97 (0.723)	7	-1.99 (0.727)	8	0.41 (0.662)	5	-0.36 (0.288)
>= 30.0%, < 2.5	3	-0.53 (0.764)	1	1.70 (.)	2	-1.60 (1.414)	1	-1.30 (.)	1	-0.70 (.)	3	-0.70 (0.889)	2	-1.10 (0.283)	1	0.50 (.)	2	-1.10 (0.000)
>= 30.0%, >= 2.5 to < 4.0	10	-0.48 (0.571)	3	-0.50 (0.300)	2	-0.30 (1.273)	3	0.03 (1.159)	5	-0.66 (0.932)	2	-1.20 (0.424)	5	-1.02 (0.650)	5	-0.44 (0.932)	2	-0.70 (0.424)
>= 30.0%, >= 4.0	13	-0.52 (0.806)	15	-0.18 (0.914)	7	-1.29 (1.548)	7	-1.16 (0.688)	4	-1.35 (0.480)	3	-1.17 (0.473)	4	-1.78 (1.348)	5	0.52 (0.593)	4	-0.30 (0.141)
Missing	0	.	0	.	0	.	0	.	1	-1.20 (.)	0	.	0	.	0	.	0	.
HOMA-B x QUICKI at baseline																		
< 30.0%, < 0.33	20	-0.46 (1.174)	27	-0.62 (0.923)	10	-0.57 (0.975)	12	-0.77 (0.754)	13	-1.08 (0.899)	8	-1.35 (1.004)	15	-0.92 (1.197)	17	-0.04 (0.885)	11	-0.38 (0.363)
< 30.0%, >= 0.33	88	-0.45 (0.662)	81	-0.62 (0.821)	42	-0.61 (0.807)	40	-0.58 (0.740)	40	-0.75 (0.638)	48	-0.77 (1.007)	36	-0.79 (0.497)	41	-0.24 (0.999)	44	-0.63 (0.621)
>= 30.0%, < 0.33	22	-0.51 (0.715)	18	-0.23 (0.844)	9	-1.07 (1.479)	10	-0.80 (0.972)	9	-0.97 (0.808)	5	-1.18 (0.396)	9	-1.36 (1.025)	10	0.04 (0.893)	6	-0.43 (0.301)
>= 30.0%, >= 0.33	4	-0.50 (0.627)	1	1.70 (.)	2	-1.60 (1.414)	1	-1.30 (.)	1	-0.70 (.)	3	-0.70 (0.889)	2	-1.10 (0.283)	1	0.50 (.)	2	-1.10 (0.000)

Parameter Subgroup	Imeglimin N = 134		Imeglimin + SU N = 127		Imeglimin + GLIN N = 64		Imeglimin + BIG N = 64		Imeglimin + AGI N = 64		Imeglimin + TZD N = 65		Imeglimin + DPP4-I N = 63		Imeglimin + GLP1-RA N = 70		Imeglimin + SGLT2-I N = 63	
Category	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Missing	0	.	0	.	0	.	0	.	1	-1.20 (.)	0	.	0	.	0	.	0	.

- Abbreviations: LOCF, Last Observation Carried Forward; SD, standard deviation; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); HOMA, Homeostasis model assessment; HOMA-IR, HOMA of insulin resistance; HOMA-B, HOMA of beta-cell function; QUICKI, Quantitative Insulin Sensitivity Check Index; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".

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イメグリミン塩酸塩
製造販売承認申請

CTD 第 2 部

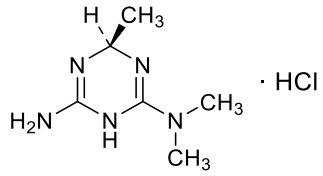
2.7　臨床概要
2.7.4　臨床的安全性の概要

大日本住友製薬株式会社

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【本項における用語の説明】

用語	定義、読み替え等
イメグリミン	一般名： イメグリミン塩酸塩 化学名： (6*R*)-N^2,N^2,6-Trimethyl-3,6-dihydro-1,3,5-triazine-2,4-diamine monohydrochloride 化学式（分子量）： $C_6H_{13}N_5$・HCl（191.66） 構造式： 
腎機能の区分の定義	
CKD 1	推算糸球体濾過量（eGFR）が 90 mL/min/1.73 m^2 以上
CKD 2	eGFR が 60～89.9 mL/min/1.73 m^2
CKD 3a	eGFR が 45～59.9 mL/min/1.73 m^2
CKD 3b	eGFR が 30～44.9 mL/min/1.73 m^2
CKD 4	eGFR が 15～29.9 mL/min/1.73 m^2
CKD 5	eGFR が 15 mL/min/1.73 m^2 未満

【一般的略号】

略号	省略しない表現	日本語
AE	Adverse event	有害事象
AGI	Alpha glucosidase inhibitor	α-グルコシダーゼ阻害薬
ALT	Alanine aminotransferase	アラニンアミノトランスフェラーゼ
AST	Aspartate aminotransferase	アスパラギン酸アミノトランスフェラーゼ
bid	Twice a day	1 日 2 回
BIG	Biganide	ビグアナイド薬
BMI	Body mass index	－
DDI	Drug-drug interaction	薬物相互作用
DPP4-I	Dipeptidyl peptidase-4 inhibitor	DPP-4 阻害薬
ECG	Electrocardiogram	心電図
eGFR	Estimated glomerular filtration rate	推算糸球体濾過量
FPG	Fasting plasma glucose	空腹時血糖
γ-GTP	γ-Glutamyltranspeptidase	γ-グルタミルトランスペプチダーゼ
GLIN	Glinide	速効型インスリン分泌促進薬
GLP1-RA	Glucagon-like peptide 1 receptor agonist	GLP1 受容体作動薬
HbA1c	Hemoglobin A1c	ヘモグロビン A1c
HLGT	High level group terms	高位グループ語
HLT	High level terms	高位語
LOCF	Last observation carried forward	－
MedDRA	Medical dictionary for regulatory activities	ICH 国際医薬用語集
PK	Pharmacokinetics	薬物動態
PR	Time between P wave and QRS in electrocardiography	PR 間隔
PT	Preferred term	基本語
qd	Once a day	1 日 1 回
QRS	Electrocardiographic wave (complex or interval)	QRS 間隔
QT	Electrocardiographic interval from the beginning of the QRS complex to the end of the T wave	QT 間隔

略号	省略しない表現	日本語
QTc	QT interval corrected for heart rate	心拍数による補正 QT 間隔
QTcF	QT interval corrected for heart rate using Fridericia's formula	Fridericia 補正法による補正 QT 間隔
SAE	Serious adverse event	重篤な有害事象
SD	Standard deviation	標準偏差
SGLT2-I	Sodium glucose cotransporter 2 inhibitor	SGLT2 阻害薬
SMBG	Self-monitoring of blood glucose	血糖自己測定
SMQ	Standardised MedDRA queries	MedDRA 標準検索式
SOC	System organ class	器官別大分類
SU	Sulfonylurea	スルホニル尿素薬
TEAE	Treatment emergent adverse event	治験薬投与以降に発現した有害事象
TZD	Thiazolidinedione	チアゾリジン薬

2.7.4.1　医薬品への曝露

2.7.4.1.1　総括的安全性評価計画及び安全性試験の記述

2.7.4.1.1.1　安全性評価に用いた臨床試験

イメグリミン（以下本剤）の安全性評価に用いた臨床試験の一覧を表 2.7.4.1-1 に示す。本剤の日本人での安全性を、主に国内で日本人 2 型糖尿病患者を対象に実施した 4 試験［国内 P2b 試験（PXL008-014 試験、以下 014 試験）、国内単独療法 P3 試験（PXL008-018 試験、以下 018 試験）、国内単独及び併用療法長期試験（PXL008-019 試験、以下 019 試験）、国内インスリン併用療法 P3 試験（PXL008-020 試験、以下 020 試験）］で評価した。加えて、本剤の心電図への影響を評価するために海外 QT 間隔検討試験（PXL008-016 試験）の結果を、内因性要因の本剤の安全性への影響を評価するために海外腎機能障害影響検討試験（RVT-1501-1002 試験）、国内腎機能障害患者 PK 試験（DD401102 試験）及び海外肝機能障害患者 PK 試験（PXL008-024 試験）の結果を示す。更に、外因性要因の本剤の安全性への影響を評価するために国内食事の影響検討試験（DD401101 試験）の結果を、薬物相互作用による本剤の安全性への影響を評価するために海外 DDI 試験［メトホルミン（PXL008-001 試験）、シタグリプチン（PXL008-003 試験）及びシメチジン（PXL008-023 試験）］の結果を示す。014 試験、018 試験、019 試験及び 020 試験のデザインを 2.7.4.1.1.1.1 項に、PXL008-016 試験（2.7.4.4.3.4）、RVT-1501-1002 試験（2.7.4.5.1.3.4）、DD401102 試験（2.7.4.5.1.3.5）、PXL008-024 試験（2.7.4.5.1.4.4）、DD401101 試験（2.7.4.5.2.1.1）、PXL008-001 試験（2.7.4.5.3.1）、PXL008-003 試験（2.7.4.5.3.2）及び PXL008-023 試験（2.7.4.5.3.3）のデザインを各項に示す。他の個々の試験の安全性評価は個々の試験のまとめ（2.7.6 項）に示す。

表 2.7.4.1-1　安全性評価に用いた試験の概要

試験名 試験番号 試験略称	実施国 又は 地域	試験の相 試験デザイン	対象	投与期間 投与量	安全性を評価した対象集団	資料番号 資料区分
国内 P2b 試験 PXL008-014 014 試験	日本	後期第 2 相 多施設共同、プラセボ対照、ランダム化、二重盲検、並行群間比較、固定用量	2 型糖尿病患者	24 週間 500 mg bid 1000 mg bid 1500 mg bid プラセボ bid	合計：299 名 500 mg bid 群：75 名 1000 mg bid 群：74 名 1500 mg bid 群：75 名 プラセボ群：75 名	5.3.5.1.01 評価
国内単独療法 P3 試験 PXL008-018 018 試験	日本	第 3 相 多施設共同、プラセボ対照、ランダム化、二重盲検、並行群間比較、固定用量	2 型糖尿病患者	24 週間 1000 mg bid プラセボ bid	合計：213 名 1000 mg bid 群：106 名 プラセボ群：107 名	5.3.5.1.02 評価
国内単独及び併用療法長期試験 PXL008-019 019 試験	日本	第 3 相 多施設共同、非盲検、並行群間比較、固定用量	2 型糖尿病患者	52 週間 1000 mg bid 1000 mg bid + SU 1000 mg bid + GLIN 1000 mg bid + BIG 1000 mg bid + AGI 1000 mg bid + TZD 1000 mg bid + DPP4-I 1000 mg bid + GLP1-RA 1000 mg bid + SGLT2-I	合計：714 名 単独療法群：134 名 SU 併用療法群：127 名 GLIN 併用療法群：64 名 BIG 併用療法群：64 名 AGI 併用療法群：64 名 TZD 併用療法群：65 名 DPP4-I 併用療法群：63 名 GLP1-RA 併用療法群：70 名 SGLT2-I 併用療法群：63 名	5.3.5.2.01 評価

試験名 試験番号 試験略称	実施国 又は 地域	試験の相 試験デザイン	対象	投与期間 投与量	安全性を評価した対象集団	資料番号 資料区分
国内インスリン併用療法 P3 試験 PXL008-020 020 試験	日本	第 3 相 二重盲検治療期 多施設共同、プラセボ対照、ランダム化、二重盲検、並行群間比較、固定用量	2 型糖尿病患者	16 週間 1000 mg bid + インスリン プラセボ bid + インスリン	合計：215 名 イメグリミン群：108 名 プラセボ群：107 名	5.3.5.1.03 評価
		非盲検治療期 多施設共同、無対照、非盲検、固定用量		36 週間 1000 mg bid + インスリン	209 名	
海外 QT 間隔検討試験 PXL008-016 試験	海外	第 1 相 単施設、プラセボ及び陽性対照、ランダム化、二重盲検、4 群 4 期クロスオーバー	健康被験者	各期に以下のいずれかを単回投与 本剤 2250 mg 本剤 6000 mg プラセボ モキシフロキサシン 400 mg	合計：55 名 ECG 解析対象集団 本剤 2250 mg：51 名 本剤 6000 mg：53 名 プラセボ：51 名 モキシフロキサシン 400 mg：50 名	5.3.4.1.01 評価
海外腎機能障害影響検討試験 RVT-1501-1002 試験	海外	後期第 1 相 多施設共同、プラセボ対照、ランダム化、二重盲検、並行群間比較	CKD 3b 又は CKD 4 の 2 型糖尿病患者	4 週間 500 mg bid コホート 500 mg bid プラセボ bid 1500 mg qd コホート 1500 mg qd プラセボ qd 1000 mg bid コホート 1000 mg bid プラセボ bid	合計：49 名 500 mg bid コホート 500 mg bid：13 名 プラセボ bid：2 名 1500 mg qd コホート 1500 mg qd：12 名 プラセボ qd：5 名 1000 mg bid コホート 1000 mg bid：13 名 プラセボ bid：4 名	5.3.3.3.03 参考

試験名 試験番号 試験略称	実施国 又は 地域	試験の相 試験デザイン	対象	投与期間 投与量	安全性を評価した対象集団	資料番号 資料区分
国内腎機能障害患者 PK 試験 DD401102 試験	日本	第 1 相 多施設共同、無対照、非盲検	腎機能正常者 腎機能障害患者	単回 腎機能正常者 1000 mg 軽度腎機能障害患者 1000 mg 中等度腎機能障害患者 1000 mg 重度腎機能障害患者 500 mg	合計：24 名 腎機能正常者：6 名 軽度腎機能障害患者：6 名 中等度腎機能障害患者：6 名 重度腎機能障害患者：6 名	5.3.3.3.01 評価
海外肝機能障害患者 PK 試験 PXL008-024 試験	海外	第 1 相 単施設、非盲検、並行群間比較	肝機能正常者 中等度肝機能障害患者	単回 1000 mg	合計：14 名 肝機能正常者：7 名 中等度肝機能障害者：7 名	5.3.3.3.02 評価
国内食事の影響検討試験 DD401101 試験	日本	第 1 相 単施設、非盲検、無作為化、2 用法 2 期クロスオーバー試験	健康被験者	単回 1000 mg	合計：12 名 食後投与先行群：6 名 空腹時投与先行群：6 名	5.3.1.1.01 評価
海外 DDI 試験（メトホルミン） PXL008-001 試験	海外	第 1 相 単施設、単盲検、one-sequence 試験	健康被験者	導入期（6 日間） メトホルミン 850 mg 及びプラセボを 1 日 2 回 上乗せ期（6 日間） メトホルミン 850 mg 及び本剤 1500 mg を 1 日 2 回	合計：16 名	5.3.3.4.01 評価

試験名 試験番号 試験略称	実施国 又は 地域	試験の相 試験デザイン	対象	投与期間 投与量	安全性を評価した対象集団	資料番号 資料区分
海外 DDI 試験（シタグリプチン） PXL008-003 試験	海外	第 1 相 単施設、単盲検、one-sequence 試験	健康被験者	導入期（6 日間） シタグリプチン 100 mg を 1 日 1 回（朝食時）、プラセボを 1 日 2 回（朝食時及び夕食時） 上乗せ期（6 日間） シタグリプチン 100 mg を 1 日 1 回（朝食時）、本剤 1500 mg を 1 日 2 回（朝食時及び夕食時）	合計：16 名	5.3.3.4.02 参考
海外 DDI 試験（シメチジン） PXL008-023 試験	海外	第 1 相 単施設、非盲検、one-sequence 試験	健康被験者	Day 1 本剤 1500 mg を単回投与 Day 5～10 シメチジン 400 mg を 1 日 2 回 6 日間投与 Day 8 本剤 1500 mg 及びシメチジンを単回投与	合計：16 名	5.3.3.4.03 評価

略語：AGI＝α-グルコシダーゼ阻害薬、bid＝1 日 2 回、BIG＝ ビグアナイド薬、DDI＝薬物相互作用、DPP4-I＝DPP-4 阻害薬、ECG＝心電図、GLIN＝ 速効型インスリン分泌促進薬（グリニド薬）、GLP1-RA＝GLP1 受容体作動薬、PK＝薬物動態、qd＝1 日 1 回、SGLT2-I＝SGLT2 阻害薬、SU＝ スルホニル尿素薬、TZD＝チアゾリジン薬（チアゾリジンジオン）。

2.7.4.1.1.1.1　安全性評価に用いた主な臨床試験のデザイン

(1) 014 試験（国内 P2b 試験、資料番号：5.3.5.1.01）

014 試験は、抗糖尿病薬による治療経験がない又は他の経口血糖降下薬の単独療法を 12 週間以上受けている日本人 2 型糖尿病患者を対象に、本剤 3 用量［500 mg 1 日 2 回（以下 bid）、1000 mg bid、1500 mg bid］を 24 週間投与したときの有効性及び安全性を評価する多施設共同、ランダム化、プラセボ対照、二重盲検、並行群間比較試験である。被験者は 6 週間［チアゾリジン薬（TZD）の単独療法を受けていた場合は 10 週間］のウォッシュアウト期間後、本剤の 3 用量又はプラセボに 1：1：1：1 の比でランダムに割り当てられた。ランダム化の際は、ランダム化前来院時の HbA1c 及び前治療歴を層別因子とした。治験薬を 1 日 2 回経口投与し、朝食及び夕食の食事中又は食事直後の服用を推奨した。

(2) 018 試験（国内単独療法 P3 試験、資料番号：5.3.5.1.02）

018 試験は、食事・運動療法以外の糖尿病の治療経験がない又は他の経口血糖降下薬の単独療法を 12 週間以上受けている日本人 2 型糖尿病患者を対象に、本剤 1000 mg bid を 24 週間投与したときの有効性及び安全性を評価する多施設共同、ランダム化、プラセボ対照、二重盲検、並行群間比較試験である。被験者は 4 週間のプラセボ導入期間後（他の経口血糖降下薬の単独療法を受けている場合、8 週間のウォッシュアウト期間及び 4 週間のプラセボ導入期間後）、本剤 1000 mg bid 又はプラセボに 1：1 の比でランダムに割り当てられた。ランダム化の際は、ランダム化前来院時の HbA1c 及び前治療歴を層別因子とした。治験薬を 1 日 2 回経口投与し、朝食及び夕食の食事中又は食事直後の服用を推奨した。服用間隔は必ず 6 時間以上空けることとした。

(3) 019 試験（国内単独及び併用療法長期試験、資料番号：5.3.5.2.01）

019 試験は、12 週間以上の食事・運動療法又はそれに加え他の血糖降下薬の単独療法で血糖コントロールが不十分な日本人 2 型糖尿病患者を対象に、本剤 1000 mg bid を 52 週間単独投与又は他の血糖降下薬と併用したときの安全性及び有効性を評価する多施設共同、非盲検、並行群間比較試験である。被験者は 2 週間のプラセボ導入期間後、本剤 1000 mg bid を単独投与又は他の血糖降下薬 1 剤［スルホニル尿素薬（SU）、速効型インスリン分泌促進薬（GLIN）、ビグアナイド薬（BIG）、α-グルコシダーゼ阻害薬（AGI）、TZD、DPP-4 阻害薬（DPP4-I）、GLP1 受容体作動薬（GLP1-RA）又は SGLT2 阻害薬（SGLT2-I）］との併用投与を受けた。治験薬を 1 日 2 回経口投与し、朝食及び夕食の食事中又は食事直後の服用を推奨した。服用間隔は必ず 6 時間以上空けることとした。治験期間中、併用する血糖降下薬の用法・用量の変更は不可とした。

(4) 020 試験（国内インスリン併用療法 P3 試験、資料番号：5.3.5.1.03）

020 試験は、二重盲検治療期と非盲検治療期からなる、インスリン治療（単独療法又はインスリンと経口血糖降下薬 1 剤の併用療法）で血糖コントロールが不十分な日本人 2 型糖

尿病患者を対象とした多施設共同試験である。二重盲検治療期は、インスリン治療に加えて本剤 1000 mg bid を投与したときの有効性及び安全性を評価するランダム化、プラセボ対照、二重盲検、並行群間比較試験で、被験者は 4 週間のプラセボ導入期間後（経口血糖降下薬を併用している場合、8 週間のウォッシュアウト期間及び 4 週間のプラセボ導入期間後）、インスリン単独療法（以下プラセボ群）又は本剤とインスリンの併用療法（以下イメグリミン群）に 1：1 の比でランダムに割り当てられた。ランダム化の際は、ランダム化前来院時の HbA1c 及び前治療歴を層別因子とした。投与期間は 16 週間で、治験薬を 1 日 2 回経口投与した。二重盲検治療期の評価を完了した被験者は非盲検治療期に移行した。非盲検治療期では、すべての被験者が本剤 1000 mg bid とインスリンの併用療法を受けた。投与期間は 36 週間で、本剤を 1 日 2 回経口投与した。二重盲検治療期及び非盲検治療期ともに、治験薬及び本剤の服用は朝食及び夕食の食事中又は食事直後を推奨した。服用間隔は必ず 6 時間以上空けることとした。インスリンの 1 日用量は、二重盲検治療期では一定（ベースラインの 1 日投与量の±10%未満、ただし安全上の理由により用量調節が必要な場合の減量は可能）に維持することとし、非盲検治療期では調節可能とした。

2.7.4.1.1.2　安全性の評価方法

2.7.4.1.1.2.1　対象患者

014 試験、018 試験、019 試験及び 020 試験の主な選択基準及び除外基準を表 2.7.4.1-2 に示す。いずれの試験も日本人で 20 歳以上の 2 型糖尿病の男女を対象とし、014 試験のみ年齢の上限を 75 歳とした。また、腎機能の基準として、014 試験及び 018 試験では推算糸球体濾過量［eGFR（mL/min/1.73 m^2)］が 45 以上、019 試験の本剤単独群では eGFR が 50 以上、019 試験の併用療法群及び 020 試験では eGFR が 60 以上の患者を対象とした。更に肝機能の基準として、014 試験ではアルカリホスファターゼ、AST 及び ALT の正常値上限の 3 倍を、018 試験、019 試験及び 020 試験では AST 及び ALT の正常値上限の 3 倍並びに総ビリルビン 2 mg/dL を用いて、肝機能異常あるいは肝疾患を有する患者を除外した。

表 2.7.4.1-2　安全性評価に用いた試験の主な選択・除外基準

	014 試験	018 試験	019 試験	020 試験
年齢	20～75 歳	20 歳以上	20 歳以上	20 歳以上
BMI	18.5 kg/m^2 以上	18.5 kg/m^2 以上	18.5 kg/m^2 以上	18.5 kg/m^2 以上
治療歴	抗糖尿病薬による治療経験がない（一度も治療経験がない又はスクリーニング 12 週間前から治療を受けていない）又はスクリーニングまでに 12 週間以上経口血糖降下薬の単独療法を受けている患者。 スクリーニング前 12 ヵ月以内にインスリン又は GLP1-RA の投与を受けた患者は除外した。	薬物治療経験がない（スクリーニング前 12 週間以内に食事･運動療法以外の治療を受けていない）患者又はスクリーニングまでに 12 週間以上経口血糖降下薬の単独療法を受けている患者。 インスリン療法（一時的な投与を除く）又はスクリーニング前 30 日以内に連続して 7 日間を超える注射剤の血糖降下薬の投与を受けた患者は除外した。	単独療法：12 週間以上の食事・運動療法で血糖コントロール不十分な患者 併用療法：12 週間以上の食事・運動療法と血糖降下薬単独療法で血糖コントロール不十分な患者 インスリン療法（一時的な投与を除く）又はスクリーニング前 30 日以内に連続して 7 日間を超える注射剤の血糖降下薬（GLP1-RA を除く）の投与を受けた患者は除外した。	食事・運動療法とインスリン単独療法で血糖コントロール不十分な患者又はインスリンと経口血糖降下薬 1 剤の併用療法で血糖コントロール不十分な患者（いずれの場合も、インスリンは持効型溶解インスリン又は 1 日 2 回を超えない混合型インスリンとした） スクリーニング前 30 日以内に連続して 7 日間を超えるインスリン以外の注射剤の血糖降下薬の投与を受けた患者は除外した。
罹病期間	3 ヵ月以上	12 週間以上	単独療法：12 週間以上 併用療法：24 週間以上	12 週間以上
スクリーニング時の HbA1c	7.0%以上 10.0%未満	治療歴なし：7.0%以上 10.0%未満 治療歴あり：7.0%以上 9.0%以下	単独療法：7.0%以上 10.0%未満 併用療法：7.5%以上 10.5%未満	インスリン単独療法：7.5%以上 11.0%未満 経口血糖降下薬 1 剤併用：7.5%以上 10.0%以下
ランダム化前来院時の HbA1c	7.0%以上 10.0%未満	7.0%以上 10.0%未満	－	7.5%以上 11.0%未満

	014 試験	018 試験	019 試験	020 試験
スクリーニング時の eGFR	50 mL/min/1.73 m^2 以上	50 mL/min/1.73 m^2 以上	単独療法：50 mL/min/1.73 m^2 以上 併用療法：60 mL/min/1.73 m^2 以上	60 mL/min/1.73 m^2 以上
ランダム化前来院時の eGFR	45 mL/min/1.73 m^2 以上	45 mL/min/1.73 m^2 以上	－	60 mL/min/1.73 m^2 以上
肝機能	肝機能障害患者（アルカリホスファターゼ、AST 又は ALT が正常値上限の 3 倍以上）を除外した。	スクリーニング時及びランダム化前来院時に以下のいずれかの基準に該当する重度な肝疾患患者（慢性活動性肝炎を含む）を除外した。 AST が正常値上限の 3 倍以上 ALT が正常値上限の 3 倍以上 総ビリルビン 2 mg/dL（34.2 μmol/L）以上	スクリーニング時に以下のいずれかの基準に該当する重度な肝疾患患者（慢性活動性肝炎を含む）を除外した。 AST が正常値上限の 3 倍以上 ALT が正常値上限の 3 倍以上 総ビリルビン 2 mg/dL（34.2 μmol/L）以上	スクリーニング時及びランダム化前来院時に以下のいずれかの基準に該当する重度な肝疾患患者（慢性活動性肝炎を含む）を除外した。 AST が正常値上限の 3 倍以上 ALT が正常値上限の 3 倍以上 総ビリルビン 2 mg/dL（34.2 μmol/L）以上

2.7.4.1.1.2.2　安全性データの評価方法

本剤の安全性を有害事象、臨床検査値、バイタルサイン、体重、心電図の結果などに基づき評価した。単独療法の安全性は、試験デザインが類似した 014 試験及び 018 試験の結果を併合し、用量別に解析して評価した。本剤の長期投与（単独及び血糖降下薬との併用療法）の安全性は、019 試験の結果を用いて評価した。本剤とインスリンとの併用療法の安全性は 020 試験の結果を用いて評価し、その長期投与の安全性は本剤を投与された被験者の合計で評価した。本項の解析対象集団、解析対象期間及びベースラインを以下のとおり定義した（図 2.7.4.1-1）。

(1) 単独療法（二重盲検試験併合）

1) Safety Population

014 試験、018 試験で二重盲検治療期の治験薬の投与を 1 回以上受けた被験者。

2) 解析対象期間

二重盲検治療期（24 週）。

3) ベースライン

二重盲検治療期の治験薬投与開始前。

(2) 単独及び血糖降下薬との併用療法（長期投与）

1) Long-term Safety Population

019 試験で非盲検治療期の治験薬の投与を 1 回以上受けた被験者。

2) 解析対象期間

非盲検治療期（52 週）。

3) ベースライン

非盲検治療期の治験薬投与開始前。

(3) インスリン製剤併用療法（二重盲検治療）

1) Safety Population

020 試験で二重盲検治療期の治験薬の投与を 1 回以上受けた被験者。

2) 解析対象期間

二重盲検治療期（16 週）。

3) ベースライン

二重盲検治療期の治験薬投与開始前。

(4) インスリン製剤併用療法（長期投与）

1) Long-term Safety Population

020 試験の以下の被験者。

a) 二重盲検治療期にイメグリミン群であった被験者で、二重盲検治療期の治験薬の

投与を 1 回以上受けた被験者。

b) 二重盲検治療期にプラセボ群であった被験者で、非盲検治療期に本剤の投与を 1 回以上受けた被験者。

2) 解析対象期間

a) 二重盲検治療期にイメグリミン群であった被験者では、二重盲検治療期及び非盲検治療期（52 週）。

b) 二重盲検治療期にプラセボ群であった被験者では、非盲検治療期（36 週）。

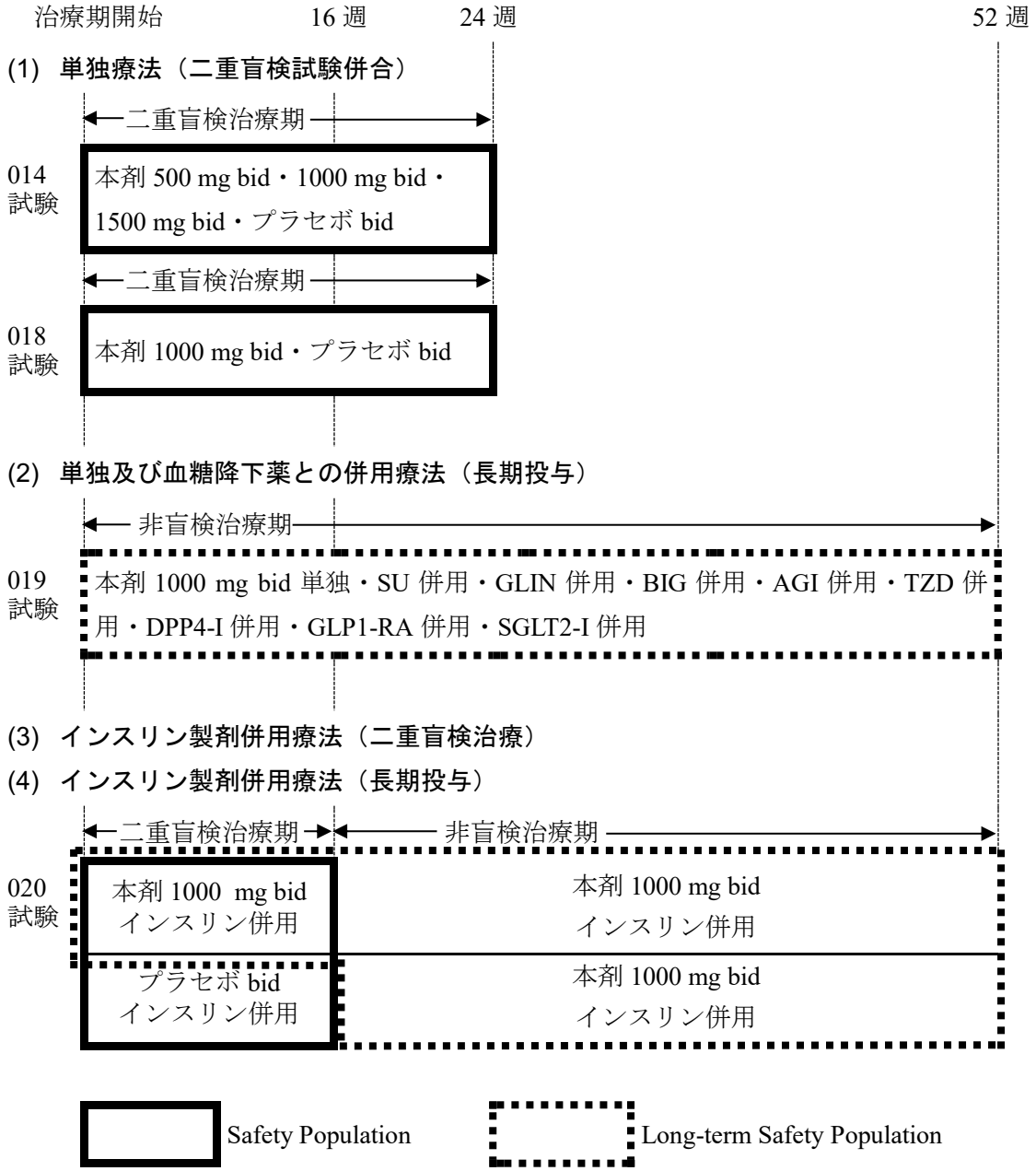
3) ベースライン

a) 二重盲検治療期にイメグリミン群であった被験者では、二重盲検治療期の治験薬投与開始前。

b) 二重盲検治療期にプラセボ群であった被験者では、非盲検治療期の治験薬投与開始前。

評価時点（週数）は、上記 (1) ～ (4) のいずれでもベースライン（Week 0）からの相対的な経過週数で表記した。ただし、 (4) の被験者背景及び部分集団区分には、020 試験の二重盲検治療期の治験薬投与開始前のデータを用いた。

図 2.7.4.1-1　解析対象集団及び解析対象期間



略語：bid = 1 日 2 回、SU = スルホニル尿素薬、GLIN = 速効型インスリン分泌促進薬、BIG = ビグアナイド薬、AGI = α-グルコシダーゼ阻害薬、TZD = チアゾリジン薬、DPP4-I = DPP-4 阻害薬、GLP1-RA = GLP1 受容体作動薬、SGLT2-I = SGLT2 阻害薬。

2.7.4.1.1.2.3　有害事象の定義及び集計

014 試験、018 試験、019 試験及び 020 試験では、有害事象を「治験薬が投与された際に新たに発現した、あらゆる好ましくない、あるいは意図しない徴候（臨床検査値の異常変動を含む）、症状、疾患のことであり、治験薬との因果関係の有無は問わない」と定義した。

試験間の有害事象名の統一を行うため、医師報告用語から ICH 国際医薬用語集日本語版（Medical Dictionary for Regulatory Activities/J；MedDRA/J）Ver.20.1 の基本語（Preferred term；PT）に読み替え、本項では、MedDRA/J（Ver.20.1）の PT 及び器官別大分類（System organ class；SOC）で表記した。

治験薬投与以降に発現した有害事象（Treatment Emergent Adverse Event；TEAE）を表 2.7.4.1-3 のとおり定義した。これ以降、本項では TEAE を「有害事象」、治験薬との因果関係が否定されなかった TEAE（Treatment related TEAE）を「副作用」と表記する。

表 2.7.4.1-3　Treatment Emergent Adverse Event の定義

(1) 単独療法（二重盲検試験併合）	014 試験： 二重盲検治療期の治験薬投与開始以降に発現した有害事象、又は二重盲検治療期の治験薬投与開始前に発現し治験薬投与開始以降に悪化した有害事象。 018 試験： 二重盲検治療期の治験薬投与開始以降、治験薬投与中止 7 日後までに発現した有害事象、又は二重盲検治療期の治験薬投与開始前に発現し治験薬投与開始以降、治験薬投与中止 7 日後までに悪化した有害事象。治験薬の投与中止 8 日後以降に発現した治験薬との因果関係が否定されなかった有害事象を含む。
(2) 単独及び血糖降下薬との併用療法（長期投与）	非盲検治療期の治験薬投与開始以降、治験薬投与中止 7 日後までに発現した有害事象、又は非盲検治療期の治験薬投与開始前に発現し治験薬投与開始以降、治験薬投与中止 7 日後までに悪化した有害事象。治験薬の投与中止 8 日後以降に発現した治験薬との因果関係が否定されなかった有害事象を含む。
(3) インスリン製剤併用療法（二重盲検治療）	二重盲検治療期の治験薬投与開始以降、二重盲検治療期の治験薬投与中止 7 日後までに発現した有害事象、又は二重盲検治療期の治験薬投与開始前に発現し二重盲検治療期の治験薬投与開始以降、二重盲検治療期の治験薬投与中止 7 日後までに悪化した有害事象。二重盲検治療期の治験薬の投与中止 8 日後以降に発現した治験薬との因果関係が否定されなかった有害事象を含む。

(4) インスリン製剤併用療法（長期投与）	二重盲検治療期にイメグリミン群であった被験者： 二重盲検治療期の治験薬投与開始以降、二重盲検治療期又は非盲検治療期の治験薬投与中止 7 日後までに発現した有害事象。若しくは二重盲検治療期の治験薬投与開始前に発現し二重盲検治療期の治験薬投与開始以降、二重盲検治療期又は非盲検治療期の治験薬投与中止 7 日後までに悪化した有害事象。二重盲検治療期又は非盲検治療期の治験薬の投与中止 8 日後以降に発現した治験薬との因果関係が否定されなかった有害事象を含む。 二重盲検治療期にプラセボ群であった被験者： 非盲検治療期の治験薬投与開始以降、非盲検治療期の治験薬投与中止 7 日後までに発現した有害事象、又は非盲検治療期の治験薬投与開始前に発現し非盲検治療期の治験薬投与開始以降、非盲検治療期の治験薬投与中止 7 日後までに悪化した有害事象。非盲検治療期の治験薬の投与中止 8 日後以降に発現した治験薬との因果関係が否定されなかった有害事象を含む。

有害事象の集計では、同一被験者に同一の有害事象（PT が同じ）が複数回発現した場合は 1 名と集計し、重症度は最も重い評価で集計した。発現時期別の集計は、初回発現時期別及び初回に限定しないすべての発現時期別に実施した。本項では前者を「初回発現時期別」、後者を「発現時期別」と記載する。初回発現時期別の集計では、同一被験者に同一の有害事象が複数回発現した場合、初回に発現した時期で集計した。発現時期別の集計では、同一発現時期に同一被験者に同一の有害事象が複数回発現した場合は 1 名と集計した。有害事象の重症度は「軽度、中等度、重度」の 3 段階で判定された。治験薬との因果関係判定は Not related（関連なし）及び Related（関連あり）の 2 段階とし、Related（関連あり）を副作用（Treatment related）とした。

2.7.4.1.1.2.3.1　高血糖の報告

2 型糖尿病の症状の一部であるため、高血糖、HbA1c 高値、尿糖は有害事象としないこととしたが、治験責任医師又は治験分担医師により医学的に意義があり救援治療が必要と考えられた高血糖又は HbA1c 高値は、有害事象として報告された。また、表 2.7.4.1-4～表 2.7.4.1-7 に示す各試験の治験薬投与中止基準に該当した場合、治験責任医師又は治験分担医師は被験者に食事及び運動療法の指導を行い、HbA1c 及び空腹時血糖（Fasting plasma glucose；FPG）を再測定した。再測定の結果、治験薬投与中止基準に該当した場合、治験責任医師又は治験分担医師は治験薬の投与を中止して救援治療を行った。治験薬の投与中止

に至った高血糖又は HbA1c 高値は有害事象（高血糖）として報告された。

表 2.7.4.1-4　014 試験の治験薬投与中止基準

二重盲検治療期の 治験薬投与開始後の経過週数	基準値	
4 週	FPG > 250 mg/dL (13.9 mmol/L)	HbA1c ≥ 10.0%
8、12 週	FPG > 240 mg/dL (13.3 mmol/L)	
16、20、24 週	FPG > 200 mg/dL (11.1 mmol/L)	

略語：FPG＝ 空腹時血糖、HbA1c＝ ヘモグロビン A1c
FPG 又は HbA1c が 2 回連続して基準を逸脱した場合、治験中止を判断することとした。

表 2.7.4.1-5　018 試験の治験薬投与中止基準

二重盲検治療期の 治験薬投与開始後の経過週数	基準値
4 週	FPG > 250 mg/dL (13.9 mmol/L)
8 週	FPG > 240 mg/dL (13.3 mmol/L)
12、16、20、24 週	HbA1c ≥ 10.0%

略語：FPG＝ 空腹時血糖、HbA1c＝ ヘモグロビン A1c

表 2.7.4.1-6　019 試験の治験薬投与中止基準

非盲検治療期の 治験薬投与開始後の経過週数	基準値	
	単独療法	併用療法
4 週	FPG > 250 mg/dL (13.9 mmol/L)	
8 週	FPG > 240 mg/dL (13.3 mmol/L)	
12、16、20、24 週	HbA1c ≥ 10.0%	HbA1c ≥ 10.5%
28、32、36、40、44、48、52 週	HbA1c ≥ 10.0%	HbA1c ≥ 10.5%

略語：FPG＝ 空腹時血糖、HbA1c＝ ヘモグロビン A1c

表 2.7.4.1-7　020 試験の治験薬投与中止基準

二重盲検治療期の治験薬投与開始後の経過週数	基準値
4、8 週	FPG > 250 mg/dL (13.9 mmol/L)
12、16、20、24、28、32、36、40、44、48、52 週	HbA1c ≥ 11.0%

略語：FPG＝ 空腹時血糖、HbA1c＝ ヘモグロビン A1c

2.7.4.1.1.2.3.2　低血糖の報告

本剤の低血糖の評価では、表 2.7.4.1-8 に示す分類を用いた。治験実施計画書では、FDA ガイダンス[文献 1)]の推奨に基づき、低血糖を表 2.7.4.1-8 の 1)～5)に分類し、それぞれ該当する医師報告用語で報告するよう規定した。020 試験で典型的な症状を伴い医師により低血糖と判断されたが血糖値は 70 mg/dL（3.9 mmol/L）以上であった事象が発現したことから、FDA ガイダンスの分類に加えて新たな分類 6)を追加した。

表 2.7.4.1-8　低血糖の分類と医師報告用語

低血糖の分類	医師報告用語
1)　炭水化物又はグルカゴンの投与のために他人の支援、若しくは他の手順を必要とする低血糖	重度の低血糖 severe hypoglycemia
2)　典型的な症状を伴う、血糖値が 70 mg/dL（3.9 mmol/L）未満の低血糖	裏付けされた症候性低血糖 documented symptomatic hypoglycemia
3)　典型的な症状を伴わない、血糖値（臨床検査機関で測定）が 70 mg/dL（3.9 mmol/L）未満の低血糖	無症候性低血糖 asymptomatic hypoglycemia
4)　典型的な症状を伴わない、血糖値（SMBG）が 70 mg/dL（3.9 mmol/L）未満の低血糖	SMBG に基づき報告された無症候性低血糖 asymptomatic hypoglycemia reported from SMBG
5)　血糖値を測定していないが、症状で立証された低血糖	可能性のある症候性低血糖 probable symptomatic hypoglycemia
6)　典型的な症状を伴い医師により低血糖と判断されたが、血糖値は 70 mg/dL（3.9 mmol/L）以上であった事象	症候性低血糖* symptomatic hypoglycemia

略語：SMBG＝ 血糖自己測定
*：020 試験でのみ報告された。

2.7.4.1.1.2.3.3　心血管イベントの報告

治験責任医師又は治験分担医師は、治験実施計画書に従って心血管系の症状を観察し、014 試験では心血管死、心筋梗塞、脳卒中、血行再建等を、018 試験、019 試験及び 020 試験では心筋梗塞、死に至らなかった脳卒中、心血管死を心血管イベントとして報告した。

2.7.4.1.1.2.3.4　注目すべき有害事象

有害事象のうち、本剤の安全性を検討するうえで特に重要と思われるものとして、低血糖、乳酸アシドーシス関連事象、心血管イベント、心血管関連事象、消化器症状、腎機能関連事象、肝機能関連事象を評価した（表 2.7.4.1-9 参照）。集計対象となった MedDRA/J ver.20.1 の PT を 2.7.4.7 項付録表 2.7.4.7-1 に示す。

表 2.7.4.1-9　注目すべき有害事象の定義

低血糖	MedDRA PT「低血糖」に該当する有害事象とした。
乳酸アシドーシス関連事象	MedDRA SMQ「乳酸アシドーシス」（広域）に含まれる PT に該当する有害事象とした。
心血管イベント	治験責任医師又は治験分担医師が心血管イベントとして報告した有害事象とした。
心血管関連事象	MedDRA SMQ「中枢神経系血管障害」、「虚血性心疾患」、「不整脈」、「心不全」（以上いずれも広域）に含まれる PT、PT「心臓瘤」、SOC「血管障害」の HLGT「動脈硬化、狭窄、血流障害および壊死」、HLGT「塞栓症および血栓症」、HLGT「瘤および動脈乖離」、HLGT「血管障害 NEC」、HLGT「血管性出血障害」、HLGT「血管損傷」、HLGT「静脈瘤」、HLGT「高血圧性血管障害」に含まれる PT に該当する有害事象とした。
消化器症状	MedDRA SOC「胃腸障害」に含まれる PT 及び HLT「食欲障害」に含まれる PT に該当する有害事象とした。
腎機能関連事象	MedDRA SOC「腎および尿路障害」に含まれる PT 及び HLGT「腎尿路検査および尿検査」に含まれる PT に該当する有害事象とした。
肝機能関連事象	MedDRA SMQ「肝障害」（広域）に含まれる PT に該当する有害事象とした。

略語：HLGT = 高位グループ語、HLT = 高位語、MedDRA = ICH 国際医薬用語集、PT = 基本語、SMQ = MedDRA 標準検索式、SOC = 器官別大分類

2.7.4.1.1.2.4　臨床検査、バイタルサイン及び体重

安全性評価のために集計した臨床検査項目を表 2.7.4.1-10 に示す。014 試験、018 試験、019 試験及び 020 試験のすべてで、臨床検査は中央の臨床検査実施機関で集中測定された。血液学的検査、生化学的検査及び血液凝固検査は、中央測定機関の定めた基準値による正異判定別の被験者数を、尿検査は定性結果別の被験者数を、評価時点ごと及びベースラインの正異ごとに集計した（以下シフトテーブル）。また、検査項目ごとに定めた基準値を超えた値を顕著な異常値として、顕著な異常値を示した被験者数を集計した。注目すべき臨床検査値として、乳酸及び eGFR の値の治療群及び評価時期ごとの要約統計量を算出した。また、eGFR では腎機能区分別の被験者数を評価時点ごと及びベースラインの腎機能区分ごとに集計した。なお、eGFR は以下の式[文献 2)、文献 3)]を用いて算出した。

$$eGFR\ (mL/min/1.73\ m^2) = 194 \times [\text{血清クレアチニン}\ (mg/dL)]^{-1.094} \times [\text{年齢}\ (年)]^{-0.287}$$

*女性の場合 0.739 をかける。

バイタルサイン（血圧及び心拍数）及び体重の測定結果の治療群及び評価時期ごとの要約統計量を算出した。

表 2.7.4.1-10　臨床検査項目一覧

血液学的検査	赤血球、ヘモグロビン、ヘマトクリット、平均赤血球容積、平均赤血球血色素量、平均赤血球血色素濃度、白血球、白血球分画（リンパ球、単球、好酸球、好塩基球、好中球：絶対値及び百分率での結果）血小板
血液生化学的検査	クレアチニン、ナトリウム、カリウム、クロール、重炭酸塩、カルシウム、無機リン酸塩、総蛋白、アルブミン、尿酸、クレアチンキナーゼ、AST、ALT、γ-グルタミルトランスペプチダーゼ、総ビリルビン、アルカリホスファターゼ、アミラーゼ、リパーゼ、血中尿素窒素
血液凝固検査	活性化部分トロンボプラスチン時間、プロトロンビン時間、プロトロンビン国際標準比
尿検査（定性）	pH、比重、蛋白、ブドウ糖、ケトン体、亜硝酸塩、ウロビリノーゲン、血液、白血球

2.7.4.1.1.2.5　心電図

014 試験、018 試験、019 試験及び 020 試験のすべてで、治験責任医師又は治験分担医師は心電図チャートを評価し、正常又は異常の判定を行った。異常の場合には臨床的に重要か、重要でないかの判断を報告した。治験責任医師又は治験分担医師による心電図チャートの判定（正常、臨床的に重要でない異常、臨床的に重要な異常）別の被験者数を、評価時点ごと及びベースラインの判定ごとに集計した（以下シフトテーブル）。また、ICH E14 ガイドライン等を参考に設定した基準を超える心電図パラメータの値を顕著な異常値として評価した。心電図パラメータの値は、014 試験では集中測定機関の解析結果を、018、019 及び 020 試験では実施医療機関で算出した結果を用いた。

2.7.4.1.2　全般的な曝露状況

2.7.4.1.2.1　被験者の内訳

2.7.4.1.2.1.1　単独療法：二重盲検試験併合（24 週）：014 試験・018 試験

被験者の内訳を表 2.7.4.1-11 に、解析対象集団を 2.7.4.7 項付録 Table S-214 示す。014 試験及び 018 試験で二重盲検治療期の治験薬の投与を開始した 512 名が安全性評価対象（Safety Population）となった。投与を完了したのは 462 名で、治療群ごとの内訳はプラセボ群、500 mg bid 群、1000 mg bid 群、1500 mg bid 群の順に（以下同順）それぞれ 161 名（88.5%）、70 名（93.3%）、164 名（91.1%）、67 名（89.3%）であった。中止した被験者の内訳は 21 名（11.5%）、5 名（6.7%）、16 名（8.9%）、8 名（10.7%）で、中止理由で最も多かったのは同意撤回［6 名（3.3%）、3 名（4.0%）、5 名（2.8%）、3 名（4.0%）］であった。

表 2.7.4.1-11　Summary of Patient Disposition in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; All Screened Subjects)

	Placebo	Imeglimin 500 mg bid	Imeglimin 1000 mg bid	Imeglimin 1500 mg bid	Imeglimin Total	Overall
Screened						696
Screen failure						114
Entered placebo run-in period						582
Received single-blind placebo						582
Run-in failure						70
Completed placebo run-in period						512
Randomized	182 (100.0%)	75 (100.0%)	180 (100.0%)	75 (100.0%)	330 (100.0%)	512 (100.0%)
Received at least one dose of IMP during the double-blind period	182 (100.0%)	75 (100.0%)	180 (100.0%)	75 (100.0%)	330 (100.0%)	512 (100.0%)
Discontinued IMP during double-blind period	21 (11.5%)	5 (6.7%)	16 (8.9%)	8 (10.7%)	29 (8.8%)	50 (9.8%)
Completed double-blind period without IMP discontinuation	161 (88.5%)	70 (93.3%)	164 (91.1%)	67 (89.3%)	301 (91.2%)	462 (90.2%)
Reason for IMP discontinuation						
Occurrence of adverse event	2 (1.1%)	0	6 (3.3%)	5 (6.7%)	11 (3.3%)	13 (2.5%)
Withdrawal of consent	6 (3.3%)	3 (4.0%)	5 (2.8%)	3 (4.0%)	11 (3.3%)	17 (3.3%)
Lack of glycemic control	11 (6.0%)	0	1 (0.6%)	0	1 (0.3%)	12 (2.3%)
Intake of non-permitted drug	1 (0.5%)	0	1 (0.6%)	0	1 (0.3%)	2 (0.4%)
Protocol deviation	0	0	2 (1.1%)	0	2 (0.6%)	2 (0.4%)
Two consecutive occurrences of HbA1c >= 10%	1 (0.5%)	2 (2.7%)	1 (0.6%)	0	3 (0.9%)	4 (0.8%)

- Abbreviations: bid, Twice a day; IMP, Investigational Medicinal Product; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c)
- Overall is the sum of Placebo and Imeglimin Total subjects.
- Percentages are based on the number of subjects who were randomized.

2.7.4.1.2.1.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

被験者の内訳を表 2.7.4.1-12 に、解析対象集団を 2.7.4.7 項付録 Table S-215 に示す。019 試験で非盲検治療期の治験薬の投与を開始した 714 名が安全性評価対象（Long-term Safety Population）となった。投与を完了したのは 632 名で、治療群ごとの内訳は、単独療法群 124 名（92.5%）、SU 併用療法群 110 名（86.6%）、GLIN 併用療法群 58 名（90.6%）、BIG 併用療法群 53 名（82.8%）、AGI 併用療法群 60 名（93.8%）、TZD 併用療法群 61 名（93.8%）、DPP4-I 併用療法群 55 名（87.3%）、GLP1-RA 併用療法群 51 名（72.9%）、SGLT2-I 併用療法群 60 名（95.2%）であった。中止した被験者の内訳は単独療法群で 10 名（7.5%）、SU 併用療法群 17 名（13.4%）、GLIN 併用療法群 6 名（9.4%）、BIG 併用療法群 11 名（17.2%）、AGI 併用療法群 4 名（6.3%）、TZD 併用療法群 4 名（6.2%）、DPP4-I 併用療法群 8 名（12.7%）、GLP1-RA 併用療法群 19 名（27.1%）、SGLT2-I 併用療法群 3 名（4.8%）であった。中止理由で最も多かったのは有害事象［単独療法群 3 名（2.2%）、SU 併用療法群 3 名（2.4%）、GLIN 併用療法群 1 名（1.6%）、BIG 併用療法群 7 名（10.9%）、AGI 併用療法群 1 名（1.6%）、TZD 併用療法群 3 名（4.6%）、DPP4-I 併用療法群 4 名（6.3%）、GLP1-RA 併用療法群 9 名（12.9%）、SGLT2-I 併用療法群 0 名］であった。

表 2.7.4.1-12　Summary of Patient Disposition in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; All Screened Subjects)

	Imeglimin	Imeglimin + SU	Imeglimin + GLIN	Imeglimin + BIG	Imeglimin + AGI	Imeglimin + TZD	Imeglimin + DPP4-I	Imeglimin + GLP1-RA	Imeglimin + SGLT2-I	Combination Total	Imeglimin Total
Screened											981
Screen failure											257
Entered run-in period											724
Received at least one dose of placebo during the run-in period											724
Discontinued during run-in period											10
Completed run-in period											714
Entered open-label treatment period	134 (100.0%)	127 (100.0%)	64 (100.0%)	64 (100.0%)	64 (100.0%)	65 (100.0%)	63 (100.0%)	70 (100.0%)	63 (100.0%)	580 (100.0%)	714 (100.0%)
Received at least one dose of IMP during the open-label treatment period	134 (100.0%)	127 (100.0%)	64 (100.0%)	64 (100.0%)	64 (100.0%)	65 (100.0%)	63 (100.0%)	70 (100.0%)	63 (100.0%)	580 (100.0%)	714 (100.0%)
Discontinued IMP during open-label treatment period	10 (7.5%)	17 (13.4%)	6 (9.4%)	11 (17.2%)	4 (6.3%)	4 (6.2%)	8 (12.7%)	19 (27.1%)	3 (4.8%)	72 (12.4%)	82 (11.5%)
Completed open-label treatment period without IMP discontinuation	124 (92.5%)	110 (86.6%)	58 (90.6%)	53 (82.8%)	60 (93.8%)	61 (93.8%)	55 (87.3%)	51 (72.9%)	60 (95.2%)	508 (87.6%)	632 (88.5%)
Reason for IMP discontinuation											
Occurrence of adverse event	3 (2.2%)	3 (2.4%)	1 (1.6%)	7 (10.9%)	1 (1.6%)	3 (4.6%)	4 (6.3%)	9 (12.9%)	0	28 (4.8%)	31 (4.3%)
Intake of non-permitted drug	0	0	0	1 (1.6%)	0	0	0	1 (1.4%)	0	2 (0.3%)	2 (0.3%)
Lack of glycemic control	1 (0.7%)	7 (5.5%)	0	0	1 (1.6%)	1 (1.5%)	1 (1.6%)	6 (8.6%)	1 (1.6%)	17 (2.9%)	18 (2.5%)
Withdrawal of consent	6 (4.5%)	7 (5.5%)	4 (6.3%)	3 (4.7%)	2 (3.1%)	0	3 (4.8%)	3 (4.3%)	2 (3.2%)	24 (4.1%)	30 (4.2%)
Lost to follow-up	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)

- Abbreviations: IMP, Investigational Medicinal Product; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I,

Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- Percentages are based on the number of subjects who were entered open-label treatment period.

2.7.4.1.2.1.3　インスリン製剤併用療法：二重盲検治療（16 週）及び長期投与（52 週）：020 試験

被験者の内訳を表 2.7.4.1-13 に、解析対象集団を 2.7.4.7 項付録 Table S-216 及び Table S-217 に示す。020 試験で二重盲検治療期の治験薬の投与を開始した 215 名が二重盲検治療の安全性評価対象（Safety Population）となった。また、二重盲検治療期にイメグリミン群で本剤の投与を開始した 108 名及び二重盲検治療期にプラセボ群で非盲検治療期に本剤の投与を開始した 101 名が長期投与の安全性評価対象（Long-term Safety Population）となった。二重盲検期の治験薬の投与を完了したのは 208 名で、治療群ごとの内訳はプラセボ群、イメグリミン群の順に（以下同順）101 名（94.4%）、107 名（99.1%）であった。中止した被験者の内訳は 6 名（5.6%）、1 名（0.9%）で、中止理由で最も多かったのは同意撤回［3 名（2.8%）、0 名］であった。非盲検治療期の治験薬の投与を完了したのは 197 名（91.6%）で、中止した被験者は 11 名（5.1%）であった。中止理由で最も多かったのは有害事象［6 名（2.8%）］であった。

表 2.7.4.1-13　Summary of Patient Disposition in 16-Week Double-blind and 52-Week Long-term Periods in Combination with Insulin Therapy (PXL008-020; All Screened Subjects)

	Placebo + Insulin	Imeglimin 1000 mg bid + Insulin	Overall
Screened			334
Screen failure			73
Entered run-in period			261
Received at least one dose of placebo in the run-in period			261
Discontinued during run-in period			46
Completed run-in period			215
Randomized into double-blind period	107 (100.0%)	108 (100.0%)	215 (100.0%)
Treated in double-blind period	107 (100.0%)	108 (100.0%)	215 (100.0%)
Discontinued IMP during double-blind period	6 (5.6%)	1 (0.9%)	7 (3.3%)
Completed double-blind period without IMP discontinuation	101 (94.4%)	107 (99.1%)	208 (96.7%)
Treated in open-label period	101 (94.4%)	107 (99.1%)	208 (96.7%)
Discontinued IMP during open-label period	7 (6.5%)	4 (3.7%)	11 (5.1%)
Completed open-label period without IMP discontinuation	94 (87.9%)	103 (95.4%)	197 (91.6%)

	Placebo + Insulin	Imeglimin 1000 mg bid + Insulin	Overall
Reason for IMP discontinuation during double-blind period			
Occurrence of an AE or SAE which is clinically relevant and affects patient's safety	1 (0.9%)	1 (0.9%)	2 (0.9%)
Lack of glycemic control	2 (1.9%)	0	2 (0.9%)
Withdrawal of consent	3 (2.8%)	0	3 (1.4%)
Reason for IMP discontinuation during open-label period			
Occurrence of an AE or SAE which is clinically relevant and affects patient's safety	4 (3.7%)	2 (1.9%)	6 (2.8%)
Protocol deviation	1 (0.9%)	0	1 (0.5%)
Lack of glycemic control	1 (0.9%)	2 (1.9%)	3 (1.4%)
Withdrawal of consent	1 (0.9%)	0	1 (0.5%)

- Abbreviations: bid, Twice a day; IMP, Investigational Medicinal Product; AE, Adverse event; SAE, Serious AE
- Overall is the sum of all subjects.
- Percentages are based on the number of subjects who were randomized.

2.7.4.1.2.2　曝露状況

014 試験、018 試験、019 試験及び 020 試験の 4 試験併合での曝露状況を 2.7.4.7 項付録 Table S-573 に示す。

2.7.4.1.2.2.1　単独療法：二重盲検試験併合（24 週）：014 試験・018 試験

投与状況を表 2.7.4.1-14 に示す。投与期間が 141 日以上であった被験者の割合はプラセボ群、500 mg bid 群、1000 mg bid 群、1500 mg bid 群の順に（以下同順）89.6%、93.3%、91.7%、89.3%であった。服薬率［平均値±標準偏差（SD）］は 98.88±4.423%、99.16±1.851%、98.78±5.590%、98.10±5.439%で、ほとんどの被験者が 80%以上、120%未満の服薬率であった。

表 2.7.4.1-14　Summary of Overall Study Treatment Exposure in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Duration of exposure (days)					
n	182	75	180	75	330
Mean (SD)	157.26 (32.155)	161.99 (25.127)	160.23 (28.111)	153.11 (44.653)	159.01 (32.112)
Median	168.00	168.00	168.00	168.00	168.00
Min, Max	14.0, 172.0	36.5, 171.5	5.0, 172.0	7.5, 171.5	5.0, 172.0

	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Duration of exposure					
<= 28 days	3 (1.6%)	0	3 (1.7%)	6 (8.0%)	9 (2.7%)
29 to 56 days	5 (2.7%)	2 (2.7%)	2 (1.1%)	1 (1.3%)	5 (1.5%)
57 to 84 days	5 (2.7%)	1 (1.3%)	3 (1.7%)	0	4 (1.2%)
85 to 112 days	5 (2.7%)	1 (1.3%)	3 (1.7%)	0	4 (1.2%)
113 to 140 days	1 (0.5%)	1 (1.3%)	4 (2.2%)	1 (1.3%)	6 (1.8%)
>= 141 days	163 (89.6%)	70 (93.3%)	165 (91.7%)	67 (89.3%)	302 (91.5%)
Compliance (%)					
n	182	75	180	75	330
Mean (SD)	98.88 (4.423)	99.16 (1.851)	98.78 (5.590)	98.10 (5.439)	98.71 (4.956)
Median	100.00	100.00	100.00	100.00	100.00
Min, Max	57.2, 100.3	86.9, 100.0	45.0, 100.9	67.6, 100.0	45.0, 100.9
Compliance					
< 80%	2 (1.1%)	0	4 (2.2%)	2 (2.7%)	6 (1.8%)
>= 80 to <= 120%	180 (98.9%)	75 (100.0%)	176 (97.8%)	73 (97.3%)	324 (98.2%)
> 120%	0	0	0	0	0

- Abbreviations: bid, Twice a day; SD, standard deviation
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- Percentages are based on Population N.

2.7.4.1.2.2.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

投与状況を表 2.7.4.1-15 に示す。投与期間が 337 日以上であった被験者の割合は、単独療法群で 93.3%、SU 併用療法群で 86.6%、GLIN 併用療法群で 92.2%、BIG 併用療法群で 82.8%、AGI 併用療法群で 93.8%、TZD 併用療法群で 93.8%、DPP4-I 併用療法群で 88.9%、GLP1-RA 併用療法群で 72.9%、SGLT2-I 併用療法群で 96.8%であった。服薬率（平均値±SD）は単独療法群で 91.16±4.947%、SU 併用療法群で 90.84±5.610%、GLIN 併用療法群で 91.34±3.263%、BIG 併用療法群で 90.68±4.354%、AGI 併用療法群で 91.20±4.763%、TZD 併用療法群で 90.33±10.326%、DPP4-I 併用療法群で 91.22±3.370%、GLP1-RA 併用療法群で 89.76±6.204%、SGLT2-I 併用療法群で 92.17±0.700%であり、ほとんどの被験者が 80%以上、120%未満の服薬率であった。

表 2.7.4.1-15　Summary of Overall Study Treatment Exposure in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Duration of exposure (days)											
n	134	127	64	64	64	65	63	70	63	580	714
Mean (SD)	349.1 (60.84)	337.2 (75.65)	345.0 (68.92)	330.6 (84.18)	353.6 (45.76)	350.1 (63.34)	334.0 (88.85)	307.0 (109.19)	359.3 (31.32)	339.0 (76.14)	340.9 (73.58)
Median	364.0	364.0	364.0	364.0	364.0	364.0	364.0	364.0	364.0	364.0	364.0
Min, Max	29, 368	29, 368	11, 367	3, 368	84, 371	4, 367	16, 366	4, 367	124, 368	3, 371	3, 371
Duration of exposure											
<= 28 days	0	0	1 (1.6%)	1 (1.6%)	0	1 (1.5%)	3 (4.8%)	2 (2.9%)	0	8 (1.4%)	8 (1.1%)
29 to 56 days	3 (2.2%)	3 (2.4%)	1 (1.6%)	0	0	1 (1.5%)	0	4 (5.7%)	0	9 (1.6%)	12 (1.7%)
57 to 112 days	1 (0.7%)	3 (2.4%)	0	3 (4.7%)	1 (1.6%)	0	1 (1.6%)	2 (2.9%)	0	10 (1.7%)	11 (1.5%)
113 to 168 days	1 (0.7%)	2 (1.6%)	1 (1.6%)	1 (1.6%)	1 (1.6%)	0	1 (1.6%)	1 (1.4%)	1 (1.6%)	8 (1.4%)	9 (1.3%)
169 to 224 days	2 (1.5%)	4 (3.1%)	2 (3.1%)	3 (4.7%)	0	1 (1.5%)	1 (1.6%)	5 (7.1%)	0	16 (2.8%)	18 (2.5%)
225 to 280 days	0	2 (1.6%)	0	1 (1.6%)	1 (1.6%)	0	1 (1.6%)	2 (2.9%)	0	7 (1.2%)	7 (1.0%)
281 to 336 days	2 (1.5%)	3 (2.4%)	0	2 (3.1%)	1 (1.6%)	1 (1.5%)	0	3 (4.3%)	1 (1.6%)	11 (1.9%)	13 (1.8%)
>= 337 days	125 (93.3%)	110 (86.6%)	59 (92.2%)	53 (82.8%)	60 (93.8%)	61 (93.8%)	56 (88.9%)	51 (72.9%)	61 (96.8%)	511 (88.1%)	636 (89.1%)
Compliance (%)											
n	134	127	63	63	64	64	60	68	63	572	706
Mean (SD)	91.16 (4.947)	90.84 (5.610)	91.34 (3.263)	90.68 (4.354)	91.20 (4.763)	90.33 (10.326)	91.22 (3.370)	89.76 (6.204)	92.17 (0.700)	90.92 (5.531)	90.96 (5.422)
Median	92.20	92.17	92.27	92.03	92.10	92.29	92.28	91.87	92.31	92.17	92.17
Min, Max	50.9, 100.0	50.9, 99.5	71.6, 94.2	66.7, 97.9	56.0, 96.7	16.7, 99.7	74.6, 99.2	63.7, 97.2	89.7, 94.4	16.7, 99.7	16.7, 100.0

	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Compliance											
< 80%	3 (2.2%)	5 (3.9%)	2 (3.1%)	2 (3.1%)	1 (1.6%)	2 (3.1%)	1 (1.6%)	4 (5.7%)	0	17 (2.9%)	20 (2.8%)
>= 80 to <= 120%	131 (97.8%)	122 (96.1%)	61 (95.3%)	61 (95.3%)	63 (98.4%)	62 (95.4%)	59 (93.7%)	64 (91.4%)	63 (100.0%)	555 (95.7%)	686 (96.1%)
> 120%	0	0	0	0	0	0	0	0	0	0	0
Missing	0	0	1 (1.6%)	1 (1.6%)	0	1 (1.5%)	3 (4.8%)	2 (2.9%)	0	8 (1.4%)	8 (1.1%)

- Abbreviations: SD, standard deviation; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- Percentages are based on Population N.

2.7.4.1.2.2.3　インスリン製剤併用療法：020 試験

(1) 二重盲検治療（16 週）

投与状況を表 2.7.4.1-16 に示す。投与期間が 85 日以上であった被験者の割合はプラセボ群及びイメグリミン群の順に（以下同順）96.3%、99.1%であった。服薬率（平均値±SD）は 99.63±1.080%、99.30±3.564%で、ほとんどの被験者が 80%以上、120%未満の服薬率であった。

表 2.7.4.1-16　Summary of Overall Study Treatment Exposure in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Duration of exposure (days)		
n	107	108
Mean (SD)	109.1 (15.18)	111.5 (7.81)
Median	112.0	112.0
Min, Max	11, 119	32, 116
Duration of exposure		
<= 28 days	2 (1.9%)	0
29 to 56 days	1 (0.9%)	1 (0.9%)
57 to 84 days	1 (0.9%)	0
>= 85 days	103 (96.3%)	107 (99.1%)
Compliance (%)		
n	107	108
Mean (SD)	99.63 (1.080)	99.30 (3.564)
Median	100.00	100.00
Min, Max	92.0, 100.9	64.1, 100.0
Compliance		
< 80%	0	1 (0.9%)
>= 80 to <= 120%	107 (100.0%)	107 (99.1%)
> 120%	0	0

- Abbreviations: bid, Twice a day; SD, standard deviation
- Percentages are based on Population N.

(2) 長期投与（52 週）

投与状況を表 2.7.4.1-17 に示す。二重盲検治療期にプラセボ群であった被験者では、投与期間が 225 日以上であった被験者の割合は 93.1%であった。二重盲検治療期にイメグリミン群であった被験者では、投与期間が 337 日以上であった被験者の割合は 95.4%であった。服薬率（平均値±SD）は、二重盲検治療期にプラセボ群であった被験者とイメグリミン群であった被験者の合計で 99.40±2.714%であり、ほとんどの被験者が 80%以上、120%未満の服薬率であった。

表 2.7.4.1-17　Summary of Overall Study Treatment Exposure in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Duration of exposure (days)			
n	101	108	209
Mean (SD)	242.7 (37.94)	357.1 (37.48)	301.8 (68.56)
Median	252.0	364.0	294.0
Min, Max	11, 259	32, 372	11, 372
Duration of exposure			
<= 28 days	1 (1.0%)	0	1 (0.5%)
29 to 56 days	0	1 (0.9%)	1 (0.5%)
57 to 112 days	3 (3.0%)	0	3 (1.4%)
113 to 168 days	1 (1.0%)	0	1 (0.5%)
169 to 224 days	2 (2.0%)	0	2 (1.0%)
225 to 280 days	94 (93.1%)	2 (1.9%)	96 (45.9%)
281 to 336 days	0	2 (1.9%)	2 (1.0%)
>= 337 days	0	103 (95.4%)	103 (49.3%)
Compliance (%)			
n	101	108	209
Mean (SD)	99.63 (1.059)	99.18 (3.630)	99.40 (2.714)
Median	100.00	100.00	100.00
Min, Max	91.7, 100.4	64.1, 100.0	64.1, 100.4
Compliance			
< 80%	0	1 (0.9%)	1 (0.5%)
>= 80 to <= 120%	101 (100.0%)	107 (99.1%)	208 (99.5%)
> 120%	0	0	0

- Abbreviations: SD, standard deviation
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- Placebo/Imeglimin + Insulin only includes data from the open-label period. Imeglimin/Imeglimin + Insulin includes data from both double-blind and open-label periods. Imeglimin + Insulin Total includes both Placebo/Imeglimin + Insulin and Imeglimin/Imeglimin + Insulin.
- Percentages are based on Population N.

2.7.4.1.3　治験対象集団の人口統計学的特性及びその他の特性

2.7.4.1.3.1　単独療法：二重盲検試験併合（24 週）：014 試験・018 試験

主な人口統計学的特性及びその他の特性を表 2.7.4.1-18 に、すべての人口統計学的特性及びその他の特性を 2.7.4.7 項付録 Table S-008 に示す。プラセボ群、500 mg bid 群、1000 mg bid 群、1500 mg bid 群の順に（以下同順）、男性の割合は 69.8%、65.3%、76.7%及び 72.0%であった。年齢（平均値±SD、以下同様）は 61.2±9.91 歳、58.7±8.51 歳、61.3±9.78 歳及び

57.7±10.76 歳、65 歳以上の高齢者の割合は 41.8%、28.0%、46.1%及び 37.3%、75 歳以上の高齢者の割合はプラセボ群及び 1000 mg bid 群でそれぞれ 7.1%及び 5.0%であった。014 試験では選択基準で年齢の上限を 75 歳としたため、500 mg bid 群及び 1500 mg bid 群では 75 歳以上の被験者は組み入れられなかった。体重は、プラセボ群、500 mg bid 群、1000 mg bid 群、1500 mg bid 群の順に（以下同順）69.74±13.668 kg、68.51±15.183 kg、69.65±13.548 kg 及び 73.13±15.486 kg、BMI は 25.518±4.2878 kg/m^2、25.241±4.5998 kg/m^2、25.465±4.0765 kg/m^2 及び 26.754±4.3512 kg/m^2 であった。HbA1c は、7.91±0.678%、7.94±0.679%、7.94±0.724%及び 7.92±0.620%であった。罹病期間は、6.86±6.222 年、7.20±6.272 年、7.12±5.557 年及び 5.29±5.124 年、罹病期間が 10 年以上の被験者の割合は 24.2%、29.3%、26.7%及び 9.3%で、1500 mg bid 群の罹病期間がやや短かった。糖尿病合併症区分ごとの被験者の割合は、糖尿病合併症あり（Yes）で 17.0%、22.7%、17.2%、20.0%、なし（No）で 83.0%、77.3%、82.8%、80.0%であった。メタボリックシンドローム区分ごとの被験者の割合は、メタボリックシンドロームに該当（Yes）で 46.7%、46.7%、43.3%、60.0%、非該当（No）で 53.3%、53.3%、56.7%、40.0%であった。腎機能区分ごとの被験者の割合は、CKD 1 で 8.8%、12.0%、11.7%及び 18.7%、CKD 2 で 75.3%、74.7%、72.8%及び 69.3%、CKD 3a で 15.9%、13.3%、15.6%及び 12.0%であった。

表 2.7.4.1-18　Summary of Demographic and Baseline Characteristics in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Sex					
Male	127 (69.8%)	49 (65.3%)	138 (76.7%)	54 (72.0%)	241 (73.0%)
Female	55 (30.2%)	26 (34.7%)	42 (23.3%)	21 (28.0%)	89 (27.0%)
Age (years)					
n	182	75	180	75	330
Mean (SD)	61.2 (9.91)	58.7 (8.51)	61.3 (9.78)	57.7 (10.76)	59.9 (9.85)
Median	61.5	59.0	62.0	61.0	61.0
Min, Max	32, 83	33, 74	34, 82	33, 72	33, 82
Age category					
< 65 years	106 (58.2%)	54 (72.0%)	97 (53.9%)	47 (62.7%)	198 (60.0%)
>= 65 years	76 (41.8%)	21 (28.0%)	83 (46.1%)	28 (37.3%)	132 (40.0%)
< 75 years	169 (92.9%)	75 (100.0%)	171 (95.0%)	75 (100.0%)	321 (97.3%)
>= 75 years	13 (7.1%)	0	9 (5.0%)	0	9 (2.7%)

	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Weight (kg) at baseline					
n	182	75	180	75	330
Mean (SD)	69.74 (13.668)	68.51 (15.183)	69.65 (13.548)	73.13 (15.486)	70.18 (14.437)
Median	67.90	67.00	68.90	73.00	69.10
Min, Max	40.2, 113.2	35.6, 115.8	42.5, 124.0	41.5, 122.3	35.6, 124.0
BMI (kg/m2) at baseline					
n	182	75	180	75	330
Mean (SD)	25.518 (4.2878)	25.241 (4.5998)	25.465 (4.0765)	26.754 (4.3512)	25.707 (4.2884)
Median	24.725	24.430	25.010	26.320	25.290
Min, Max	18.53, 43.46	18.07, 39.14	18.36, 40.26	18.51, 41.60	18.07, 41.60
BMI category at baseline					
< 25 kg/m2	95 (52.2%)	39 (52.0%)	90 (50.0%)	28 (37.3%)	157 (47.6%)
>= 25 kg/m2	87 (47.8%)	36 (48.0%)	90 (50.0%)	47 (62.7%)	173 (52.4%)
>= 25 to < 30 kg/m2	64 (35.2%)	22 (29.3%)	66 (36.7%)	33 (44.0%)	121 (36.7%)
>= 30 kg/m2	23 (12.6%)	14 (18.7%)	24 (13.3%)	14 (18.7%)	52 (15.8%)
HbA1c (%) at baseline					
n	182	75	180	75	330
Mean (SD)	7.91 (0.678)	7.94 (0.679)	7.94 (0.724)	7.92 (0.620)	7.94 (0.689)
Median	7.80	7.80	7.80	7.90	7.80
Min, Max	6.9, 10.2	6.9, 9.5	6.7, 9.8	6.9, 9.6	6.7, 9.8
HbA1c category at baseline					
< 8.0%	107 (58.8%)	47 (62.7%)	107 (59.4%)	42 (56.0%)	196 (59.4%)
>= 8.0%	75 (41.2%)	28 (37.3%)	73 (40.6%)	33 (44.0%)	134 (40.6%)
>= 8.0 to < 9.0%	59 (32.4%)	20 (26.7%)	50 (27.8%)	30 (40.0%)	100 (30.3%)
>= 9.0%	16 (8.8%)	8 (10.7%)	23 (12.8%)	3 (4.0%)	34 (10.3%)
Duration of diabetes (year)					
n	182	75	180	75	330
Mean (SD)	6.86 (6.222)	7.20 (6.272)	7.12 (5.557)	5.29 (5.124)	6.72 (5.671)
Median	5.04	6.00	5.87	4.21	5.51
Min, Max	0.2, 35.0	0.3, 31.0	0.3, 27.9	0.2, 24.0	0.2, 31.0

	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Duration of diabetes category					
< 1 year	25 (13.7%)	10 (13.3%)	20 (11.1%)	13 (17.3%)	43 (13.0%)
>= 1 to < 5 years	64 (35.2%)	22 (29.3%)	56 (31.1%)	29 (38.7%)	107 (32.4%)
>= 5 to < 10 years	49 (26.9%)	21 (28.0%)	56 (31.1%)	26 (34.7%)	103 (31.2%)
>= 10 years	44 (24.2%)	22 (29.3%)	48 (26.7%)	7 (9.3%)	77 (23.3%)
Complication of diabetes					
Yes	31 (17.0%)	17 (22.7%)	31 (17.2%)	15 (20.0%)	63 (19.1%)
No	151 (83.0%)	58 (77.3%)	149 (82.8%)	60 (80.0%)	267 (80.9%)
Metabolic Syndrome at baseline					
Yes	85 (46.7%)	35 (46.7%)	78 (43.3%)	45 (60.0%)	158 (47.9%)
No	97 (53.3%)	40 (53.3%)	102 (56.7%)	30 (40.0%)	172 (52.1%)
CKD stage at baseline					
CKD Stage 1	16 (8.8%)	9 (12.0%)	21 (11.7%)	14 (18.7%)	44 (13.3%)
CKD Stage 2	137 (75.3%)	56 (74.7%)	131 (72.8%)	52 (69.3%)	239 (72.4%)
CKD Stage 3a	29 (15.9%)	10 (13.3%)	28 (15.6%)	9 (12.0%)	47 (14.2%)

- Abbreviations: bid, Twice a day; SD, standard deviation; BMI, body mass index; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); CKD, Chronic Kidney Disease;
- Complication of diabetes is defined as any MedDRA Preferred Term (PT) of medical history which are included in High-Level Group Term (HLGT) of diabetic complication.
- Metabolic Syndrome is defined as an excessive waist circumference (>= 85 cm in men and >= 90 cm in women) as well as the presence of two or more of the following symptoms: (1) Hypertension: systolic blood pressure >= 130 mmHg, or diastolic blood pressure >= 85 mmHg; (2) Glucose intolerance: fasting glucose >= 110 mg/dL; (3) Dyslipidemia: triglyceride >= 150 mg/dL, or HDL cholesterol < 40 mg/dL.
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2, CKD Stage 3a includes subjects with eGFR >= 45 to < 60 mL/min/1.73m2.
- Percentages are based on Population N.

2.7.4.1.3.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

主な人口統計学的特性及びその他の特性を表 2.7.4.1-19 に、すべての人口統計学的特性及びその他の特性を 2.7.4.7 項付録 Table S-009 に示す。

- 単独療法群では男性の割合は 79.1%であった。年齢（平均値±SD、以下同様）は 59.4±10.78 歳、65 歳以上の高齢者の割合は 35.8%、75 歳以上の高齢者の割合は 5.2%であった。体重は 71.02±13.785 kg、BMI は 25.550±3.8825 kg/m^2 であった。HbA1c は 7.83±0.730%であった。罹病期間は 5.85±5.954 年、罹病期間ごとの被験者の割合は 1 年未満が 17.2%、1 年以上 5 年未満が 36.6%、5 年以上 10 年未満が 27.6%、10 年以上が 18.7%であった。糖尿病合併症区分ごとの被験者の割合は、糖尿病合併症あり（Yes）

が 17.2%、なし（No）が 82.8%であった。メタボリックシンドローム区分ごとの被験者の割合は、メタボリックシンドロームに該当（Yes）が 46.3%、非該当（No）が 53.7%であった。腎機能区分ごとの被験者の割合は、CKD 1 が 17.9%、CKD 2 が 67.9%、CKD 3a が 14.2%であった。

- SU 併用療法群では男性の割合は 79.5%であった。年齢は 60.3±10.38 歳、65 歳以上の高齢者の割合は 40.2%、75 歳以上の高齢者の割合は 3.9%であった。体重は 70.64±13.761 kg、BMI は 25.607±4.2137 kg/m^2 であった。HbA1c は 8.63±0.903%であった。罹病期間は 10.59±6.585 年、罹病期間ごとの被験者の割合は 1 年未満が 0%、1 年以上 5 年未満が 18.1%、5 年以上 10 年未満が 39.4%、10 年以上が 42.5%であった。糖尿病合併症区分ごとの被験者の割合は、糖尿病合併症あり（Yes）が 36.2%、なし（No）が 63.8%であった。メタボリックシンドローム区分ごとの被験者の割合は、メタボリックシンドロームに該当（Yes）が 50.4%、非該当（No）が 49.6%であった。腎機能区分ごとの被験者の割合は、CKD 1 が 17.3%、CKD 2 が 75.6%、CKD 3a が 7.1%であった。
- GLIN 併用療法群では男性の割合は 67.2%であった。年齢は 58.1±10.81 歳、65 歳以上の高齢者の割合は 34.4%、75 歳以上の高齢者の割合は 4.7%であった。体重は 68.28±13.850 kg、BMI は 25.268±4.5984 kg/m^2 であった。HbA1c は 8.48±0.837%であった。罹病期間は 7.90±4.893 年、罹病期間ごとの被験者の割合は 1 年未満が 6.3%、1 年以上 5 年未満が 21.9%、5 年以上 10 年未満が 43.8%、10 年以上が 28.1%であった。糖尿病合併症区分ごとの被験者の割合は、糖尿病合併症あり（Yes）が 37.5%、なし（No）が 62.5%であった。メタボリックシンドローム区分ごとの被験者の割合は、メタボリックシンドロームに該当（Yes）が 43.8%、非該当（No）が 56.3%であった。腎機能区分ごとの被験者の割合は、CKD 1 が 18.8%、CKD 2 が 78.1%、CKD 3a が 3.1%であった。
- BIG 併用療法群では男性の割合は 71.9%であった。年齢は 57.6±10.83 歳、65 歳以上の高齢者の割合は 26.6%、75 歳以上の高齢者の割合は 4.7%であった。体重は 72.25±11.451 kg、BMI は 26.185±3.6807 kg/m^2 であった。HbA1c は 8.16±0.607%であった。罹病期間は 8.96±6.266 年、罹病期間ごとの被験者の割合は 1 年未満が 3.1%、1 年以上 5 年未満が 31.3%、5 年以上 10 年未満が 23.4%、10 年以上が 42.2%であった。糖尿病合併症区分ごとの被験者の割合は、糖尿病合併症あり（Yes）が 37.5%、なし（No）が 62.5%であった。メタボリックシンドローム区分ごとの被験者の割合は、メタボリックシンドロームに該当（Yes）が 56.3%、非該当（No）が 43.8%であった。腎機能区分ごとの被験者の割合は、CKD 1 が 28.1%、CKD 2 が 65.6%、CKD 3a が 6.3%であった。
- AGI 併用療法群では男性の割合は 75.0%であった。年齢は 56.6±12.01 歳、65 歳以上の高齢者の割合は 35.9%、75 歳以上の高齢者の割合は 3.1%であった。体重は 72.62±16.757 kg、BMI は 26.248±4.6020 kg/m^2 であった。HbA1c は 8.37±0.771%であっ

た。罹病期間は 7.47±6.826 年、罹病期間ごとの被験者の割合は 1 年未満が 9.4%、1 年以上 5 年未満が 31.3%、5 年以上 10 年未満が 34.4%、10 年以上が 25.0%であった。糖尿病合併症区分ごとの被験者の割合は、糖尿病合併症あり（Yes）が 25.0%、なし（No）が 75.0%であった。メタボリックシンドローム区分ごとの被験者の割合は、メタボリックシンドロームに該当（Yes）が 50.0%、非該当（No）が 50.0%であった。腎機能区分ごとの被験者の割合は、CKD 1 が 20.3%、CKD 2 が 76.6%、CKD 3a が 3.1%であった。

- TZD 併用療法群では男性の割合は 83.1%であった。年齢は 57.1±10.72 歳、65 歳以上の高齢者の割合は 32.3%、75 歳以上の高齢者の割合は 6.2%であった。体重は 75.57±16.133 kg、BMI は 27.247±4.9274 kg/m^2 であった。HbA1c は 8.72±0.942%であった。罹病期間は 9.27±6.597 年、罹病期間ごとの被験者の割合は 1 年未満が 3.1%、1 年以上 5 年未満が 27.7%、5 年以上 10 年未満が 29.2%、10 年以上が 40.0%であった。糖尿病合併症区分ごとの被験者の割合は、糖尿病合併症あり（Yes）が 15.4%、なし（No）が 84.6%であった。メタボリックシンドローム区分ごとの被験者の割合は、メタボリックシンドロームに該当（Yes）が 49.2%、非該当（No）が 50.8%であった。腎機能区分ごとの被験者の割合は、CKD 1 が 24.6%、CKD 2 が 67.7%、CKD 3a が 7.7%であった。
- DPP4-I 併用療法群では男性の割合は 61.9%であった。年齢は 63.6±8.95 歳、65 歳以上の高齢者の割合は 55.6%、75 歳以上の高齢者の割合は 7.9%であった。体重は 64.88±12.882 kg、BMI は 24.548±3.4297 kg/m^2 であった。HbA1c は 8.23±0.750%であった。罹病期間は 7.96±5.600 年、罹病期間ごとの被験者の割合は 1 年未満が 3.2%、1 年以上 5 年未満が 28.6%、5 年以上 10 年未満が 38.1%、10 年以上が 30.2%であった。糖尿病合併症区分ごとの被験者の割合は、糖尿病合併症あり（Yes）が 34.9%、なし（No）が 65.1%であった。メタボリックシンドローム区分ごとの被験者の割合は、メタボリックシンドロームに該当（Yes）が 39.7%、非該当（No）が 60.3%であった。腎機能区分ごとの被験者の割合は、CKD 1 が 14.3%、CKD 2 が 74.6%、CKD 3a が 11.1%であった。
- GLP1-RA 併用療法群では男性の割合は 62.9%であった。年齢は 57.4±10.95 歳、65 歳以上の高齢者の割合は 34.3%、75 歳以上の高齢者の割合は 4.3%であった。体重は 70.85±15.130 kg、BMI は 26.198±4.3576 kg/m^2 であった。HbA1c は 8.66±0.848%であった。罹病期間は 10.73±5.895 年、罹病期間ごとの被験者の割合は 1 年未満が 1.4%、1 年以上 5 年未満が 20.0%、5 年以上 10 年未満が 25.7%、10 年以上が 52.9%であった。糖尿病合併症区分ごとの被験者の割合は、糖尿病合併症あり（Yes）が 45.7%、なし（No）が 54.3%であった。メタボリックシンドローム区分ごとの被験者の割合は、メタボリックシンドロームに該当（Yes）が 55.7%、非該当（No）が 44.3%であった。腎機能区分ごとの被験者の割合は、CKD 1 が 22.9%、CKD 2 が 72.9%、CKD 3a が 4.3%であった。

- SGLT2-I 併用療法群では男性の割合は 71.4%であった。年齢は 57.1±10.04 歳、65 歳以上の高齢者の割合は 28.6%、75 歳以上の高齢者の割合は 3.2%であった。体重は 72.76±16.512 kg、BMI は 26.320±4.3463 kg/m^2 であった。HbA1c は 8.50±0.748%であった。罹病期間は 9.55±5.651 年、罹病期間ごとの被験者の割合は 1 年未満が 1.6%、1 年以上 5 年未満が 17.5%、5 年以上 10 年未満が 41.3%、10 年以上が 39.7%であった。糖尿病合併症区分ごとの被験者の割合は、糖尿病合併症あり（Yes）が 25.4%、なし（No）が 74.6%であった。メタボリックシンドローム区分ごとの被験者の割合は、メタボリックシンドロームに該当（Yes）が 49.2%、非該当（No）が 50.8%であった。腎機能区分ごとの被験者の割合は、CKD 1 が 33.3%、CKD 2 が 63.5%、CKD 3a が 3.2%であった。

表 2.7.4.1-19　Summary of Demographic and Baseline Characteristics in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Sex											
Male	106 (79.1%)	101 (79.5%)	43 (67.2%)	46 (71.9%)	48 (75.0%)	54 (83.1%)	39 (61.9%)	44 (62.9%)	45 (71.4%)	420 (72.4%)	526 (73.7%)
Female	28 (20.9%)	26 (20.5%)	21 (32.8%)	18 (28.1%)	16 (25.0%)	11 (16.9%)	24 (38.1%)	26 (37.1%)	18 (28.6%)	160 (27.6%)	188 (26.3%)
Age (years)											
n	134	127	64	64	64	65	63	70	63	580	714
Mean (SD)	59.4 (10.78)	60.3 (10.38)	58.1 (10.81)	57.6 (10.83)	56.6 (12.01)	57.1 (10.72)	63.6 (8.95)	57.4 (10.95)	57.1 (10.04)	58.7 (10.75)	58.8 (10.75)
Median	59.0	60.0	58.0	58.5	56.0	55.0	66.0	58.0	57.0	59.0	59.0
Min, Max	23, 84	25, 83	33, 77	21, 75	30, 77	34, 78	44, 80	35, 78	30, 78	21, 83	21, 84
Age category											
< 65 years	86 (64.2%)	76 (59.8%)	42 (65.6%)	47 (73.4%)	41 (64.1%)	44 (67.7%)	28 (44.4%)	46 (65.7%)	45 (71.4%)	369 (63.6%)	455 (63.7%)
>= 65 years	48 (35.8%)	51 (40.2%)	22 (34.4%)	17 (26.6%)	23 (35.9%)	21 (32.3%)	35 (55.6%)	24 (34.3%)	18 (28.6%)	211 (36.4%)	259 (36.3%)
< 75 years	127 (94.8%)	122 (96.1%)	61 (95.3%)	61 (95.3%)	62 (96.9%)	61 (93.8%)	58 (92.1%)	67 (95.7%)	61 (96.8%)	553 (95.3%)	680 (95.2%)
>= 75 years	7 (5.2%)	5 (3.9%)	3 (4.7%)	3 (4.7%)	2 (3.1%)	4 (6.2%)	5 (7.9%)	3 (4.3%)	2 (3.2%)	27 (4.7%)	34 (4.8%)

	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Weight (kg) at baseline											
n	134	127	64	64	64	65	63	70	63	580	714
Mean (SD)	71.02 (13.785)	70.64 (13.761)	68.28 (13.850)	72.25 (11.451)	72.62 (16.757)	75.57 (16.133)	64.88 (12.882)	70.85 (15.130)	72.76 (16.512)	70.96 (14.764)	70.97 (14.576)
Median	69.10	67.80	68.30	72.30	68.55	74.00	63.00	72.60	70.70	68.90	69.00
Min, Max	44.6, 129.0	44.3, 114.6	43.3, 104.7	46.9, 99.1	46.6, 132.8	44.2, 117.2	45.4, 117.4	39.0, 119.2	41.2, 129.8	39.0, 132.8	39.0, 132.8
BMI (kg/m2) at baseline											
n	134	127	64	64	64	65	63	70	63	580	714
Mean (SD)	25.550 (3.8825)	25.607 (4.2137)	25.268 (4.5984)	26.185 (3.6807)	26.248 (4.6020)	27.247 (4.9274)	24.548 (3.4297)	26.198 (4.3576)	26.320 (4.3463)	25.922 (4.3232)	25.852 (4.2438)
Median	24.970	24.690	24.415	26.115	25.260	27.340	24.200	25.890	24.960	25.265	25.155
Min, Max	18.51, 42.03	18.20, 37.41	18.46, 38.76	18.51, 34.08	19.34, 44.28	19.48, 41.84	18.63, 40.01	18.20, 37.77	18.91, 38.63	18.20, 44.28	18.20, 44.28
BMI category at baseline											
< 25 kg/m2	67 (50.0%)	65 (51.2%)	35 (54.7%)	22 (34.4%)	31 (48.4%)	24 (36.9%)	38 (60.3%)	27 (38.6%)	32 (50.8%)	274 (47.2%)	341 (47.8%)
>= 25 kg/m2	67 (50.0%)	62 (48.8%)	29 (45.3%)	42 (65.6%)	33 (51.6%)	41 (63.1%)	25 (39.7%)	43 (61.4%)	31 (49.2%)	306 (52.8%)	373 (52.2%)
>= 25 to < 30 kg/m2	51 (38.1%)	43 (33.9%)	18 (28.1%)	29 (45.3%)	26 (40.6%)	25 (38.5%)	23 (36.5%)	31 (44.3%)	24 (38.1%)	219 (37.8%)	270 (37.8%)
>= 30 kg/m2	16 (11.9%)	19 (15.0%)	11 (17.2%)	13 (20.3%)	7 (10.9%)	16 (24.6%)	2 (3.2%)	12 (17.1%)	7 (11.1%)	87 (15.0%)	103 (14.4%)

	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
HbA1c (%) at baseline											
n	134	127	64	64	64	65	63	70	63	580	714
Mean (SD)	7.83 (0.730)	8.63 (0.903)	8.48 (0.837)	8.16 (0.607)	8.37 (0.771)	8.72 (0.942)	8.23 (0.750)	8.66 (0.848)	8.50 (0.748)	8.49 (0.835)	8.37 (0.856)
Median	7.60	8.40	8.50	8.15	8.20	8.40	8.10	8.65	8.30	8.30	8.20
Min, Max	6.3, 10.2	6.9, 11.1	7.1, 10.2	7.1, 10.0	7.3, 10.8	7.4, 11.5	7.1, 10.4	7.3, 10.4	7.5, 10.8	6.9, 11.5	6.3, 11.5
HbA1c category at baseline											
< 8.0%	89 (66.4%)	33 (26.0%)	23 (35.9%)	26 (40.6%)	20 (31.3%)	16 (24.6%)	24 (38.1%)	17 (24.3%)	16 (25.4%)	175 (30.2%)	264 (37.0%)
>= 8.0%	45 (33.6%)	94 (74.0%)	41 (64.1%)	38 (59.4%)	44 (68.8%)	49 (75.4%)	39 (61.9%)	53 (75.7%)	47 (74.6%)	405 (69.8%)	450 (63.0%)
>= 8.0 to < 9.0%	34 (25.4%)	52 (40.9%)	22 (34.4%)	32 (50.0%)	31 (48.4%)	24 (36.9%)	28 (44.4%)	26 (37.1%)	31 (49.2%)	246 (42.4%)	280 (39.2%)
>= 9.0%	11 (8.2%)	42 (33.1%)	19 (29.7%)	6 (9.4%)	13 (20.3%)	25 (38.5%)	11 (17.5%)	27 (38.6%)	16 (25.4%)	159 (27.4%)	170 (23.8%)
Duration of diabetes (year)											
n	134	127	64	64	64	65	63	70	63	580	714
Mean (SD)	5.85 (5.954)	10.59 (6.585)	7.90 (4.893)	8.96 (6.266)	7.47 (6.826)	9.27 (6.597)	7.96 (5.600)	10.73 (5.895)	9.55 (5.651)	9.24 (6.207)	8.60 (6.297)
Median	4.17	8.92	6.94	7.17	5.63	7.71	7.11	10.63	8.50	8.19	7.41
Min, Max	0.3, 42.9	1.0, 37.2	0.5, 29.2	0.5, 27.3	0.5, 30.8	0.5, 33.7	0.6, 27.8	1.0, 28.7	0.6, 31.2	0.5, 37.2	0.3, 42.9

	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Duration of diabetes category											
< 1 year	23 (17.2%)	0	4 (6.3%)	2 (3.1%)	6 (9.4%)	2 (3.1%)	2 (3.2%)	1 (1.4%)	1 (1.6%)	18 (3.1%)	41 (5.7%)
>= 1 to < 5 years	49 (36.6%)	23 (18.1%)	14 (21.9%)	20 (31.3%)	20 (31.3%)	18 (27.7%)	18 (28.6%)	14 (20.0%)	11 (17.5%)	138 (23.8%)	187 (26.2%)
>= 5 to < 10 years	37 (27.6%)	50 (39.4%)	28 (43.8%)	15 (23.4%)	22 (34.4%)	19 (29.2%)	24 (38.1%)	18 (25.7%)	26 (41.3%)	202 (34.8%)	239 (33.5%)
>= 10 years	25 (18.7%)	54 (42.5%)	18 (28.1%)	27 (42.2%)	16 (25.0%)	26 (40.0%)	19 (30.2%)	37 (52.9%)	25 (39.7%)	222 (38.3%)	247 (34.6%)
Complication of diabetes											
Yes	23 (17.2%)	46 (36.2%)	24 (37.5%)	24 (37.5%)	16 (25.0%)	10 (15.4%)	22 (34.9%)	32 (45.7%)	16 (25.4%)	190 (32.8%)	213 (29.8%)
No	111 (82.8%)	81 (63.8%)	40 (62.5%)	40 (62.5%)	48 (75.0%)	55 (84.6%)	41 (65.1%)	38 (54.3%)	47 (74.6%)	390 (67.2%)	501 (70.2%)
Metabolic Syndrome at baseline											
Yes	62 (46.3%)	64 (50.4%)	28 (43.8%)	36 (56.3%)	32 (50.0%)	32 (49.2%)	25 (39.7%)	39 (55.7%)	31 (49.2%)	287 (49.5%)	349 (48.9%)
No	72 (53.7%)	63 (49.6%)	36 (56.3%)	28 (43.8%)	32 (50.0%)	33 (50.8%)	38 (60.3%)	31 (44.3%)	32 (50.8%)	293 (50.5%)	365 (51.1%)

	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
CKD stage at baseline											
CKD Stage 1	24 (17.9%)	22 (17.3%)	12 (18.8%)	18 (28.1%)	13 (20.3%)	16 (24.6%)	9 (14.3%)	16 (22.9%)	21 (33.3%)	127 (21.9%)	151 (21.1%)
CKD Stage 2	91 (67.9%)	96 (75.6%)	50 (78.1%)	42 (65.6%)	49 (76.6%)	44 (67.7%)	47 (74.6%)	51 (72.9%)	40 (63.5%)	419 (72.2%)	510 (71.4%)
CKD Stage 3a	19 (14.2%)	9 (7.1%)	2 (3.1%)	4 (6.3%)	2 (3.1%)	5 (7.7%)	7 (11.1%)	3 (4.3%)	2 (3.2%)	34 (5.9%)	53 (7.4%)

- Abbreviations: SD, standard deviation; BMI, body mass index; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor; CKD, Chronic Kidney Disease.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- Complication of diabetes is defined as any MedDRA Preferred Term (PT) of medical history which are included in High-Level Group Term (HLGT) of diabetic complication.
- Metabolic Syndrome is defined as an excessive waist circumference (>= 85 cm in men and >= 90 cm in women) as well as the presence of two or more of the following symptoms: (1) Hypertension: systolic blood pressure >= 130 mmHg, or diastolic blood pressure >= 85 mmHg; (2) Glucose intolerance: fasting glucose >= 110 mg/dL; (3) Dyslipidemia: triglyceride >= 150 mg/dL, or HDL cholesterol < 40 mg/dL.
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2, CKD Stage 3a includes subjects with eGFR >= 45 to < 60 mL/min/1.73m2.
- Percentages are based on Population N.

2.7.4.1.3.3　インスリン製剤併用療法：020 試験

(1) 二重盲検治療（16 週）

主な人口統計学的特性及びその他の特性を表 2.7.4.1-20 に、すべての人口統計学的特性及びその他の特性を 2.7.4.7 項付録 Table S-010 に示す。プラセボ群、イメグリミン群の順に（以下同順）、男性の割合は 64.5%、61.1%であった。年齢（平均値±SD、以下同様）は 57.6±10.10 歳、59.3±10.49 歳、65 歳以上の高齢者の割合は 29.0%、37.0%、75 歳以上の高齢者の割合は 2.8%及び 6.5%であった。体重は 67.54±11.816 kg、67.13±12.266 kg、BMI は 24.887±3.5104 kg/m^2 及び 25.244±3.6302 kg/m^2 であった。HbA1c は、8.83±0.814%、8.74±0.721%であった。罹病期間は 13.37±7.400 年、13.26±8.151 年であった。罹病期間ごとの被験者の割合は 1 年未満が 0.9%、1.9%、1 年以上 5 年未満が 10.3%、13.0%、5 年以上 10 年未満が 21.5%、26.9%、10 年以上が 67.3%、58.3%であった。糖尿病合併症区分ごとの被験者の割合は、糖尿病合併症あり（Yes）で 49.5%、41.7%、なし（No）で 50.5%、58.3%であった。メタボリックシンドローム区分ごとの被験者の割合は、メタボリックシンドロームに該当（Yes）で 46.7%、36.1%、非該当（No）で 53.3%、63.9%であった。腎機能区分ごとの被験者の割合は、CKD 1 で 13.1%、14.8%、CKD 2 で 86.9%、85.2%であった。いずれの被験者背景も群間で大きな違いはなかった。

表 2.7.4.1-20　Summary of Demographic and Baseline Characteristics in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Sex		
Male	69 (64.5%)	66 (61.1%)
Female	38 (35.5%)	42 (38.9%)
Age (years)		
n	107	108
Mean (SD)	57.6 (10.10)	59.3 (10.49)
Median	59.0	60.0
Min, Max	26, 77	34, 76
Age category		
< 65 years	76 (71.0%)	68 (63.0%)
>= 65 years	31 (29.0%)	40 (37.0%)
< 75 years	104 (97.2%)	101 (93.5%)
>= 75 years	3 (2.8%)	7 (6.5%)
Weight (kg) at baseline		
n	107	108
Mean (SD)	67.54 (11.816)	67.13 (12.266)
Median	66.90	65.40

	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Min, Max	44.2, 106.2	41.8, 104.1
BMI (kg/m2) at baseline		
n	107	108
Mean (SD)	24.887 (3.5104)	25.244 (3.6302)
Median	24.220	24.940
Min, Max	16.82, 34.28	18.17, 38.80
BMI category at baseline		
< 25 kg/m2	60 (56.1%)	56 (51.9%)
>= 25 kg/m2	47 (43.9%)	52 (48.1%)
>= 25 to < 30 kg/m2	35 (32.7%)	44 (40.7%)
>= 30 kg/m2	12 (11.2%)	8 (7.4%)
HbA1c (%) at baseline		
n	107	108
Mean (SD)	8.83 (0.814)	8.74 (0.721)
Median	8.80	8.70
Min, Max	7.4, 10.8	7.4, 10.4
HbA1c category at baseline		
< 8.0%	16 (15.0%)	16 (14.8%)
>= 8.0%	91 (85.0%)	92 (85.2%)
>= 8.0 to < 9.0%	44 (41.1%)	53 (49.1%)
>= 9.0%	47 (43.9%)	39 (36.1%)
Duration of diabetes (year)		
n	107	108
Mean (SD)	13.37 (7.400)	13.26 (8.151)
Median	12.37	11.74
Min, Max	0.3, 37.7	0.4, 36.4
Duration of diabetes category		
< 1 year	1 (0.9%)	2 (1.9%)
>= 1 to < 5 years	11 (10.3%)	14 (13.0%)
>= 5 to < 10 years	23 (21.5%)	29 (26.9%)
>= 10 years	72 (67.3%)	63 (58.3%)
Complication of diabetes		
Yes	53 (49.5%)	45 (41.7%)
No	54 (50.5%)	63 (58.3%)
Metabolic Syndrome at baseline		

	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Yes	50 (46.7%)	39 (36.1%)
No	57 (53.3%)	69 (63.9%)
CKD stage at baseline		
CKD Stage 1	14 (13.1%)	16 (14.8%)
CKD Stage 2	93 (86.9%)	92 (85.2%)

- Abbreviations: bid, Twice a day; SD, standard deviation; BMI, body mass index; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); CKD, Chronic Kidney Disease.
- Complication of diabetes is defined as any MedDRA Preferred Term (PT) of medical history which are included in High-Level Group Term (HLGT) of diabetic complication.
- Metabolic Syndrome is defined as an excessive waist circumference (>= 85 cm in men and >= 90 cm in women) as well as the presence of two or more of the following symptoms: (1) Hypertension: systolic blood pressure >= 130 mmHg, or diastolic blood pressure >= 85 mmHg; (2) Glucose intolerance: fasting glucose >= 110 mg/dL; (3) Dyslipidemia: triglyceride >= 150 mg/dL, or HDL cholesterol < 40 mg/dL.
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2.
- Percentages are based on Population N.

(2) 長期投与（52 週）

主な人口統計学的特性及びその他の特性を表 2.7.4.1-21 に、すべての人口統計学的特性及びその他の特性を 2.7.4.7 項付録 Table S-011 に示す。男性の割合は 62.2%であった。年齢（平均値±SD、以下同様）は 58.7±10.07 歳、65 歳以上の高齢者の割合は 33.0%、75 歳以上の高齢者の割合は 4.8%であった。体重は 66.99±11.642 kg、BMI は 25.002±3.5374 kg/m^2 であった。HbA1c は 8.78±0.762%であった。罹病期間は 13.40±7.837 年、罹病期間ごとの被験者の割合は 1 年未満が 1.4%、1 年以上 5 年未満が 11.5%、5 年以上 10 年未満が 24.4%、10 年以上が 62.7%であった。糖尿病合併症区分ごとの被験者の割合は、糖尿病合併症あり（Yes）が 44.5%、なし（No）が 55.5%であった。メタボリックシンドローム区分ごとの被験者の割合は、メタボリックシンドロームに該当（Yes）が 40.7%、非該当（No）が 59.3%であった。腎機能区分ごとの被験者の割合は、CKD 1 が 13.9%、CKD 2 が 86.1%であった。

表 2.7.4.1-21　Summary of Demographic and Baseline Characteristics in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Sex			
Male	64 (63.4%)	66 (61.1%)	130 (62.2%)
Female	37 (36.6%)	42 (38.9%)	79 (37.8%)

	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Age (years)			
n	101	108	209
Mean (SD)	58.0 (9.61)	59.3 (10.49)	58.7 (10.07)
Median	59.0	60.0	59.0
Min, Max	35, 77	34, 76	34, 77
Age category			
< 65 years	72 (71.3%)	68 (63.0%)	140 (67.0%)
>= 65 years	29 (28.7%)	40 (37.0%)	69 (33.0%)
< 75 years	98 (97.0%)	101 (93.5%)	199 (95.2%)
>= 75 years	3 (3.0%)	7 (6.5%)	10 (4.8%)
Weight (kg) at baseline			
n	101	108	209
Mean (SD)	66.84 (10.994)	67.13 (12.266)	66.99 (11.642)
Median	66.80	65.40	66.60
Min, Max	44.2, 98.8	41.8, 104.1	41.8, 104.1
BMI (kg/m2) at baseline			
n	101	108	209
Mean (SD)	24.742 (3.4345)	25.244 (3.6302)	25.002 (3.5374)
Median	24.130	24.940	24.610
Min, Max	16.82, 34.22	18.17, 38.80	16.82, 38.80
BMI category at baseline			
< 25 kg/m2	58 (57.4%)	56 (51.9%)	114 (54.5%)
>= 25 kg/m2	43 (42.6%)	52 (48.1%)	95 (45.5%)
>= 25 to < 30 kg/m2	33 (32.7%)	44 (40.7%)	77 (36.8%)
>= 30 kg/m2	10 (9.9%)	8 (7.4%)	18 (8.6%)
HbA1c (%) at baseline			
n	101	108	209
Mean (SD)	8.82 (0.806)	8.74 (0.721)	8.78 (0.762)
Median	8.80	8.70	8.70
Min, Max	7.4, 10.8	7.4, 10.4	7.4, 10.8
HbA1c category at baseline			
< 8.0%	16 (15.8%)	16 (14.8%)	32 (15.3%)
>= 8.0%	85 (84.2%)	92 (85.2%)	177 (84.7%)
>= 8.0 to < 9.0%	41 (40.6%)	53 (49.1%)	94 (45.0%)
>= 9.0%	44 (43.6%)	39 (36.1%)	83 (39.7%)

	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Duration of diabetes (year)			
n	101	108	209
Mean (SD)	13.54 (7.525)	13.26 (8.151)	13.40 (7.837)
Median	12.37	11.74	12.32
Min, Max	0.3, 37.7	0.4, 36.4	0.3, 37.7
Duration of diabetes category			
< 1 year	1 (1.0%)	2 (1.9%)	3 (1.4%)
>= 1 to < 5 years	10 (9.9%)	14 (13.0%)	24 (11.5%)
>= 5 to < 10 years	22 (21.8%)	29 (26.9%)	51 (24.4%)
>= 10 years	68 (67.3%)	63 (58.3%)	131 (62.7%)
Complication of diabetes			
Yes	48 (47.5%)	45 (41.7%)	93 (44.5%)
No	53 (52.5%)	63 (58.3%)	116 (55.5%)
Metabolic Syndrome at baseline			
Yes	46 (45.5%)	39 (36.1%)	85 (40.7%)
No	55 (54.5%)	69 (63.9%)	124 (59.3%)
CKD stage at baseline			
CKD Stage 1	13 (12.9%)	16 (14.8%)	29 (13.9%)
CKD Stage 2	88 (87.1%)	92 (85.2%)	180 (86.1%)

- Abbreviations: SD, standard deviation; BMI, body mass index; HbA1c, Glycosylated Hemoglobin (Hemoglobin A1c); CKD, Chronic Kidney Disease.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- Baseline values in the double-blind period were used for the summary "at baseline" for Placebo/Imeglimin + Insulin group.
- Complication of diabetes is defined as any MedDRA Preferred Term (PT) of medical history which are included in High-Level Group Term (HLGT) of diabetic complication.
- Metabolic Syndrome is defined as an excessive waist circumference (>= 85 cm in men and >= 90 cm in women) as well as the presence of two or more of the following symptoms: (1) Hypertension: systolic blood pressure >= 130 mmHg, or diastolic blood pressure >= 85 mmHg; (2) Glucose intolerance: fasting glucose >= 110 mg/dL; (3) Dyslipidemia: triglyceride >= 150 mg/dL, or HDL cholesterol < 40 mg/dL.
- CKD Stage 1 includes subjects with eGFR >= 90 mL/min/1.73m2, CKD Stage 2 includes subjects with eGFR >= 60 to < 90 mL/min/1.73m2
- Percentages are based on Population N.

2.7.4.2　有害事象

2.7.4.2.1　有害事象の解析

014 試験、018 試験、019 試験及び 020 試験で本剤を投与された被験者に発現した、すべ

ての有害事象及び副作用の発現割合（4 試験併合）をそれぞれ 2.7.4.7 項付録 Table S-160 及び Table S-161 に示す。また、単独療法（二重盲検試験併合）の試験ごとの有害事象及び副作用の発現状況を 2.7.6.18 項及び 2.7.6.19 項に示す。

2.7.4.2.1.1　有害事象の全般的評価

2.7.4.2.1.1.1　単独療法：二重盲検試験併合（24 週）：014 試験・018 試験

有害事象及び副作用の発現状況を表 2.7.4.2-1 に示す。二重盲検治療期の有害事象の発現割合［発現被験者数、発現件数（以下同様）］は、プラセボ群、500 mg bid 群、1000 mg bid 群、1500 mg bid 群の順に（以下同順）54.4%（99/182 名、186 件）、68.0%（51/75 名、101 件）、51.7%（93/180 名、169 件）、73.3%（55/75 名、129 件）であった。副作用の発現割合は、7.1%（13/182 名、20 件）、5.3%（4/75 名、5 件）、5.0%（9/180 名、13 件）、24.0%（18/75 名、27 件）であった。

1500 mg bid 群の 1 名が有害事象により死亡した（2.7.4.2.1.3.1 項）。死亡を含む重篤な有害事象の発現割合は 1.1%（2/182 名、2 件）、0%、4.4%（8/180 名、9 件）、1.3%（1/75 名、1 件）であった。治験薬の投与中止に至った有害事象の発現割合は 7.7%（14/182 名、14 件）、2.7%（2/75 名、2 件）、3.3%（6/180 名、7 件）、6.7%（5/75 名、5 件）であった。

表 2.7.4.2-1　Overall Frequency of Treatment Emergent Adverse Events in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

	Placebo N = 182		Imeglimin 500 mg bid N = 75		Imeglimin 1000 mg bid N = 180		Imeglimin 1500 mg bid N = 75		Imeglimin Total N = 330	
	n (%)	e	n (%)	e	n (%)	e	n (%)	e	n (%)	e
Any TEAE	99 (54.4%)	186	51 (68.0%)	101	93 (51.7%)	169	55 (73.3%)	129	199 (60.3%)	399
Treatment related TEAE	13 (7.1%)	20	4 (5.3%)	5	9 (5.0%)	13	18 (24.0%)	27	31 (9.4%)	45
Severe TEAE	1 (0.5%)	1	0	0	6 (3.3%)	8	1 (1.3%)	1	7 (2.1%)	9
TEAE leading to death	0	0	0	0	0	0	1 (1.3%)	1	1 (0.3%)	1
Serious TEAE	2 (1.1%)	2	0	0	8 (4.4%)	9	1 (1.3%)	1	9 (2.7%)	10
TEAE leading to treatment discontinuation	14 (7.7%)	14	2 (2.7%)	2	6 (3.3%)	7	5 (6.7%)	5	13 (3.9%)	14

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- n and % are respectively the number and proportion of subjects who experienced the event. e is the number of events.
- Percentages are based on Population N.

2.7.4.2.1.1.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

有害事象及び副作用の発現状況を表 2.7.4.2-2 に示す。

- 単独療法群では、有害事象の発現割合［発現被験者数、発現件数（以下同様）］は 73.1%（98/134 名、225 件）、副作用の発現割合は 9.7%（13/134 名、19 件）であった。1 名が有害事象により死亡した（2.7.4.2.1.3.2 項）。死亡を含む重篤な有害事象の発現割合は 3.0%（4/134 名、4 件）、治験薬の投与中止に至った有害事象の発現割合は 2.2%（3/134 名、3 件）であった。
- SU 併用療法群では、有害事象の発現割合は 80.3%（102/127 名、342 件）、副作用の発現割合は 21.3%（27/127 名、51 件）であった。死亡した被験者はなく、重篤な有害事象の発現割合は 8.7%（11/127 名、11 件）、治験薬の投与中止に至った有害事象の発現割合は 7.1%（9/127 名、9 件）であった。
- GLIN 併用療法群では、有害事象の発現割合は 84.4%（54/64 名、183 件）、副作用の発現割合は 15.6%（10/64 名、35 件）であった。死亡した被験者はなく、重篤な有害事象の発現割合は 1.6%（1/64 名、1 件）、治験薬の投与中止に至った有害事象の発現割合は 1.6%（1/64 名、1 件）であった。
- BIG 併用療法群では、有害事象の発現割合は 75.0%（48/64 名、159 件）、副作用の発現割合は 37.5%（24/64 名、52 件）であった。死亡した被験者はなく、重篤な有害事象の発現割合は 6.3%（4/64 名、4 件）、治験薬の投与中止に至った有害事象の発現割合は 10.9%（7/64 名、7 件）であった。
- AGI 併用療法群では、有害事象の発現割合は 51.6%（33/64 名、68 件）、副作用の発現割合は 9.4%（6/64 名、7 件）であった。死亡した被験者はなく、重篤な有害事象の発現割合は 6.3%（4/64 名、5 件）、治験薬の投与中止に至った有害事象の発現割合は 3.1%（2/64 名、2 件）であった。
- TZD 併用療法群では、有害事象の発現割合は 76.9%（50/65 名、143 件）、副作用の発現割合は 9.2%（6/65 名、13 件）であった。死亡した被験者はなく、重篤な有害事象の発現割合は 6.2%（4/65 名、4 件）、治験薬の投与中止に至った有害事象の発現割合は 6.2%（4/65 名、4 件）であった。
- DPP4-I 併用療法群では、有害事象の発現割合は 79.4%（50/63 名、192 件）、副作用の発現割合は 22.2%（14/63 名、27 件）であった。死亡した被験者はなく、重篤な有害事象の発現割合は 4.8%（3/63 名、3 件）、治験薬の投与中止に至った有害事象の発現割合は 7.9%（5/63 名、5 件）であった。
- GLP1-RA 併用療法群では、有害事象の発現割合は 80.0%（56/70 名、162 件）、副作用の発現割合は 11.4%（8/70 名、14 件）であった。死亡した被験者はなく、重篤な有害事象の発現割合は 7.1%（5/70 名、6 件）、治験薬の投与中止に至った有害事象の発現割合は 21.4%（15/70 名、15 件）であった。
- SGLT2-I 併用療法群では、有害事象の発現割合は 76.2%（48/63 名、127 件）、副作用の発現割合は 11.1%（7/63 名、7 件）であった。死亡した被験者はなく、重篤な有害

事象の発現割合は 6.3%（4/63 名、5 件）、治験薬の投与中止に至った有害事象の発現割合は 1.6%（1/63 名、1 件）であった。

表 2.7.4.2-2　Overall Frequency of Treatment Emergent Adverse Events in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

	Imeglimin N = 134		Imeglimin + SU N = 127		Imeglimin + GLIN N = 64		Imeglimin + BIG N = 64		Imeglimin + AGI N = 64		Imeglimin + TZD N = 65		Imeglimin + DPP4-I N = 63		Imeglimin + GLP1-RA N = 70		Imeglimin + SGLT2-I N = 63		Combination Total N = 580		Imeglimin Total N = 714	
	n (%)	e	n (%)	e	n (%)	e	n (%)	e	n (%)	e	n (%)	e	n (%)	e	n (%)	e	n (%)	e	n (%)	e	n (%)	e
Any TEAE	98 (73.1%)	225	102 (80.3%)	342	54 (84.4%)	183	48 (75.0%)	159	33 (51.6%)	68	50 (76.9%)	143	50 (79.4%)	192	56 (80.0%)	162	48 (76.2%)	127	441 (76.0%)	1376	539 (75.5%)	1601
Treatment related TEAE	13 (9.7%)	19	27 (21.3%)	51	10 (15.6%)	35	24 (37.5%)	52	6 (9.4%)	7	6 (9.2%)	13	14 (22.2%)	27	8 (11.4%)	14	7 (11.1%)	7	102 (17.6%)	206	115 (16.1%)	225
Severe TEAE	2 (1.5%)	2	5 (3.9%)	6	0	0	4 (6.3%)	4	1 (1.6%)	2	1 (1.5%)	1	1 (1.6%)	1	2 (2.9%)	3	1 (1.6%)	2	15 (2.6%)	19	17 (2.4%)	21
TEAE leading to death	1 (0.7%)	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.1%)	1
Serious TEAE	4 (3.0%)	4	11 (8.7%)	11	1 (1.6%)	1	4 (6.3%)	4	4 (6.3%)	5	4 (6.2%)	4	3 (4.8%)	3	5 (7.1%)	6	4 (6.3%)	5	36 (6.2%)	39	40 (5.6%)	43
TEAE leading to treatment discontinuation	3 (2.2%)	3	9 (7.1%)	9	1 (1.6%)	1	7 (10.9%)	7	2 (3.1%)	2	4 (6.2%)	4	5 (7.9%)	5	15 (21.4%)	15	1 (1.6%)	1	44 (7.6%)	44	47 (6.6%)	47

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- n and % are respectively the number and proportion of subjects who experienced the event. e is the number of events.
- Percentages are based on Population N.

2.7.4.2.1.1.3　インスリン製剤併用療法：020 試験

(1) 二重盲検治療（16 週）

有害事象及び副作用の発現状況を表 2.7.4.2-3 に示す。二重盲検治療期の有害事象の発現割合［発現被験者数、発現件数（以下同様）］は、プラセボ群、イメグリミン群の順に（以下同順）47.7%（51/107 名、80 件）、52.8%（57/108 名、166 件）であった。副作用の発現割合は、12.1%（13/107 名、19 件）、14.8%（16/108 名、82 件）であった。

死亡した被験者はなく、重篤な有害事象の発現割合は 2.8%（3/107 名、3 件）、0.9%（1/108 名、2 件）であった。治験薬の投与中止に至った有害事象の発現割合は 3.7%（4/107 名、4 件）、0.9%（1/108 名、1 件）であった。

表 2.7.4.2-3　Overall Frequency of Treatment Emergent Adverse Events in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

	Placebo + Insulin N = 107		Imeglimin 1000 mg bid + Insulin N = 108	
	n (%)	e	n (%)	e
Any TEAE	51 (47.7%)	80	57 (52.8%)	166
Treatment related TEAE	13 (12.1%)	19	16 (14.8%)	82
Severe TEAE	2 (1.9%)	2	0	0
TEAE leading to death	0	0	0	0
Serious TEAE	3 (2.8%)	3	1 (0.9%)	2
TEAE leading to treatment discontinuation	4 (3.7%)	4	1 (0.9%)	1

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- n and % are respectively the number and proportion of subjects who experienced the event. e is the number of events.
- Percentages are based on Population N.

(2) 長期投与（52 週）

有害事象及び副作用の発現状況を表 2.7.4.2-4 に示す。有害事象の発現割合［発現被験者数、発現件数（以下同様）］は、80.9%（169/209 名、904 件）、であった。副作用の発現割合は、21.1%（44/209 名、340 件）であった。

1 名が有害事象により死亡した（2.7.4.2.1.3.3 項 (2) ）。死亡を含む重篤な有害事象の発現割合は 5.7%（12/209 名、13 件）、治験薬の投与中止に至った有害事象の発現割合は 3.8%（8/209 名、8 件）であった。

表 2.7.4.2-4　Overall Frequency of Treatment Emergent Adverse Events in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

	Placebo/Imeglimin + Insulin N = 101		Imeglimin/Imeglimin + Insulin N = 108		Imeglimin + Insulin Total N = 209	
	n (%)	e	n (%)	e	n (%)	e
Any TEAE	77 (76.2%)	292	92 (85.2%)	612	169 (80.9%)	904
Treatment related TEAE	16 (15.8%)	92	28 (25.9%)	248	44 (21.1%)	340
Severe TEAE	3 (3.0%)	3	1 (0.9%)	1	4 (1.9%)	4
TEAE leading to death	1 (1.0%)	1	0	0	1 (0.5%)	1
Serious TEAE	6 (5.9%)	6	6 (5.6%)	7	12 (5.7%)	13
TEAE leading to treatment discontinuation	3 (3.0%)	3	5 (4.6%)	5	8 (3.8%)	8

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- n and % are respectively the number and proportion of subjects who experienced the event. e is the number of events.
- Percentages are based on Population N.

2.7.4.2.1.2　比較的よく見られる有害事象

2.7.4.2.1.2.1　単独療法：二重盲検試験併合（24 週）：014 試験・018 試験

主な有害事象（いずれかの群で発現割合が 2%以上の有害事象）の発現割合を表 2.7.4.2-5 に、その副作用の発現割合を表 2.7.4.2-6 に示す。また、すべての有害事象の発現割合を 2.7.4.7 項付録 Table S-024 に、すべての副作用の発現割合を 2.7.4.7 項付録 Table S-025 に示す。

発現割合が高かった有害事象は、上咽頭炎［プラセボ群、500 mg bid 群、1000 mg bid 群、1500 mg bid 群の順に（以下同順）、11.0%、26.7%、18.3%、24.0%］、下痢（0.5%、4.0%、2.8%、8.0%）、腹部不快感（0%、1.3%、1.7%、9.3%）、嘔吐（2.2%、0%、0.6%、5.3%）、悪心（0.5%、1.3%、0.6%、6.7%）、高血糖（8.8%、4.0%、0.6%、1.3%）、低血糖（1.1%、6.7%、2.8%、5.3%）、背部痛（0%、5.3%、0.6%、1.3%）、尿培養陽性（0.5%、1.3%、0%、5.3%）であった。発現割合が高かった有害事象のうち治験薬との因果関係が否定されなかった事象は、下痢（0.5%、0%、1.1%、4.0%）、腹部不快感（0%、0%、0.6%、5.3%）、嘔吐（0%、0%、0.6%、2.7%）、悪心（0.5%、0%、0.6%、5.3%）、高血糖（1.6%、1.3%、0%、0%）、低血糖（1.1%、1.3%、1.7%、5.3%）、尿培養陽性（0%、0%、0%、1.3%）であった。

重症度別の主な有害事象の発現割合を表 2.7.4.2-7 に、重症度別のすべての有害事象の発現割合を 2.7.4.7 項付録 Table S-061 に示す。有害事象の多くは軽度又は中等度であった。重度の有害事象はプラセボ群で下肢骨折が 1 名、1000 mg bid 群で処置後出血、失神寸前の状態、脊椎炎性脊髄症、徐脈、前立腺癌、膵の充実性偽乳頭状腫瘍が各 1 名、大腿骨骨折及び

橈骨骨折が 1 名、1500 mg bid 群で遠隔転移を伴う膵癌が 1 名に発現した。下肢骨折、脊椎炎性脊髄症、徐脈、前立腺癌、膵の充実性偽乳頭状腫瘍、大腿骨骨折、橈骨骨折、遠隔転移を伴う膵癌は重篤な有害事象として報告された（2.7.4.2.1.4.1 項）。遠隔転移を伴う膵癌を発現した被験者は死亡した（2.7.4.2.1.3.1 項）。

初回発現時期別の主な有害事象の発現割合を 2.7.4.7 項付録 Table S-068 に示す。いずれの群でも Week 1～4 にいずれかの有害事象を初回発現した被験者の割合が最も高かった。下痢の初回発現時期はプラセボ群で Week 9～12（0.6%）、500 mg bid 群で Week 5～8（1.3%）、Week 17～20 及び Week 21 以降（それぞれ 1.4%）、1000 mg bid 群で Week 1～4（1.7%）、Week 5～8 及び Week 9～12（それぞれ 0.6%）、1500 mg bid 群で Week 1～4（6.7%）、Week 5～8（1.4%）で、1000 mg bid 群及び 1500 mg bid 群で投与開始後早期に初回発現する傾向がみられた。腹部不快感、嘔吐、悪心も同様の傾向がみられた。その他の有害事象では初回発現時期に一定の傾向はみられなかった。

発現時期別の主な有害事象の発現割合を 2.7.4.7 項付録 Table S-069 に示す。有害事象の発現時期に一定の傾向はみられなかった。

表 2.7.4.2-5　Summary of Treatment Emergent Adverse Events (Incidence >= 2%) by System Organ Class and Preferred Term in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

System Organ Class Preferred Term	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Any TEAE	99 (54.4%)	51 (68.0%)	93 (51.7%)	55 (73.3%)	199 (60.3%)
Infections and infestations (感染症および寄生虫症)					
Nasopharyngitis (上咽頭炎)	20 (11.0%)	20 (26.7%)	33 (18.3%)	18 (24.0%)	71 (21.5%)
Bronchitis (気管支炎)	1 (0.5%)	3 (4.0%)	2 (1.1%)	1 (1.3%)	6 (1.8%)
Gastroenteritis (胃腸炎)	2 (1.1%)	2 (2.7%)	2 (1.1%)	0	4 (1.2%)
Cystitis (膀胱炎)	1 (0.5%)	2 (2.7%)	0	0	2 (0.6%)
Gastrointestinal disorders (胃腸障害)					
Diarrhoea (下痢)	1 (0.5%)	3 (4.0%)	5 (2.8%)	6 (8.0%)	14 (4.2%)
Abdominal discomfort (腹部不快感)	0	1 (1.3%)	3 (1.7%)	7 (9.3%)	11 (3.3%)
Vomiting (嘔吐)	4 (2.2%)	0	1 (0.6%)	4 (5.3%)	5 (1.5%)
Nausea (悪心)	1 (0.5%)	1 (1.3%)	1 (0.6%)	5 (6.7%)	7 (2.1%)
Dental caries (齲歯)	4 (2.2%)	0	2 (1.1%)	1 (1.3%)	3 (0.9%)
Abdominal pain upper (上腹部痛)	1 (0.5%)	2 (2.7%)	1 (0.6%)	0	3 (0.9%)

System Organ Class Preferred Term	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Metabolism and nutrition disorders (代謝および栄養障害)					
Hyperglycaemia (高血糖)	16 (8.8%)	3 (4.0%)	1 (0.6%)	1 (1.3%)	5 (1.5%)
Hypoglycaemia (低血糖)	2 (1.1%)	5 (6.7%)	5 (2.8%)	4 (5.3%)	14 (4.2%)
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)					
Arthralgia (関節痛)	4 (2.2%)	1 (1.3%)	1 (0.6%)	1 (1.3%)	3 (0.9%)
Back pain (背部痛)	0	4 (5.3%)	1 (0.6%)	1 (1.3%)	6 (1.8%)
Nervous system disorders (神経系障害)					
Dizziness (浮動性めまい)	4 (2.2%)	1 (1.3%)	1 (0.6%)	0	2 (0.6%)
Headache (頭痛)	2 (1.1%)	2 (2.7%)	1 (0.6%)	0	3 (0.9%)
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)					
Contusion (挫傷)	1 (0.5%)	2 (2.7%)	1 (0.6%)	1 (1.3%)	4 (1.2%)
Arthropod sting (節足動物刺傷)	0	2 (2.7%)	0	2 (2.7%)	4 (1.2%)
Skin and subcutaneous tissue disorders (皮膚および皮下組織障害)					
Eczema (湿疹)	2 (1.1%)	2 (2.7%)	2 (1.1%)	3 (4.0%)	7 (2.1%)
Investigations (臨床検査)					
Culture urine positive (尿培養陽性)	1 (0.5%)	1 (1.3%)	0	4 (5.3%)	5 (1.5%)
Vascular disorders (血管障害)					
Hypertension (高血圧)	2 (1.1%)	2 (2.7%)	1 (0.6%)	1 (1.3%)	4 (1.2%)
General disorders and administration site conditions (一般・全身障害および投与部位の状態)					
Fatigue (疲労)	1 (0.5%)	0	2 (1.1%)	2 (2.7%)	4 (1.2%)
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)					
Oropharyngeal pain (口腔咽頭痛)	1 (0.5%)	0	0	2 (2.7%)	2 (0.6%)
Rhinitis allergic (アレルギー性鼻炎)	0	2 (2.7%)	0	0	2 (0.6%)
Ear and labyrinth disorders (耳および迷路障害)					
Vertigo (回転性めまい)	0	0	1 (0.6%)	2 (2.7%)	3 (0.9%)

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.

- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

表 2.7.4.2-6 Summary of Treatment Emergent Adverse Events (Incidence >= 2%) Related to Treatment by System Organ Class and Preferred Term in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

System Organ Class Preferred Term	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Any TEAE related to treatment	13 (7.1%)	4 (5.3%)	9 (5.0%)	18 (24.0%)	31 (9.4%)
Infections and infestations (感染症および寄生虫症)					
Nasopharyngitis (上咽頭炎)	0	0	0	0	0
Bronchitis (気管支炎)	0	0	0	0	0
Gastroenteritis (胃腸炎)	0	0	0	0	0
Cystitis (膀胱炎)	0	0	0	0	0
Gastrointestinal disorders (胃腸障害)					
Diarrhoea (下痢)	1 (0.5%)	0	2 (1.1%)	3 (4.0%)	5 (1.5%)
Abdominal discomfort (腹部不快感)	0	0	1 (0.6%)	4 (5.3%)	5 (1.5%)
Vomiting (嘔吐)	0	0	1 (0.6%)	2 (2.7%)	3 (0.9%)
Nausea (悪心)	1 (0.5%)	0	1 (0.6%)	4 (5.3%)	5 (1.5%)
Dental caries (齲歯)	0	0	0	0	0
Abdominal pain upper (上腹部痛)	0	0	0	0	0
Metabolism and nutrition disorders (代謝および栄養障害)					
Hyperglycaemia (高血糖)	3 (1.6%)	1 (1.3%)	0	0	1 (0.3%)
Hypoglycaemia (低血糖)	2 (1.1%)	1 (1.3%)	3 (1.7%)	4 (5.3%)	8 (2.4%)
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)					
Arthralgia (関節痛)	0	0	0	0	0
Back pain (背部痛)	0	0	0	0	0
Nervous system disorders (神経系障害)					
Dizziness (浮動性めまい)	0	0	0	0	0
Headache (頭痛)	0	0	0	0	0

System Organ Class Preferred Term	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)					
Contusion (挫傷)	0	0	0	0	0
Arthropod sting (節足動物刺傷)	0	0	0	0	0
Skin and subcutaneous tissue disorders (皮膚および皮下組織障害)					
Eczema (湿疹)	1 (0.5%)	0	0	0	0
Investigations (臨床検査)					
Culture urine positive (尿培養陽性)	0	0	0	1 (1.3%)	1 (0.3%)
Vascular disorders (血管障害)					
Hypertension (高血圧)	0	0	0	0	0
General disorders and administration site conditions (一般・全身障害および投与部位の状態)					
Fatigue (疲労)	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)					
Oropharyngeal pain (口腔咽頭痛)	0	0	0	0	0
Rhinitis allergic (アレルギー性鼻炎)	0	0	0	0	0
Ear and labyrinth disorders (耳および迷路障害)					
Vertigo (回転性めまい)	0	0	0	0	0

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

表 2.7.4.2-7　Summary of Treatment Emergent Adverse Events (Incidence >= 2%) by Maximum Severity, System Organ Class and Preferred Term in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

System Organ Class Preferred Term Maximum Severity	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Any TEAE					
Mild	88 (48.4%)	48 (64.0%)	80 (44.4%)	45 (60.0%)	173 (52.4%)
Moderate	10 (5.5%)	3 (4.0%)	7 (3.9%)	9 (12.0%)	19 (5.8%)
Severe	1 (0.5%)	0	6 (3.3%)	1 (1.3%)	7 (2.1%)
Infections and infestations (感染症および寄生虫症)					
Nasopharyngitis (上咽頭炎)					
Mild	20 (11.0%)	20 (26.7%)	33 (18.3%)	18 (24.0%)	71 (21.5%)
Bronchitis (気管支炎)					
Mild	1 (0.5%)	3 (4.0%)	2 (1.1%)	1 (1.3%)	6 (1.8%)
Gastroenteritis (胃腸炎)					
Mild	1 (0.5%)	2 (2.7%)	2 (1.1%)	0	4 (1.2%)
Moderate	1 (0.5%)	0	0	0	0
Cystitis (膀胱炎)					
Mild	1 (0.5%)	2 (2.7%)	0	0	2 (0.6%)
Gastrointestinal disorders (胃腸障害)					
Diarrhoea (下痢)					
Mild	1 (0.5%)	3 (4.0%)	5 (2.8%)	6 (8.0%)	14 (4.2%)
Abdominal discomfort (腹部不快感)					
Mild	0	1 (1.3%)	3 (1.7%)	7 (9.3%)	11 (3.3%)
Vomiting (嘔吐)					
Mild	3 (1.6%)	0	1 (0.6%)	3 (4.0%)	4 (1.2%)
Moderate	1 (0.5%)	0	0	1 (1.3%)	1 (0.3%)
Nausea (悪心)					
Mild	1 (0.5%)	1 (1.3%)	1 (0.6%)	3 (4.0%)	5 (1.5%)
Moderate	0	0	0	2 (2.7%)	2 (0.6%)
Dental caries (齲歯)					
Mild	3 (1.6%)	0	1 (0.6%)	1 (1.3%)	2 (0.6%)
Moderate	1 (0.5%)	0	1 (0.6%)	0	1 (0.3%)
Abdominal pain upper (上腹部痛)					
Mild	1 (0.5%)	2 (2.7%)	1 (0.6%)	0	3 (0.9%)
Metabolism and nutrition disorders (代謝および栄養障害)					
Hyperglycaemia (高血糖)					
Mild	15 (8.2%)	2 (2.7%)	0	1 (1.3%)	3 (0.9%)
Moderate	1 (0.5%)	1 (1.3%)	1 (0.6%)	0	2 (0.6%)

System Organ Class Preferred Term Maximum Severity	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Hypoglycaemia (低血糖)					
Mild	2 (1.1%)	5 (6.7%)	5 (2.8%)	4 (5.3%)	14 (4.2%)
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)					
Arthralgia (関節痛)					
Mild	4 (2.2%)	1 (1.3%)	1 (0.6%)	1 (1.3%)	3 (0.9%)
Back pain (背部痛)					
Mild	0	3 (4.0%)	1 (0.6%)	1 (1.3%)	5 (1.5%)
Moderate	0	1 (1.3%)	0	0	1 (0.3%)
Nervous system disorders (神経系障害)					
Dizziness (浮動性めまい)					
Mild	3 (1.6%)	1 (1.3%)	1 (0.6%)	0	2 (0.6%)
Moderate	1 (0.5%)	0	0	0	0
Headache (頭痛)					
Mild	2 (1.1%)	2 (2.7%)	1 (0.6%)	0	3 (0.9%)
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)					
Contusion (挫傷)					
Mild	1 (0.5%)	2 (2.7%)	1 (0.6%)	1 (1.3%)	4 (1.2%)
Arthropod sting (節足動物刺傷)					
Mild	0	2 (2.7%)	0	2 (2.7%)	4 (1.2%)
Skin and subcutaneous tissue disorders (皮膚および皮下組織障害)					
Eczema (湿疹)					
Mild	2 (1.1%)	2 (2.7%)	2 (1.1%)	3 (4.0%)	7 (2.1%)
Investigations (臨床検査)					
Culture urine positive (尿培養陽性)					
Mild	1 (0.5%)	1 (1.3%)	0	4 (5.3%)	5 (1.5%)
Vascular disorders (血管障害)					
Hypertension (高血圧)					
Mild	2 (1.1%)	2 (2.7%)	1 (0.6%)	1 (1.3%)	4 (1.2%)

System Organ Class Preferred Term Maximum Severity	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
General disorders and administration site conditions (一般・全身障害および投与部位の状態)					
Fatigue (疲労)					
Mild	1 (0.5%)	0	2 (1.1%)	2 (2.7%)	4 (1.2%)
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)					
Oropharyngeal pain (口腔咽頭痛)					
Mild	1 (0.5%)	0	0	2 (2.7%)	2 (0.6%)
Rhinitis allergic (アレルギー性鼻炎)					
Mild	0	2 (2.7%)	0	0	2 (0.6%)
Ear and labyrinth disorders (耳および迷路障害)					
Vertigo (回転性めまい)					
Mild	0	0	1 (0.6%)	2 (2.7%)	3 (0.9%)

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once by the maximum severity.
- Percentages are based on Population N.

2.7.4.2.1.2.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

主な有害事象（いずれかの群で発現割合が 2%以上の有害事象）の発現割合を表 2.7.4.2-8 に、その副作用の発現割合を表 2.7.4.2-9 に示す。また、重症度別の主な有害事象の発現割合を表 2.7.4.2-10 に、初回発現時期別の主な有害事象の発現割合を 2.7.4.7 項付録 Table S-072 に、発現時期別の主な有害事象の発現割合を 2.7.4.7 項付録 Table S-073 に示す。更に、すべての有害事象及びすべての副作用の発現割合を 2.7.6.24 項に、重症度別のすべての有害事象の発現割合を 2.7.4.7 項付録 Table S-063 に示す。

- 単独療法群で発現割合が高かった有害事象は、上咽頭炎（29.9%）、悪心（6.7%）、咽頭炎（6.0%）であった。このうち治験薬との因果関係が否定されなかった事象は、悪心（3.0%）であった。有害事象の多くは軽度又は中等度であった。重度の有害事象は虫垂炎及びくも膜下出血で、各 1 名に発現し、重篤な有害事象として報告された（2.7.4.2.1.4.2 項）。くも膜下出血を発現した被験者は死亡した（2.7.4.2.1.3.2 項）。ほとんどの有害事象が Week 32 までに初回発現した。初回発現別及び発現時期別の有害事象の発現割合に一定の傾向はみられなかった。
- SU 併用療法群で発現割合が高かった有害事象は、上咽頭炎（30.7%）、低血糖（16.5%）、背部痛（7.9%）、インフルエンザ（7.1%）、胃食道逆流性疾患（7.1%）、便秘（6.3%）、

高血糖（5.5%）、高血圧（5.5%）であった。このうち治験薬との因果関係が否定されなかった事象は、低血糖（11.8%）、胃食道逆流性疾患（0.8%）、便秘（3.1%）であった。有害事象の多くは軽度又は中等度であった。重度の有害事象は鎖骨骨折、外傷性気胸、硬膜下血腫、急性心筋梗塞、直腸癌で各 1 名に発現し、重篤な有害事象として報告された（2.7.4.2.1.4.2 項）。初回発現別及び発現時期別の有害事象の発現割合に一定の傾向はみられなかった。

- GLIN 併用療法群で発現割合が高かった有害事象は、上咽頭炎（42.2%）、低血糖（14.1%）、咽頭炎（6.3%）、気管支炎（6.3%）、下痢（6.3%）であった。このうち治験薬との因果関係が否定されなかった事象は、低血糖（6.3%）及び下痢（4.7%）であった。有害事象はいずれも軽度又は中等度であった。初回発現別及び発現時期別の有害事象の発現割合に一定の傾向はみられなかった。
- BIG 併用療法群で発現割合が高かった有害事象は、上咽頭炎（25.0%）、下痢（17.2%）、悪心（12.5%）、低血糖（9.4%）、インフルエンザ（7.8%）、嘔吐（6.3%）であった。このうち治験薬との因果関係が否定されなかった事象は、下痢（15.6%）、悪心（10.9%）、低血糖（7.8%）、嘔吐（4.7%）であった。有害事象の多くは軽度又は中等度であった。重度の有害事象は悪心、虫垂炎、心筋梗塞、胆管細胞癌で、各 1 名に発現した。虫垂炎、心筋梗塞、胆管細胞癌は重篤な有害事象として報告され（2.7.4.2.1.4.2 項）、悪心を発現した被験者は治験薬の投与を中止した（2.7.4.2.1.5.2 項）。悪心、下痢、嘔吐はほとんどが Week 1～4 に初回発現した。そのほかの有害事象では初回発現時期に一定の傾向はみられなかった。また、発現時期別の有害事象の発現割合に一定の傾向はみられなかった。
- AGI 併用療法群で発現割合が高かった有害事象は、上咽頭炎（7.8%）のみで、いずれの上咽頭炎も治験薬との因果関係は否定された。有害事象の多くは軽度又は中等度であった。重度の有害事象は胆嚢炎で 1 名に発現し、重篤な有害事象として報告された（2.7.4.2.1.4.2 項）。初回発現別及び発現時期別の有害事象の発現割合に一定の傾向はみられなかった。
- TZD 併用療法群で発現割合が高かった有害事象は、上咽頭炎（27.7%）、気管支炎（6.2%）、背部痛（6.2%）で、いずれも治験薬との因果関係は否定された。有害事象の多くは軽度又は中等度であった。重度の有害事象は頭蓋脳損傷で 1 名に発現し、重篤な有害事象として報告された（2.7.4.2.1.4.2 項）。初回発現別及び発現時期別の有害事象の発現割合に一定の傾向はみられなかった。
- DPP4-I 併用療法群で発現割合が高かった有害事象は、上咽頭炎（30.2%）、悪心（7.9%）、便秘（7.9%）、低血糖（7.9%）、湿疹（7.9%）変形性脊椎症（6.3%）、椎間板突出（6.3%）であった。このうち治験薬との因果関係が否定されなかった事象は、悪心（6.3%）、便秘（1.6%）、低血糖（3.2%）であった。有害事象の多くは軽度又は中等度であった。重度の有害事象は多発骨折で、1 名に発現し、重篤な有害事象として報告された（2.7.4.2.1.4.2 項）。悪心はほとんどが Week 1～4 に初回発現した。そのほかの有害事

象では初回発現時期に一定の傾向はみられなかった。また、発現時期別の有害事象の発現割合に一定の傾向はみられなかった。

- GLP1-RA 併用療法群で発現割合が高かった有害事象は、上咽頭炎（28.6%）、高血糖（11.4%）、湿疹（5.7%）で、いずれも治験薬との因果関係は否定された。有害事象の多くは軽度又は中等度であった。重度の有害事象は冠動脈狭窄及び脳梗塞が 1 名に、冠動脈狭窄が 1 名に発現し、重篤な有害事象として報告された（2.7.4.2.1.4.2 項）。初回発現別及び発現時期別の有害事象の発現割合に一定の傾向はみられなかった。
- SGLT2-1 併用療法群で発現割合が高かった有害事象は、上咽頭炎（31.7%）、咽頭炎（7.9%）、悪心（6.3%）、低血糖（6.3%）であった。このうち治験薬との因果関係が否定されなかった事象は、悪心（3.2%）、低血糖（3.2%）であった。有害事象の多くは軽度又は中等度であった。重度の有害事象は肺炎及び心不全が 1 名に発現し、重篤な有害事象として報告された（2.7.4.2.1.4.2 項）。初回発現別及び発現時期別の有害事象の発現割合に一定の傾向はみられなかった。

表 2.7.4.2-8　Summary of Treatment Emergent Adverse Events (Incidence >= 2%) by System Organ Class and Preferred Term in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Any TEAE	98 (73.1%)	102 (80.3%)	54 (84.4%)	48 (75.0%)	33 (51.6%)	50 (76.9%)	50 (79.4%)	56 (80.0%)	48 (76.2%)	441 (76.0%)	539 (75.5%)
Infections and infestations (感染症および寄生虫症)											
Nasopharyngitis (上咽頭炎)	40 (29.9%)	39 (30.7%)	27 (42.2%)	16 (25.0%)	5 (7.8%)	18 (27.7%)	19 (30.2%)	20 (28.6%)	20 (31.7%)	164 (28.3%)	204 (28.6%)
Pharyngitis (咽頭炎)	8 (6.0%)	5 (3.9%)	4 (6.3%)	0	2 (3.1%)	3 (4.6%)	3 (4.8%)	1 (1.4%)	5 (7.9%)	23 (4.0%)	31 (4.3%)
Influenza (インフルエンザ)	4 (3.0%)	9 (7.1%)	2 (3.1%)	5 (7.8%)	1 (1.6%)	3 (4.6%)	1 (1.6%)	1 (1.4%)	2 (3.2%)	24 (4.1%)	28 (3.9%)
Bronchitis (気管支炎)	1 (0.7%)	1 (0.8%)	4 (6.3%)	2 (3.1%)	0	4 (6.2%)	0	0	2 (3.2%)	13 (2.2%)	14 (2.0%)
Gastroenteritis (胃腸炎)	2 (1.5%)	0	3 (4.7%)	3 (4.7%)	1 (1.6%)	1 (1.5%)	1 (1.6%)	2 (2.9%)	1 (1.6%)	12 (2.1%)	14 (2.0%)
Periodontitis (歯周炎)	0	3 (2.4%)	1 (1.6%)	2 (3.1%)	0	3 (4.6%)	2 (3.2%)	1 (1.4%)	0	12 (2.1%)	12 (1.7%)
Cystitis (膀胱炎)	1 (0.7%)	2 (1.6%)	2 (3.1%)	0	0	1 (1.5%)	2 (3.2%)	2 (2.9%)	1 (1.6%)	10 (1.7%)	11 (1.5%)
Herpes zoster (帯状疱疹)	2 (1.5%)	1 (0.8%)	1 (1.6%)	0	0	1 (1.5%)	1 (1.6%)	1 (1.4%)	2 (3.2%)	7 (1.2%)	9 (1.3%)
Upper respiratory tract infection (上気道感染)	2 (1.5%)	1 (0.8%)	0	0	0	0	2 (3.2%)	0	1 (1.6%)	4 (0.7%)	6 (0.8%)
Urinary tract infection (尿路感染)	0	0	0	0	3 (4.7%)	2 (3.1%)	0	0	0	5 (0.9%)	5 (0.7%)
Gingivitis (歯肉炎)	0	1 (0.8%)	0	0	0	1 (1.5%)	0	2 (2.9%)	0	4 (0.7%)	4 (0.6%)
Pericoronitis (歯冠周囲炎)	0	0	0	0	1 (1.6%)	0	0	2 (2.9%)	1 (1.6%)	4 (0.7%)	4 (0.6%)
Gastrointestinal disorders (胃腸障害)											
Nausea (悪心)	9 (6.7%)	1 (0.8%)	0	8 (12.5%)	1 (1.6%)	1 (1.5%)	5 (7.9%)	3 (4.3%)	4 (6.3%)	23 (4.0%)	32 (4.5%)
Diarrhoea (下痢)	4 (3.0%)	3 (2.4%)	4 (6.3%)	11 (17.2%)	0	2 (3.1%)	2 (3.2%)	3 (4.3%)	2 (3.2%)	27 (4.7%)	31 (4.3%)
Constipation (便秘)	5 (3.7%)	8 (6.3%)	2 (3.1%)	1 (1.6%)	2 (3.1%)	1 (1.5%)	5 (7.9%)	1 (1.4%)	2 (3.2%)	22 (3.8%)	27 (3.8%)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Gastrooesophageal reflux disease (胃食道逆流性疾患)	3 (2.2%)	9 (7.1%)	1 (1.6%)	2 (3.1%)	0	0	0	1 (1.4%)	0	13 (2.2%)	16 (2.2%)
Abdominal pain upper (上腹部痛)	4 (3.0%)	1 (0.8%)	1 (1.6%)	3 (4.7%)	0	0	2 (3.2%)	1 (1.4%)	0	8 (1.4%)	12 (1.7%)
Dental caries (齲歯)	5 (3.7%)	0	1 (1.6%)	1 (1.6%)	0	3 (4.6%)	2 (3.2%)	0	0	7 (1.2%)	12 (1.7%)
Vomiting (嘔吐)	1 (0.7%)	0	0	4 (6.3%)	0	2 (3.1%)	2 (3.2%)	2 (2.9%)	1 (1.6%)	11 (1.9%)	12 (1.7%)
Abdominal discomfort (腹部不快感)	0	2 (1.6%)	1 (1.6%)	3 (4.7%)	1 (1.6%)	0	2 (3.2%)	0	0	9 (1.6%)	9 (1.3%)
Chronic gastritis (慢性胃炎)	0	2 (1.6%)	0	1 (1.6%)	0	0	2 (3.2%)	1 (1.4%)	1 (1.6%)	7 (1.2%)	7 (1.0%)
Dyspepsia (消化不良)	0	2 (1.6%)	1 (1.6%)	0	0	0	2 (3.2%)	2 (2.9%)	0	7 (1.2%)	7 (1.0%)
Faeces soft (軟便)	1 (0.7%)	1 (0.8%)	1 (1.6%)	2 (3.1%)	0	0	0	0	1 (1.6%)	5 (0.9%)	6 (0.8%)
Large intestine polyp (大腸ポリープ)	1 (0.7%)	0	0	2 (3.1%)	0	0	1 (1.6%)	1 (1.4%)	1 (1.6%)	5 (0.9%)	6 (0.8%)
Gastritis (胃炎)	0	0	0	0	1 (1.6%)	0	0	1 (1.4%)	2 (3.2%)	4 (0.7%)	4 (0.6%)
Abdominal distension (腹部膨満)	0	0	0	0	0	0	1 (1.6%)	0	2 (3.2%)	3 (0.5%)	3 (0.4%)
Metabolism and nutrition disorders (代謝および栄養障害)											
Hypoglycaemia (低血糖)	5 (3.7%)	21 (16.5%)	9 (14.1%)	6 (9.4%)	2 (3.1%)	2 (3.1%)	5 (7.9%)	2 (2.9%)	4 (6.3%)	51 (8.8%)	56 (7.8%)
Hyperglycaemia (高血糖)	5 (3.7%)	7 (5.5%)	0	0	1 (1.6%)	1 (1.5%)	2 (3.2%)	8 (11.4%)	1 (1.6%)	20 (3.4%)	25 (3.5%)
Decreased appetite (食欲減退)	3 (2.2%)	0	0	2 (3.1%)	0	2 (3.1%)	2 (3.2%)	3 (4.3%)	1 (1.6%)	10 (1.7%)	13 (1.8%)
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)											
Back pain (背部痛)	5 (3.7%)	10 (7.9%)	3 (4.7%)	1 (1.6%)	2 (3.1%)	4 (6.2%)	1 (1.6%)	0	0	21 (3.6%)	26 (3.6%)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Arthralgia (関節痛)	1 (0.7%)	3 (2.4%)	0	2 (3.1%)	0	2 (3.1%)	2 (3.2%)	2 (2.9%)	1 (1.6%)	12 (2.1%)	13 (1.8%)
Pain in extremity (四肢痛)	1 (0.7%)	3 (2.4%)	2 (3.1%)	0	0	0	1 (1.6%)	1 (1.4%)	1 (1.6%)	8 (1.4%)	9 (1.3%)
Myalgia (筋肉痛)	2 (1.5%)	1 (0.8%)	1 (1.6%)	1 (1.6%)	1 (1.6%)	0	0	0	2 (3.2%)	6 (1.0%)	8 (1.1%)
Spinal osteoarthritis (変形性脊椎症)	1 (0.7%)	0	0	0	1 (1.6%)	0	4 (6.3%)	1 (1.4%)	1 (1.6%)	7 (1.2%)	8 (1.1%)
Intervertebral disc protrusion (椎間板突出)	0	0	1 (1.6%)	0	1 (1.6%)	0	4 (6.3%)	1 (1.4%)	0	7 (1.2%)	7 (1.0%)
Osteoarthritis (変形性関節症)	2 (1.5%)	0	1 (1.6%)	1 (1.6%)	0	0	2 (3.2%)	0	0	4 (0.7%)	6 (0.8%)
Lumbar spinal stenosis (腰部脊柱管狭窄症)	1 (0.7%)	0	0	0	0	0	1 (1.6%)	2 (2.9%)	0	3 (0.5%)	4 (0.6%)
Muscle spasms (筋痙縮)	0	1 (0.8%)	2 (3.1%)	0	0	0	1 (1.6%)	0	0	4 (0.7%)	4 (0.6%)
Musculoskeletal stiffness (筋骨格硬直)	0	2 (1.6%)	2 (3.1%)	0	0	0	0	0	0	4 (0.7%)	4 (0.6%)
Trigger finger (弾発指)	0	0	0	0	0	0	2 (3.2%)	2 (2.9%)	0	4 (0.7%)	4 (0.6%)
Skin and subcutaneous tissue disorders (皮膚および皮下組織障害)											
Eczema (湿疹)	2 (1.5%)	4 (3.1%)	3 (4.7%)	0	0	1 (1.5%)	5 (7.9%)	4 (5.7%)	2 (3.2%)	19 (3.3%)	21 (2.9%)
Acne (ざ瘡)	0	1 (0.8%)	2 (3.1%)	1 (1.6%)	0	0	0	0	0	4 (0.7%)	4 (0.6%)
Hyperkeratosis (過角化)	0	1 (0.8%)	0	0	0	0	0	0	2 (3.2%)	3 (0.5%)	3 (0.4%)
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)											
Contusion (挫傷)	3 (2.2%)	3 (2.4%)	0	2 (3.1%)	0	0	3 (4.8%)	0	0	8 (1.4%)	11 (1.5%)
Ligament sprain (靭帯捻挫)	1 (0.7%)	1 (0.8%)	2 (3.1%)	0	0	1 (1.5%)	0	1 (1.4%)	0	5 (0.9%)	6 (0.8%)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Thermal burn (熱傷)	1 (0.7%)	0	0	2 (3.1%)	0	0	1 (1.6%)	1 (1.4%)	0	4 (0.7%)	5 (0.7%)
Radius fracture (橈骨骨折)	1 (0.7%)	0	0	0	0	0	2 (3.2%)	0	0	2 (0.3%)	3 (0.4%)
Tendon rupture (腱断裂)	0	0	2 (3.1%)	0	0	0	0	0	0	2 (0.3%)	2 (0.3%)
Nervous system disorders (神経系障害)											
Headache (頭痛)	2 (1.5%)	1 (0.8%)	1 (1.6%)	0	1 (1.6%)	2 (3.1%)	0	0	1 (1.6%)	6 (1.0%)	8 (1.1%)
Diabetic neuropathy (糖尿病性ニューロパチー)	1 (0.7%)	0	0	0	0	0	2 (3.2%)	2 (2.9%)	1 (1.6%)	5 (0.9%)	6 (0.8%)
Carotid arteriosclerosis (頚動脈硬化症)	0	0	1 (1.6%)	1 (1.6%)	0	2 (3.1%)	0	0	0	4 (0.7%)	4 (0.6%)
Cervicobrachial syndrome (頚腕症候群)	1 (0.7%)	0	0	0	2 (3.1%)	0	0	0	0	2 (0.3%)	3 (0.4%)
Intercostal neuralgia (肋間神経痛)	0	0	3 (4.7%)	0	0	0	0	0	0	3 (0.5%)	3 (0.4%)
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)											
Upper respiratory tract inflammation (上気道の炎症)	1 (0.7%)	1 (0.8%)	2 (3.1%)	0	1 (1.6%)	2 (3.1%)	2 (3.2%)	0	3 (4.8%)	11 (1.9%)	12 (1.7%)
Cough (咳嗽)	3 (2.2%)	2 (1.6%)	1 (1.6%)	1 (1.6%)	0	1 (1.5%)	0	1 (1.4%)	0	6 (1.0%)	9 (1.3%)
Vascular disorders (血管障害)											
Hypertension (高血圧)	0	7 (5.5%)	2 (3.1%)	1 (1.6%)	3 (4.7%)	3 (4.6%)	1 (1.6%)	2 (2.9%)	1 (1.6%)	20 (3.4%)	20 (2.8%)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Renal and urinary disorders (腎および尿路障害)											
Diabetic nephropathy (糖尿病性腎症)	0	1 (0.8%)	0	1 (1.6%)	2 (3.1%)	1 (1.5%)	1 (1.6%)	0	1 (1.6%)	7 (1.2%)	7 (1.0%)
Nephrolithiasis (腎結石症)	1 (0.7%)	0	0	0	2 (3.1%)	2 (3.1%)	1 (1.6%)	1 (1.4%)	0	6 (1.0%)	7 (1.0%)
Pollakiuria (頻尿)	0	0	0	0	0	0	0	2 (2.9%)	1 (1.6%)	3 (0.5%)	3 (0.4%)
Eye disorders (眼障害)											
Diabetic retinopathy (糖尿病網膜症)	2 (1.5%)	1 (0.8%)	1 (1.6%)	0	0	2 (3.1%)	3 (4.8%)	1 (1.4%)	0	8 (1.4%)	10 (1.4%)
Asthenopia (眼精疲労)	0	1 (0.8%)	2 (3.1%)	0	0	0	0	1 (1.4%)	0	4 (0.7%)	4 (0.6%)
Psychiatric disorders (精神障害)											
Insomnia (不眠症)	2 (1.5%)	1 (0.8%)	0	2 (3.1%)	0	1 (1.5%)	3 (4.8%)	1 (1.4%)	1 (1.6%)	9 (1.6%)	11 (1.5%)
Hepatobiliary disorders (肝胆道系障害)											
Hepatic steatosis (脂肪肝)	0	1 (0.8%)	1 (1.6%)	0	0	1 (1.5%)	0	2 (2.9%)	0	5 (0.9%)	5 (0.7%)
Alcoholic liver disease (アルコール性肝疾患)	0	1 (0.8%)	0	0	0	0	0	2 (2.9%)	0	3 (0.5%)	3 (0.4%)
Cholelithiasis (胆石症)	0	0	0	0	1 (1.6%)	0	0	2 (2.9%)	0	3 (0.5%)	3 (0.4%)
Gallbladder polyp (胆嚢ポリープ)	0	0	0	0	0	0	0	2 (2.9%)	0	2 (0.3%)	2 (0.3%)
Investigations (臨床検査)											
Lipase increased (リパーゼ増加)	1 (0.7%)	2 (1.6%)	0	0	1 (1.6%)	1 (1.5%)	3 (4.8%)	0	0	7 (1.2%)	8 (1.1%)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Surgical and medical procedures (外科および内科処置)											
Cataract operation (白内障手術)	1 (0.7%)	3 (2.4%)	1 (1.6%)	2 (3.1%)	1 (1.6%)	0	0	0	0	7 (1.2%)	8 (1.1%)
Cardiac disorders (心臓障害)											
Coronary artery stenosis (冠動脈狭窄)	0	0	0	0	0	0	0	2 (2.9%)	0	2 (0.3%)	2 (0.3%)
Palpitations (動悸)	0	0	0	2 (3.1%)	0	0	0	0	0	2 (0.3%)	2 (0.3%)
Sinus bradycardia (洞性徐脈)	0	0	0	0	0	2 (3.1%)	0	0	0	2 (0.3%)	2 (0.3%)
General disorders and administration site conditions (一般・全身障害および投与部位の状態)											
Fatigue (疲労)	1 (0.7%)	0	1 (1.6%)	0	0	0	2 (3.2%)	0	1 (1.6%)	4 (0.7%)	5 (0.7%)
Ear and labyrinth disorders (耳および迷路障害)											
Vertigo (回転性めまい)	1 (0.7%)	0	0	2 (3.1%)	0	0	0	1 (1.4%)	0	3 (0.5%)	4 (0.6%)
Reproductive system and breast disorders (生殖系および乳房障害)											
Benign prostatic hyperplasia (良性前立腺肥大症)	1 (0.7%)	0	2 (3.1%)	0	0	0	0	0	0	2 (0.3%)	3 (0.4%)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Immune system disorders (免疫系障害)											
Allergy to arthropod sting (節足動物刺傷アレルギー)	0	0	0	0	0	0	0	2 (2.9%)	0	2 (0.3%)	2 (0.3%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

表 2.7.4.2-9　Summary of Treatment Emergent Adverse Events (Incidence >= 2%) Related to Treatment by System Organ Class and Preferred Term in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Any TEAE related to treatment	13 (9.7%)	27 (21.3%)	10 (15.6%)	24 (37.5%)	6 (9.4%)	6 (9.2%)	14 (22.2%)	8 (11.4%)	7 (11.1%)	102 (17.6%)	115 (16.1%)
Infections and infestations (感染症および寄生虫症)											
Nasopharyngitis (上咽頭炎)	0	0	0	0	0	0	0	0	0	0	0
Pharyngitis (咽頭炎)	0	0	0	0	0	0	0	0	0	0	0
Influenza (インフルエンザ)	0	0	0	0	0	0	0	0	0	0	0
Bronchitis (気管支炎)	0	0	0	0	0	0	0	0	0	0	0
Gastroenteritis (胃腸炎)	0	0	0	0	0	0	0	0	0	0	0
Periodontitis (歯周炎)	0	0	0	0	0	0	0	0	0	0	0
Cystitis (膀胱炎)	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Herpes zoster (帯状疱疹)	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Upper respiratory tract infection (上気道感染)	0	0	0	0	0	0	0	0	0	0	0
Urinary tract infection (尿路感染)	0	0	0	0	0	0	0	0	0	0	0
Gingivitis (歯肉炎)	0	0	0	0	0	0	0	0	0	0	0
Pericoronitis (歯冠周囲炎)	0	0	0	0	0	0	0	0	0	0	0
Gastrointestinal disorders (胃腸障害)											
Nausea (悪心)	4 (3.0%)	0	0	7 (10.9%)	0	1 (1.5%)	4 (6.3%)	3 (4.3%)	2 (3.2%)	17 (2.9%)	21 (2.9%)
Diarrhoea (下痢)	1 (0.7%)	1 (0.8%)	3 (4.7%)	10 (15.6%)	0	2 (3.1%)	0	0	0	16 (2.8%)	17 (2.4%)
Constipation (便秘)	3 (2.2%)	4 (3.1%)	0	0	2 (3.1%)	0	1 (1.6%)	0	1 (1.6%)	8 (1.4%)	11 (1.5%)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Gastrooesophageal reflux disease (胃食道逆流性疾患)	0	1 (0.8%)	0	1 (1.6%)	0	0	0	0	0	2 (0.3%)	2 (0.3%)
Abdominal pain upper (上腹部痛)	0	0	0	2 (3.1%)	0	0	0	1 (1.4%)	0	3 (0.5%)	3 (0.4%)
Dental caries (齲歯)	0	0	0	0	0	0	0	0	0	0	0
Vomiting (嘔吐)	0	0	0	3 (4.7%)	0	2 (3.1%)	1 (1.6%)	2 (2.9%)	0	8 (1.4%)	8 (1.1%)
Abdominal discomfort (腹部不快感)	0	2 (1.6%)	1 (1.6%)	2 (3.1%)	1 (1.6%)	0	1 (1.6%)	0	0	7 (1.2%)	7 (1.0%)
Chronic gastritis (慢性胃炎)	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)
Dyspepsia (消化不良)	0	0	0	0	0	0	1 (1.6%)	2 (2.9%)	0	3 (0.5%)	3 (0.4%)
Faeces soft (軟便)	1 (0.7%)	1 (0.8%)	0	1 (1.6%)	0	0	0	0	0	2 (0.3%)	3 (0.4%)
Large intestine polyp (大腸ポリープ)	0	0	0	0	0	0	0	0	0	0	0
Gastritis (胃炎)	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
Abdominal distension (腹部膨満)	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Metabolism and nutrition disorders (代謝および栄養障害)											
Hypoglycaemia (低血糖)	2 (1.5%)	15 (11.8%)	4 (6.3%)	5 (7.8%)	2 (3.1%)	0	2 (3.2%)	0	2 (3.2%)	30 (5.2%)	32 (4.5%)
Hyperglycaemia (高血糖)	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Decreased appetite (食欲減退)	2 (1.5%)	0	0	2 (3.1%)	0	1 (1.5%)	2 (3.2%)	2 (2.9%)	0	7 (1.2%)	9 (1.3%)
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)											
Back pain (背部痛)	0	0	0	0	0	0	0	0	0	0	0

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Arthralgia (関節痛)	0	0	0	0	0	0	0	0	0	0	0
Pain in extremity (四肢痛)	0	0	0	0	0	0	0	0	0	0	0
Myalgia (筋肉痛)	0	0	0	0	0	0	0	0	0	0	0
Spinal osteoarthritis (変形性脊椎症)	0	0	0	0	0	0	0	0	0	0	0
Intervertebral disc protrusion (椎間板突出)	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Osteoarthritis (変形性関節症)	0	0	0	0	0	0	0	0	0	0	0
Lumbar spinal stenosis (腰部脊柱管狭窄症)	0	0	0	0	0	0	0	0	0	0	0
Muscle spasms (筋痙縮)	0	0	0	0	0	0	0	0	0	0	0
Musculoskeletal stiffness (筋骨格硬直)	0	0	0	0	0	0	0	0	0	0	0
Trigger finger (弾発指)	0	0	0	0	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders (皮膚および皮下組織障害)											
Eczema (湿疹)	0	0	0	0	0	0	0	0	0	0	0
Acne (ざ瘡)	0	0	0	0	0	0	0	0	0	0	0
Hyperkeratosis (過角化)	0	0	0	0	0	0	0	0	0	0	0
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)											
Contusion (挫傷)	0	0	0	0	0	0	0	0	0	0	0
Ligament sprain (靭帯捻挫)	0	0	0	0	0	0	0	0	0	0	0

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Thermal burn (熱傷)	0	0	0	0	0	0	0	0	0	0	0
Radius fracture (橈骨骨折)	0	0	0	0	0	0	0	0	0	0	0
Tendon rupture (腱断裂)	0	0	0	0	0	0	0	0	0	0	0
Nervous system disorders (神経系障害)											
Headache (頭痛)	0	0	0	0	0	0	0	0	0	0	0
Diabetic neuropathy (糖尿病性ニューロパチー)	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Carotid arteriosclerosis (頚動脈硬化症)	0	0	0	0	0	0	0	0	0	0	0
Cervicobrachial syndrome (頚腕症候群)	0	0	0	0	0	0	0	0	0	0	0
Intercostal neuralgia (肋間神経痛)	0	0	0	0	0	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)											
Upper respiratory tract inflammation (上気道の炎症)	0	0	0	0	0	0	0	0	0	0	0
Cough (咳嗽)	0	0	0	0	0	0	0	0	0	0	0
Vascular disorders (血管障害)											
Hypertension (高血圧)	0	0	0	0	0	0	0	0	0	0	0

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Renal and urinary disorders (腎および尿路障害)											
Diabetic nephropathy (糖尿病性腎症)	0	0	0	0	0	0	0	0	0	0	0
Nephrolithiasis (腎結石症)	0	0	0	0	0	0	0	0	0	0	0
Pollakiuria (頻尿)	0	0	0	0	0	0	0	0	0	0	0
Eye disorders (眼障害)											
Diabetic retinopathy (糖尿病網膜症)	0	0	1 (1.6%)	0	0	2 (3.1%)	1 (1.6%)	0	0	4 (0.7%)	4 (0.6%)
Asthenopia (眼精疲労)	0	0	0	0	0	0	0	0	0	0	0
Psychiatric disorders (精神障害)											
Insomnia (不眠症)	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Hepatobiliary disorders (肝胆道系障害)											
Hepatic steatosis (脂肪肝)	0	0	0	0	0	0	0	0	0	0	0
Alcoholic liver disease (アルコール性肝疾患)	0	0	0	0	0	0	0	0	0	0	0
Cholelithiasis (胆石症)	0	0	0	0	0	0	0	0	0	0	0
Gallbladder polyp (胆嚢ポリープ)	0	0	0	0	0	0	0	0	0	0	0
Investigations (臨床検査)											
Lipase increased (リパーゼ増加)	0	1 (0.8%)	0	0	0	0	1 (1.6%)	0	0	2 (0.3%)	2 (0.3%)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Surgical and medical procedures (外科および内科処置)											
Cataract operation (白内障手術)	0	0	0	0	0	0	0	0	0	0	0
Cardiac disorders (心臓障害)											
Coronary artery stenosis (冠動脈狭窄)	0	0	0	0	0	0	0	0	0	0	0
Palpitations (動悸)	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Sinus bradycardia (洞性徐脈)	0	0	0	0	0	0	0	0	0	0	0
General disorders and administration site conditions (一般・全身障害および投与部位の状態)											
Fatigue (疲労)	0	0	0	0	0	0	0	0	0	0	0
Ear and labyrinth disorders (耳および迷路障害)											
Vertigo (回転性めまい)	0	0	0	0	0	0	0	0	0	0	0
Reproductive system and breast disorders (生殖系および乳房障害)											
Benign prostatic hyperplasia (良性前立腺肥大症)	0	0	0	0	0	0	0	0	0	0	0

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Immune system disorders (免疫系障害)											
Allergy to arthropod sting (節足動物刺傷アレルギー)	0	0	0	0	0	0	0	0	0	0	0

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

表 2.7.4.2-10　Summary of Treatment Emergent Adverse Events (Incidence >= 2%) by Maximum Severity, System Organ Class and Preferred Term in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Any TEAE											
Mild	87 (64.9%)	83 (65.4%)	49 (76.6%)	41 (64.1%)	29 (45.3%)	38 (58.5%)	41 (65.1%)	50 (71.4%)	44 (69.8%)	375 (64.7%)	462 (64.7%)
Moderate	9 (6.7%)	14 (11.0%)	5 (7.8%)	3 (4.7%)	3 (4.7%)	11 (16.9%)	8 (12.7%)	4 (5.7%)	3 (4.8%)	51 (8.8%)	60 (8.4%)
Severe	2 (1.5%)	5 (3.9%)	0	4 (6.3%)	1 (1.6%)	1 (1.5%)	1 (1.6%)	2 (2.9%)	1 (1.6%)	15 (2.6%)	17 (2.4%)
Infections and infestations (感染症および寄生虫症)											
Nasopharyngitis (上咽頭炎)											
Mild	40 (29.9%)	39 (30.7%)	27 (42.2%)	16 (25.0%)	5 (7.8%)	17 (26.2%)	18 (28.6%)	20 (28.6%)	19 (30.2%)	161 (27.8%)	201 (28.2%)
Moderate	0	0	0	0	0	1 (1.5%)	1 (1.6%)	0	1 (1.6%)	3 (0.5%)	3 (0.4%)
Pharyngitis (咽頭炎)											
Mild	8 (6.0%)	5 (3.9%)	4 (6.3%)	0	2 (3.1%)	3 (4.6%)	3 (4.8%)	1 (1.4%)	5 (7.9%)	23 (4.0%)	31 (4.3%)
Influenza (インフルエンザ)											
Mild	2 (1.5%)	6 (4.7%)	2 (3.1%)	4 (6.3%)	1 (1.6%)	2 (3.1%)	1 (1.6%)	1 (1.4%)	2 (3.2%)	19 (3.3%)	21 (2.9%)
Moderate	2 (1.5%)	3 (2.4%)	0	1 (1.6%)	0	1 (1.5%)	0	0	0	5 (0.9%)	7 (1.0%)
Bronchitis (気管支炎)											
Mild	1 (0.7%)	1 (0.8%)	4 (6.3%)	2 (3.1%)	0	4 (6.2%)	0	0	2 (3.2%)	13 (2.2%)	14 (2.0%)
Gastroenteritis (胃腸炎)											
Mild	2 (1.5%)	0	2 (3.1%)	3 (4.7%)	1 (1.6%)	1 (1.5%)	1 (1.6%)	2 (2.9%)	1 (1.6%)	11 (1.9%)	13 (1.8%)
Moderate	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Periodontitis (歯周炎)											
Mild	0	3 (2.4%)	1 (1.6%)	2 (3.1%)	0	3 (4.6%)	2 (3.2%)	1 (1.4%)	0	12 (2.1%)	12 (1.7%)

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Cystitis (膀胱炎)											
Mild	1 (0.7%)	2 (1.6%)	2 (3.1%)	0	0	1 (1.5%)	2 (3.2%)	2 (2.9%)	1 (1.6%)	10 (1.7%)	11 (1.5%)
Herpes zoster (帯状疱疹)											
Mild	1 (0.7%)	1 (0.8%)	1 (1.6%)	0	0	0	1 (1.6%)	0	2 (3.2%)	5 (0.9%)	6 (0.8%)
Moderate	1 (0.7%)	0	0	0	0	1 (1.5%)	0	1 (1.4%)	0	2 (0.3%)	3 (0.4%)
Upper respiratory tract infection (上気道感染)											
Mild	2 (1.5%)	1 (0.8%)	0	0	0	0	2 (3.2%)	0	1 (1.6%)	4 (0.7%)	6 (0.8%)
Urinary tract infection (尿路感染)											
Mild	0	0	0	0	3 (4.7%)	2 (3.1%)	0	0	0	5 (0.9%)	5 (0.7%)
Gingivitis (歯肉炎)											
Mild	0	1 (0.8%)	0	0	0	1 (1.5%)	0	2 (2.9%)	0	4 (0.7%)	4 (0.6%)
Pericoronitis (歯冠周囲炎)											
Mild	0	0	0	0	1 (1.6%)	0	0	2 (2.9%)	1 (1.6%)	4 (0.7%)	4 (0.6%)
Gastrointestinal disorders (胃腸障害)											
Nausea (悪心)											
Mild	7 (5.2%)	1 (0.8%)	0	6 (9.4%)	1 (1.6%)	0	4 (6.3%)	3 (4.3%)	4 (6.3%)	19 (3.3%)	26 (3.6%)
Moderate	2 (1.5%)	0	0	1 (1.6%)	0	1 (1.5%)	1 (1.6%)	0	0	3 (0.5%)	5 (0.7%)
Severe	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Diarrhoea (下痢)											
Mild	4 (3.0%)	3 (2.4%)	3 (4.7%)	11 (17.2%)	0	1 (1.5%)	2 (3.2%)	3 (4.3%)	2 (3.2%)	25 (4.3%)	29 (4.1%)
Moderate	0	0	1 (1.6%)	0	0	1 (1.5%)	0	0	0	2 (0.3%)	2 (0.3%)

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Constipation (便秘)											
Mild	5 (3.7%)	8 (6.3%)	2 (3.1%)	1 (1.6%)	1 (1.6%)	1 (1.5%)	5 (7.9%)	1 (1.4%)	2 (3.2%)	21 (3.6%)	26 (3.6%)
Moderate	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
Gastrooesophageal reflux disease (胃食道逆流性疾患)											
Mild	3 (2.2%)	8 (6.3%)	1 (1.6%)	2 (3.1%)	0	0	0	1 (1.4%)	0	12 (2.1%)	15 (2.1%)
Moderate	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Abdominal pain upper (上腹部痛)											
Mild	4 (3.0%)	1 (0.8%)	1 (1.6%)	3 (4.7%)	0	0	2 (3.2%)	1 (1.4%)	0	8 (1.4%)	12 (1.7%)
Dental caries (齲歯)											
Mild	5 (3.7%)	0	1 (1.6%)	1 (1.6%)	0	3 (4.6%)	2 (3.2%)	0	0	7 (1.2%)	12 (1.7%)
Vomiting (嘔吐)											
Mild	1 (0.7%)	0	0	3 (4.7%)	0	1 (1.5%)	2 (3.2%)	2 (2.9%)	1 (1.6%)	9 (1.6%)	10 (1.4%)
Moderate	0	0	0	1 (1.6%)	0	1 (1.5%)	0	0	0	2 (0.3%)	2 (0.3%)
Abdominal discomfort (腹部不快感)											
Mild	0	2 (1.6%)	1 (1.6%)	3 (4.7%)	1 (1.6%)	0	2 (3.2%)	0	0	9 (1.6%)	9 (1.3%)
Chronic gastritis (慢性胃炎)											
Mild	0	2 (1.6%)	0	1 (1.6%)	0	0	1 (1.6%)	1 (1.4%)	1 (1.6%)	6 (1.0%)	6 (0.8%)
Moderate	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Dyspepsia (消化不良)											
Mild	0	2 (1.6%)	1 (1.6%)	0	0	0	2 (3.2%)	2 (2.9%)	0	7 (1.2%)	7 (1.0%)
Faeces soft (軟便)											
Mild	1 (0.7%)	1 (0.8%)	1 (1.6%)	2 (3.1%)	0	0	0	0	1 (1.6%)	5 (0.9%)	6 (0.8%)

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Large intestine polyp (大腸ポリープ)											
Mild	1 (0.7%)	0	0	2 (3.1%)	0	0	1 (1.6%)	1 (1.4%)	1 (1.6%)	5 (0.9%)	6 (0.8%)
Gastritis (胃炎)											
Mild	0	0	0	0	0	0	0	1 (1.4%)	2 (3.2%)	3 (0.5%)	3 (0.4%)
Moderate	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
Abdominal distension (腹部膨満)											
Mild	0	0	0	0	0	0	1 (1.6%)	0	2 (3.2%)	3 (0.5%)	3 (0.4%)
Metabolism and nutrition disorders (代謝および栄養障害)											
Hypoglycaemia (低血糖)											
Mild	5 (3.7%)	21 (16.5%)	9 (14.1%)	6 (9.4%)	2 (3.1%)	2 (3.1%)	5 (7.9%)	2 (2.9%)	4 (6.3%)	51 (8.8%)	56 (7.8%)
Hyperglycaemia (高血糖)											
Mild	5 (3.7%)	7 (5.5%)	0	0	1 (1.6%)	1 (1.5%)	2 (3.2%)	8 (11.4%)	1 (1.6%)	20 (3.4%)	25 (3.5%)
Decreased appetite (食欲減退)											
Mild	3 (2.2%)	0	0	1 (1.6%)	0	1 (1.5%)	2 (3.2%)	3 (4.3%)	1 (1.6%)	8 (1.4%)	11 (1.5%)
Moderate	0	0	0	1 (1.6%)	0	1 (1.5%)	0	0	0	2 (0.3%)	2 (0.3%)
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)											
Back pain (背部痛)											
Mild	5 (3.7%)	9 (7.1%)	3 (4.7%)	1 (1.6%)	1 (1.6%)	3 (4.6%)	1 (1.6%)	0	0	18 (3.1%)	23 (3.2%)
Moderate	0	1 (0.8%)	0	0	1 (1.6%)	1 (1.5%)	0	0	0	3 (0.5%)	3 (0.4%)

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Arthralgia (関節痛)											
Mild	1 (0.7%)	3 (2.4%)	0	2 (3.1%)	0	2 (3.1%)	2 (3.2%)	2 (2.9%)	1 (1.6%)	12 (2.1%)	13 (1.8%)
Pain in extremity (四肢痛)											
Mild	1 (0.7%)	3 (2.4%)	2 (3.1%)	0	0	0	1 (1.6%)	1 (1.4%)	1 (1.6%)	8 (1.4%)	9 (1.3%)
Myalgia (筋肉痛)											
Mild	2 (1.5%)	1 (0.8%)	1 (1.6%)	1 (1.6%)	1 (1.6%)	0	0	0	2 (3.2%)	6 (1.0%)	8 (1.1%)
Spinal osteoarthritis (変形性脊椎症)											
Mild	0	0	0	0	1 (1.6%)	0	4 (6.3%)	1 (1.4%)	1 (1.6%)	7 (1.2%)	7 (1.0%)
Moderate	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Intervertebral disc protrusion (椎間板突出)											
Mild	0	0	1 (1.6%)	0	1 (1.6%)	0	4 (6.3%)	1 (1.4%)	0	7 (1.2%)	7 (1.0%)
Osteoarthritis (変形性関節症)											
Mild	2 (1.5%)	0	1 (1.6%)	1 (1.6%)	0	0	2 (3.2%)	0	0	4 (0.7%)	6 (0.8%)
Lumbar spinal stenosis (腰部脊柱管狭窄症)											
Mild	0	0	0	0	0	0	1 (1.6%)	1 (1.4%)	0	2 (0.3%)	2 (0.3%)
Moderate	1 (0.7%)	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	2 (0.3%)
Muscle spasms (筋痙縮)											
Mild	0	1 (0.8%)	2 (3.1%)	0	0	0	1 (1.6%)	0	0	4 (0.7%)	4 (0.6%)
Musculoskeletal stiffness (筋骨格硬直)											
Mild	0	2 (1.6%)	2 (3.1%)	0	0	0	0	0	0	4 (0.7%)	4 (0.6%)
Trigger finger (弾発指)											
Mild	0	0	0	0	0	0	2 (3.2%)	2 (2.9%)	0	4 (0.7%)	4 (0.6%)

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Skin and subcutaneous tissue disorders (皮膚および皮下組織障害)											
Eczema (湿疹)											
Mild	2 (1.5%)	4 (3.1%)	3 (4.7%)	0	0	1 (1.5%)	5 (7.9%)	4 (5.7%)	2 (3.2%)	19 (3.3%)	21 (2.9%)
Acne (ざ瘡)											
Mild	0	1 (0.8%)	2 (3.1%)	1 (1.6%)	0	0	0	0	0	4 (0.7%)	4 (0.6%)
Hyperkeratosis (過角化)											
Mild	0	1 (0.8%)	0	0	0	0	0	0	2 (3.2%)	3 (0.5%)	3 (0.4%)
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)											
Contusion (挫傷)											
Mild	3 (2.2%)	2 (1.6%)	0	2 (3.1%)	0	0	3 (4.8%)	0	0	7 (1.2%)	10 (1.4%)
Moderate	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Ligament sprain (靭帯捻挫)											
Mild	1 (0.7%)	1 (0.8%)	2 (3.1%)	0	0	1 (1.5%)	0	1 (1.4%)	0	5 (0.9%)	6 (0.8%)
Thermal burn (熱傷)											
Mild	1 (0.7%)	0	0	2 (3.1%)	0	0	0	1 (1.4%)	0	3 (0.5%)	4 (0.6%)
Moderate	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Radius fracture (橈骨骨折)											
Mild	1 (0.7%)	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	2 (0.3%)
Moderate	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Tendon rupture (腱断裂)											
Mild	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Moderate	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Nervous system disorders (神経系障害)											
Headache (頭痛)											
Mild	2 (1.5%)	1 (0.8%)	1 (1.6%)	0	1 (1.6%)	2 (3.1%)	0	0	1 (1.6%)	6 (1.0%)	8 (1.1%)
Diabetic neuropathy (糖尿病性ニューロパチー)											
Mild	1 (0.7%)	0	0	0	0	0	2 (3.2%)	2 (2.9%)	1 (1.6%)	5 (0.9%)	6 (0.8%)
Carotid arteriosclerosis (頚動脈硬化症)											
Mild	0	0	1 (1.6%)	1 (1.6%)	0	2 (3.1%)	0	0	0	4 (0.7%)	4 (0.6%)
Cervicobrachial syndrome (頚腕症候群)											
Mild	1 (0.7%)	0	0	0	2 (3.1%)	0	0	0	0	2 (0.3%)	3 (0.4%)
Intercostal neuralgia (肋間神経痛)											
Mild	0	0	3 (4.7%)	0	0	0	0	0	0	3 (0.5%)	3 (0.4%)
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)											
Upper respiratory tract inflammation (上気道の炎症)											
Mild	1 (0.7%)	1 (0.8%)	2 (3.1%)	0	1 (1.6%)	2 (3.1%)	2 (3.2%)	0	3 (4.8%)	11 (1.9%)	12 (1.7%)

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Cough (咳嗽)											
Mild	3 (2.2%)	2 (1.6%)	1 (1.6%)	1 (1.6%)	0	1 (1.5%)	0	1 (1.4%)	0	6 (1.0%)	9 (1.3%)
Vascular disorders (血管障害)											
Hypertension (高血圧)											
Mild	0	7 (5.5%)	2 (3.1%)	1 (1.6%)	3 (4.7%)	3 (4.6%)	0	2 (2.9%)	1 (1.6%)	19 (3.3%)	19 (2.7%)
Moderate	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Renal and urinary disorders (腎および尿路障害)											
Diabetic nephropathy (糖尿病性腎症)											
Mild	0	1 (0.8%)	0	1 (1.6%)	2 (3.1%)	1 (1.5%)	1 (1.6%)	0	1 (1.6%)	7 (1.2%)	7 (1.0%)
Nephrolithiasis (腎結石症)											
Mild	1 (0.7%)	0	0	0	2 (3.1%)	2 (3.1%)	1 (1.6%)	1 (1.4%)	0	6 (1.0%)	7 (1.0%)
Pollakiuria (頻尿)											
Mild	0	0	0	0	0	0	0	2 (2.9%)	1 (1.6%)	3 (0.5%)	3 (0.4%)
Eye disorders (眼障害)											
Diabetic retinopathy (糖尿病網膜症)											
Mild	2 (1.5%)	1 (0.8%)	1 (1.6%)	0	0	2 (3.1%)	3 (4.8%)	1 (1.4%)	0	8 (1.4%)	10 (1.4%)
Asthenopia (眼精疲労)											
Mild	0	1 (0.8%)	2 (3.1%)	0	0	0	0	1 (1.4%)	0	4 (0.7%)	4 (0.6%)

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Psychiatric disorders (精神障害)											
Insomnia (不眠症)											
Mild	2 (1.5%)	1 (0.8%)	0	2 (3.1%)	0	1 (1.5%)	2 (3.2%)	1 (1.4%)	1 (1.6%)	8 (1.4%)	10 (1.4%)
Moderate	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Hepatobiliary disorders (肝胆道系障害)											
Hepatic steatosis (脂肪肝)											
Mild	0	1 (0.8%)	1 (1.6%)	0	0	1 (1.5%)	0	2 (2.9%)	0	5 (0.9%)	5 (0.7%)
Alcoholic liver disease (アルコール性肝疾患)											
Mild	0	1 (0.8%)	0	0	0	0	0	2 (2.9%)	0	3 (0.5%)	3 (0.4%)
Cholelithiasis (胆石症)											
Mild	0	0	0	0	1 (1.6%)	0	0	2 (2.9%)	0	3 (0.5%)	3 (0.4%)
Gallbladder polyp (胆嚢ポリープ)											
Mild	0	0	0	0	0	0	0	2 (2.9%)	0	2 (0.3%)	2 (0.3%)
Investigations (臨床検査)											
Lipase increased (リパーゼ増加)											
Mild	1 (0.7%)	2 (1.6%)	0	0	1 (1.6%)	1 (1.5%)	3 (4.8%)	0	0	7 (1.2%)	8 (1.1%)
Surgical and medical procedures (外科および内科処置)											

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Cataract operation (白内障手術)											
Mild	1 (0.7%)	3 (2.4%)	1 (1.6%)	2 (3.1%)	1 (1.6%)	0	0	0	0	7 (1.2%)	8 (1.1%)
Cardiac disorders (心臓障害)											
Coronary artery stenosis (冠動脈狭窄)											
Severe	0	0	0	0	0	0	0	2 (2.9%)	0	2 (0.3%)	2 (0.3%)
Palpitations (動悸)											
Mild	0	0	0	2 (3.1%)	0	0	0	0	0	2 (0.3%)	2 (0.3%)
Sinus bradycardia (洞性徐脈)											
Mild	0	0	0	0	0	2 (3.1%)	0	0	0	2 (0.3%)	2 (0.3%)
General disorders and administration site conditions (一般・全身障害および投与部位の状態)											
Fatigue (疲労)											
Mild	1 (0.7%)	0	1 (1.6%)	0	0	0	2 (3.2%)	0	1 (1.6%)	4 (0.7%)	5 (0.7%)
Ear and labyrinth disorders (耳および迷路障害)											
Vertigo (回転性めまい)											
Mild	1 (0.7%)	0	0	2 (3.1%)	0	0	0	1 (1.4%)	0	3 (0.5%)	4 (0.6%)

System Organ Class Preferred Term Maximum Severity	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Reproductive system and breast disorders (生殖系および乳房障害)											
Benign prostatic hyperplasia (良性前立腺肥大症)											
Mild	1 (0.7%)	0	2 (3.1%)	0	0	0	0	0	0	2 (0.3%)	3 (0.4%)
Immune system disorders (免疫系障害)											
Allergy to arthropod sting (節足動物刺傷アレルギー)											
Mild	0	0	0	0	0	0	0	2 (2.9%)	0	2 (0.3%)	2 (0.3%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once by the maximum severity.
- Percentages are based on Population N.

2.7.4.2.1.2.3　インスリン製剤併用療法：020 試験

(1) 二重盲検治療（16 週）

主な有害事象（いずれかの群で発現割合が 2%以上の有害事象）の発現割合を表 2.7.4.2-11 に、その副作用の発現割合を表 2.7.4.2-12 に示す。また、すべての有害事象及びすべての副作用の発現割合を 2.7.6.20 項に示す。発現割合が高かった有害事象は、低血糖［プラセボ群、イメグリミン群の順に（以下同順）、15.9%、21.3%］、上咽頭炎（7.5%、14.8%）であった。このうち治験薬との因果関係が否定されなかった事象は低血糖（6.5%、12.0%）であった。

重症度別の主な有害事象の発現割合を表 2.7.4.2-13 に、重症度別のすべての有害事象の発現割合を 2.7.4.7 項付録 Table S-065 に示す。有害事象の多くは軽度又は中等度であった。重度の有害事象は、浮動性めまい及びギラン・バレー症候群がプラセボ群の各 1 名で発現し、重篤な有害事象として報告された［2.7.4.2.1.4.3 項 (1) ］。

初回発現時期別の主な有害事象の発現割合を 2.7.4.7 項付録 Table S-076 に示す。いずれの群でも Week 1～4 にいずれかの有害事象を初回発現した被験者の割合が最も高かった。主な有害事象のうち低血糖の初回発現時期別の発現割合は、Week 1～4、Week 5～8、Week 9～12、Week 13 以降の順に、プラセボ群で 5.6%、2.8%、2.8%、4.8%、イメグリミン群で 11.1%、6.5%、2.8%、0.9%で、イメグリミン群で投与開始後早期に初回発現する傾向がみられた。その他の有害事象では初回発現時期に一定の傾向はみられなかった。

発現時期別の主な有害事象の発現割合を 2.7.4.7 項付録 Table S-077 に示す。発現時期別の有害事象の発現割合に一定の傾向はみられなかった。

表 2.7.4.2-11　Summary of Treatment Emergent Adverse Events (Incidence >= 2%) by System Organ Class and Preferred Term in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

System Organ Class Preferred Term	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Any TEAE	51 (47.7%)	57 (52.8%)
Metabolism and nutrition disorders (代謝および栄養障害)		
Hypoglycaemia (低血糖)	17 (15.9%)	23 (21.3%)
Hyperglycaemia (高血糖)	3 (2.8%)	0
Infections and infestations (感染症および寄生虫症)		
Nasopharyngitis (上咽頭炎)	8 (7.5%)	16 (14.8%)
Bronchitis (気管支炎)	0	3 (2.8%)
Gastrointestinal disorders (胃腸障害)		
Constipation (便秘)	1 (0.9%)	3 (2.8%)

System Organ Class Preferred Term	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
General disorders and administration site conditions (一般・全身障害および投与部位の状態)		
Pyrexia (発熱)	3 (2.8%)	1 (0.9%)
Nervous system disorders (神経系障害)		
Dizziness (浮動性めまい)	3 (2.8%)	1 (0.9%)

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

表 2.7.4.2-12　Summary of Treatment Emergent Adverse Events (Incidence >= 2%) Related to Treatment by System Organ Class and Preferred Term in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

System Organ Class Preferred Term	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Any TEAE related to treatment	13 (12.1%)	16 (14.8%)
Metabolism and nutrition disorders (代謝および栄養障害)		
Hypoglycaemia (低血糖)	7 (6.5%)	13 (12.0%)
Hyperglycaemia (高血糖)	1 (0.9%)	0
Infections and infestations (感染症および寄生虫症)		
Nasopharyngitis (上咽頭炎)	0	0
Bronchitis (気管支炎)	0	0
Gastrointestinal disorders (胃腸障害)		
Constipation (便秘)	0	2 (1.9%)
General disorders and administration site conditions (一般・全身障害および投与部位の状態)		
Pyrexia (発熱)	0	0
Nervous system disorders (神経系障害)		
Dizziness (浮動性めまい)	2 (1.9%)	0

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

表 2.7.4.2-13　Summary of Treatment Emergent Adverse Events (Incidence >= 2%) by Maximum Severity, System Organ Class and Preferred Term in 16-Week Double-blind Period in Combination with Insulin Therapy (PXL008-020; Safety Population)

System Organ Class Preferred Term Maximum Severity	Placebo + Insulin N = 107	Imeglimin 1000 mg bid + Insulin N = 108
Any TEAE		
Mild	45 (42.1%)	51 (47.2%)
Moderate	4 (3.7%)	6 (5.6%)
Severe	2 (1.9%)	0
Metabolism and nutrition disorders (代謝および栄養障害)		
Hypoglycaemia (低血糖)		
Mild	16 (15.0%)	23 (21.3%)
Moderate	1 (0.9%)	0
Hyperglycaemia (高血糖)		
Mild	2 (1.9%)	0
Moderate	1 (0.9%)	0
Infections and infestations (感染症および寄生虫症)		
Nasopharyngitis (上咽頭炎)		
Mild	8 (7.5%)	16 (14.8%)
Bronchitis (気管支炎)		
Mild	0	3 (2.8%)
Gastrointestinal disorders (胃腸障害)		
Constipation (便秘)		
Mild	1 (0.9%)	3 (2.8%)
General disorders and administration site conditions (一般・全身障害および投与部位の状態)		
Pyrexia (発熱)		
Mild	3 (2.8%)	1 (0.9%)
Nervous system disorders (神経系障害)		
Dizziness (浮動性めまい)		
Mild	2 (1.9%)	1 (0.9%)
Severe	1 (0.9%)	0

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once by the maximum severity.
- Percentages are based on Population N.

(2) 長期投与（52 週）

主な有害事象（いずれかの群で発現割合が 2%以上の有害事象）の発現割合を表 2.7.4.2-14 に、その副作用の発現割合を表 2.7.4.2-15 に示す。また、すべての有害事象の発現割合を 2.7.4.7 項付録 Table S-057 に、すべての副作用の発現割合を 2.7.4.7 項付録 Table S-058 に示す。発現割合が高かった有害事象は、低血糖（35.9%）、上咽頭炎（24.9%）であった。このうち治験薬との因果関係が否定されなかった事象は低血糖（18.7%）であった。

重症度別の主な有害事象の発現割合を表 2.7.4.2-16 に、重症度別のすべての有害事象の発現割合を 2.7.4.7 項付録 Table S-067 に示す。有害事象の多くは軽度又は中等度であった。重度の有害事象は、坐骨神経痛、膵癌、突然死、肝機能異常が各 1 名に発現し、いずれも重篤な有害事象として報告された［2.7.4.2.1.4.3 項 (2) ］。

初回発現時期別の主な有害事象の発現割合を 2.7.4.7 項付録 Table S-080 に示す。初回発現時期別の有害事象の発現割合に一定の傾向はみられなかった。

発現時期別の主な有害事象の発現割合を 2.7.4.7 項付録 Table S-081 に示す。発現時期別の有害事象の発現割合に一定の傾向はみられなかった。

表 2.7.4.2-14　Summary of Treatment Emergent Adverse Events (Incidence >= 2%) by System Organ Class and Preferred Term in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

System Organ Class Preferred Term	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Any TEAE	77 (76.2%)	92 (85.2%)	169 (80.9%)
Metabolism and nutrition disorders (代謝および栄養障害)			
Hypoglycaemia (低血糖)	36 (35.6%)	39 (36.1%)	75 (35.9%)
Infections and infestations (感染症および寄生虫症)			
Nasopharyngitis (上咽頭炎)	16 (15.8%)	36 (33.3%)	52 (24.9%)
Bronchitis (気管支炎)	5 (5.0%)	4 (3.7%)	9 (4.3%)
Influenza (インフルエンザ)	4 (4.0%)	5 (4.6%)	9 (4.3%)
Gastroenteritis (胃腸炎)	4 (4.0%)	1 (0.9%)	5 (2.4%)
Cystitis (膀胱炎)	1 (1.0%)	3 (2.8%)	4 (1.9%)
Conjunctivitis (結膜炎)	2 (2.0%)	0	2 (1.0%)
Gastrointestinal disorders (胃腸障害)			
Constipation (便秘)	0	6 (5.6%)	6 (2.9%)
Gastrooesophageal reflux disease (胃食道逆流性疾患)	2 (2.0%)	3 (2.8%)	5 (2.4%)
Nausea (悪心)	2 (2.0%)	3 (2.8%)	5 (2.4%)

System Organ Class Preferred Term	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Abdominal discomfort (腹部不快感)	1 (1.0%)	3 (2.8%)	4 (1.9%)
Diarrhoea (下痢)	2 (2.0%)	2 (1.9%)	4 (1.9%)
Toothache (歯痛)	2 (2.0%)	1 (0.9%)	3 (1.4%)
Chronic gastritis (慢性胃炎)	2 (2.0%)	0	2 (1.0%)
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)			
Back pain (背部痛)	1 (1.0%)	6 (5.6%)	7 (3.3%)
Muscle spasms (筋痙縮)	1 (1.0%)	4 (3.7%)	5 (2.4%)
Arthralgia (関節痛)	1 (1.0%)	3 (2.8%)	4 (1.9%)
Spinal osteoarthritis (変形性脊椎症)	0	4 (3.7%)	4 (1.9%)
Vascular disorders (血管障害)			
Hypertension (高血圧)	2 (2.0%)	5 (4.6%)	7 (3.3%)
Nervous system disorders (神経系障害)			
Headache (頭痛)	3 (3.0%)	3 (2.8%)	6 (2.9%)
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)			
Upper respiratory tract inflammation (上気道の炎症)	3 (3.0%)	1 (0.9%)	4 (1.9%)
Sputum increased (喀痰増加)	2 (2.0%)	0	2 (1.0%)
Immune system disorders (免疫系障害)			
Seasonal allergy (季節性アレルギー)	1 (1.0%)	4 (3.7%)	5 (2.4%)
General disorders and administration site conditions (一般・全身障害および投与部位の状態)			
Pyrexia (発熱)	2 (2.0%)	2 (1.9%)	4 (1.9%)
Eye disorders (眼障害)			
Diabetic retinopathy (糖尿病網膜症)	2 (2.0%)	1 (0.9%)	3 (1.4%)
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)			
Contusion (挫傷)	0	3 (2.8%)	3 (1.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）)			

System Organ Class Preferred Term	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Papillary thyroid cancer (乳頭様甲状腺癌)	2 (2.0%)	0	2 (1.0%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

表 2.7.4.2-15 Summary of Treatment Emergent Adverse Events (Incidence >= 2%) Related to Treatment by System Organ Class and Preferred Term in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

System Organ Class Preferred Term	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Any TEAE related to treatment	16 (15.8%)	28 (25.9%)	44 (21.1%)
Metabolism and nutrition disorders (代謝および栄養障害)			
Hypoglycaemia (低血糖)	16 (15.8%)	23 (21.3%)	39 (18.7%)
Infections and infestations (感染症および寄生虫症)			
Nasopharyngitis (上咽頭炎)	0	0	0
Bronchitis (気管支炎)	0	0	0
Influenza (インフルエンザ)	0	0	0
Gastroenteritis (胃腸炎)	0	0	0
Cystitis (膀胱炎)	0	1 (0.9%)	1 (0.5%)
Conjunctivitis (結膜炎)	0	0	0
Gastrointestinal disorders (胃腸障害)			
Constipation (便秘)	0	3 (2.8%)	3 (1.4%)
Gastrooesophageal reflux disease (胃食道逆流性疾患)	0	0	0
Nausea (悪心)	0	1 (0.9%)	1 (0.5%)
Abdominal discomfort (腹部不快感)	0	0	0
Diarrhoea (下痢)	1 (1.0%)	1 (0.9%)	2 (1.0%)
Toothache (歯痛)	0	0	0
Chronic gastritis (慢性胃炎)	0	0	0

System Organ Class Preferred Term	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)			
Back pain (背部痛)	0	0	0
Muscle spasms (筋痙縮)	0	0	0
Arthralgia (関節痛)	0	0	0
Spinal osteoarthritis (変形性脊椎症)	0	0	0
Vascular disorders (血管障害)			
Hypertension (高血圧)	0	0	0
Nervous system disorders (神経系障害)			
Headache (頭痛)	0	0	0
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)			
Upper respiratory tract inflammation (上気道の炎症)	0	0	0
Sputum increased (喀痰増加)	0	0	0
Immune system disorders (免疫系障害)			
Seasonal allergy (季節性アレルギー)	0	0	0
General disorders and administration site conditions (一般・全身障害および投与部位の状態)			
Pyrexia (発熱)	0	0	0
Eye disorders (眼障害)			
Diabetic retinopathy (糖尿病網膜症)	0	0	0
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)			
Contusion (挫傷)	0	0	0

System Organ Class Preferred Term	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）)			
Papillary thyroid cancer (乳頭様甲状腺癌)	0	0	0

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

表 2.7.4.2-16 Summary of Treatment Emergent Adverse Events (Incidence >= 2%) by Maximum Severity, System Organ Class and Preferred Term in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

System Organ Class Preferred Term Maximum Severity	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Any TEAE			
Mild	69 (68.3%)	80 (74.1%)	149 (71.3%)
Moderate	5 (5.0%)	11 (10.2%)	16 (7.7%)
Severe	3 (3.0%)	1 (0.9%)	4 (1.9%)
Metabolism and nutrition disorders (代謝および栄養障害)			
Hypoglycaemia (低血糖)			
Mild	36 (35.6%)	39 (36.1%)	75 (35.9%)
Infections and infestations (感染症および寄生虫症)			
Nasopharyngitis (上咽頭炎)			
Mild	16 (15.8%)	36 (33.3%)	52 (24.9%)
Bronchitis (気管支炎)			
Mild	5 (5.0%)	4 (3.7%)	9 (4.3%)
Influenza (インフルエンザ)			
Mild	4 (4.0%)	5 (4.6%)	9 (4.3%)
Gastroenteritis (胃腸炎)			
Mild	3 (3.0%)	1 (0.9%)	4 (1.9%)
Moderate	1 (1.0%)	0	1 (0.5%)

System Organ Class Preferred Term Maximum Severity	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Cystitis (膀胱炎)			
Mild	1 (1.0%)	3 (2.8%)	4 (1.9%)
Conjunctivitis (結膜炎)			
Mild	2 (2.0%)	0	2 (1.0%)
Gastrointestinal disorders (胃腸障害)			
Constipation (便秘)			
Mild	0	6 (5.6%)	6 (2.9%)
Gastrooesophageal reflux disease (胃食道逆流性疾患)			
Mild	2 (2.0%)	3 (2.8%)	5 (2.4%)
Nausea (悪心)			
Mild	2 (2.0%)	2 (1.9%)	4 (1.9%)
Moderate	0	1 (0.9%)	1 (0.5%)
Abdominal discomfort (腹部不快感)			
Mild	1 (1.0%)	3 (2.8%)	4 (1.9%)
Diarrhoea (下痢)			
Mild	2 (2.0%)	2 (1.9%)	4 (1.9%)
Toothache (歯痛)			
Mild	2 (2.0%)	1 (0.9%)	3 (1.4%)
Chronic gastritis (慢性胃炎)			
Mild	2 (2.0%)	0	2 (1.0%)
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)			
Back pain (背部痛)			
Mild	1 (1.0%)	4 (3.7%)	5 (2.4%)
Moderate	0	2 (1.9%)	2 (1.0%)
Muscle spasms (筋痙縮)			
Mild	1 (1.0%)	4 (3.7%)	5 (2.4%)
Arthralgia (関節痛)			
Mild	1 (1.0%)	3 (2.8%)	4 (1.9%)
Spinal osteoarthritis (変形性脊椎症)			
Mild	0	4 (3.7%)	4 (1.9%)
Vascular disorders (血管障害)			
Hypertension (高血圧)			
Mild	2 (2.0%)	5 (4.6%)	7 (3.3%)
Nervous system disorders (神経系障害)			
Headache (頭痛)			
Mild	3 (3.0%)	3 (2.8%)	6 (2.9%)

System Organ Class Preferred Term Maximum Severity	Placebo/Imeglimin + Insulin N = 101	Imeglimin/Imeglimin + Insulin N = 108	Imeglimin + Insulin Total N = 209
Respiratory, thoracic and mediastinal disorders (呼吸器、胸郭および縦隔障害)			
Upper respiratory tract inflammation (上気道の炎症)			
Mild	3 (3.0%)	1 (0.9%)	4 (1.9%)
Sputum increased (喀痰増加)			
Mild	2 (2.0%)	0	2 (1.0%)
Immune system disorders (免疫系障害)			
Seasonal allergy (季節性アレルギー)			
Mild	1 (1.0%)	4 (3.7%)	5 (2.4%)
General disorders and administration site conditions (一般・全身障害および投与部位の状態)			
Pyrexia (発熱)			
Mild	2 (2.0%)	2 (1.9%)	4 (1.9%)
Eye disorders (眼障害)			
Diabetic retinopathy (糖尿病網膜症)			
Mild	2 (2.0%)	1 (0.9%)	3 (1.4%)
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)			
Contusion (挫傷)			
Mild	0	3 (2.8%)	3 (1.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）)			
Papillary thyroid cancer (乳頭様甲状腺癌)			
Moderate	2 (2.0%)	0	2 (1.0%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- "Imeglimin + Insulin Total" is the sum of subjects in the placebo group in the open-label period and Imeglimin group in the double-blind and open-label periods.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once by the maximum severity.
- Percentages are based on Population N.

2.7.4.2.1.3　死亡

2.7.4.2.1.3.1　単独療法：二重盲検試験併合（24 週）：　014 試験・018 試験

有害事象による死亡の一覧を表 2.7.4.2-17 に示す。014 試験（1500 mg bid 群）の 7[redacted]歳の男性が、治験薬投与 121 日目（Day 121、以下同様）に遠隔転移を伴う膵癌と診断された。同日に治験薬の投与は中止され、Day 128 に治験を中止した。遠隔転移を伴う膵癌に対する治療が開始されたが、被験者は Day 184 に死亡した。被験者は脊柱管狭窄症、皮膚炎、高血圧、背部痛、びらん性胃炎、坐骨神経痛を合併していた。治験責任医師又は治験分担医師は、本事象は重度で治験薬との因果関係はなしと判断した。詳細な叙述は 2.7.6 項別添 2.7.6.18 に示す。

表 2.7.4.2-17　Listing of Treatment Emergent Adverse Events Leading to Death in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

Study	Treatment Group	Patient	Age (years)/ Sex/ CKD/ Hepatic	Preferred Term	Period/ Start Day/ End Day/ Duration (days)	Relationship/ Action Taken	Severity/ Serious	Outcome
014	Imeglimin 1500 mg bid	[redacted]-002	7[redacted]/ M/ Stage 2/ No	Pancreatic carcinoma metastatic (遠隔転移を伴う膵癌)	DB/ 121/ 184/ 64	NOT RELATED TO STUDY DRUG/ Drug Withdrawn	Severe/ Yes	Fatal

- Abbreviations: bid, Twice a day; M, Male; F, Female; CKD, Chronic Kidney Disease; Hepatic, Hepatic parameter abnormality; DB, Double-blind
- All adverse events were coded using MedDRA dictionary version 20.1.
- Duration (days): (End Day) - (Start Day) +1
- End Day and Duration were set to missing if the stop date of the event was missing.

2.7.4.2.1.3.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

有害事象による死亡の一覧を表 2.7.4.2-18 に示す。単独療法群の 6[redacted]歳の男性が、治験薬投与 195 日目（Day 195、以下同様）に交通事故によってくも膜下出血を発現し、Day 197 に死亡した。治験薬の最終投与日は不明である。治験責任医師又は治験分担医師は本事象を重度と判断した。また、被験者が歩行中に交通事故にあったこと、低血糖によって事故が起こった可能性は低いことから、本事象と治験薬との因果関係をなしと判断した。詳細な叙述は 2.7.6 項別添 2.7.6.24 に示す。

表 2.7.4.2-18　Listing of Treatment Emergent Adverse Events Leading to Death in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

Study	Treatment Group	Patient	Age (years)/ Sex/ CKD/ Hepatic	Preferred Term	Period/ Start Day/ End Day/ Duration (days)	Relationship/ Action Taken	Severity/ Serious	Outcome
019	Imeglimin	019-[redacted]-003	6[redacted]/ M/ Stage 2/ No	Subarachnoid haemorrhage (くも膜下出血)	OL/ 195/ 197/ 3	NOT RELATED/ Not Applicable	Severe/ Yes	Fatal

- Abbreviations: M, Male; F, Female; CKD, Chronic Kidney Disease; Hepatic, Hepatic parameter abnormality; OL, Open-label; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- All adverse events were coded using MedDRA dictionary version 20.1.
- Duration (days): (End Day) - (Start Day) +1
- End Day and Duration were set to missing if the stop date of the event was missing.

2.7.4.2.1.3.3　インスリン製剤併用療法：020 試験

(1) 二重盲検治療（16 週）

020 試験の二重盲検治療期に死亡した被験者はいなかった。

(2) 長期投与（52 週）

有害事象による死亡の一覧を表 2.7.4.2-19 に示す。6[redacted]歳の男性が二重盲検治療期の治験薬（プラセボ）を 112 日間、非盲検治療期の治験薬（本剤）を 216 日間投与された後、治験薬投与 328 日目（Day 328、以下同様）に死亡した。Week 44（Day 309）の診察結果は正常で、臨床検査結果に臨床的意義のある異常はみられなかった。Day 328 に被験者は心肺停止状態で発見され、病院で死亡が確認された。他院から死因不明の連絡を受け、治験責任医師は突然死と診断した。被験者は頸動脈狭窄、脂肪肝、胃食道逆流性疾患、十二指腸炎、慢性胃炎を合併していた。治験責任医師は、本事象は重度で治験薬との因果関係はなしと判断した。詳細な叙述は 2.7.6 項別添 2.7.6.20 に示す。

表 2.7.4.2-19　Listing of Treatment Emergent Adverse Events Leading to Death in 52-Week Long-term Period in Combination with Insulin Therapy (PXL008-020; Long-term Safety Population)

Study	Treatment Group	Patient	Age (years)/ Sex/ CKD/ Hepatic	Preferred Term	Period/ Start Day/ End Day/ Duration (days)	Relationship/ Action Taken	Severity/ Serious	Outcome
020	Placebo/Imeglimin + Insulin	020-[redacted]-002	6[redacted]/ M/ Stage 2/ No	Sudden death (突然死)	OL/ 328/ 328/ 1	NOT RELATED/ Not Applicable	Severe/ Yes	Fatal

- Abbreviations: M, Male; F, Female; CKD, Chronic Kidney Disease; Hepatic, Hepatic parameter abnormality; DB, Double-blind; OL, Open-label
- All adverse events were coded using MedDRA dictionary version 20.1.
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- The Long-term Safety Population excludes data during administration of placebo in the double-blind period.
- Start/End Days were relative to the day of first dose of study treatment in the double-blind period.
- Duration (days): (End Day) - (Start Day) +1
- End Day and Duration were set to missing if the stop date of the event was missing.

2.7.4.2.1.4　他の重篤な有害事象

2.7.4.2.1.4.1　単独療法：二重盲検試験併合（24 週）：014 試験・018 試験

重篤な有害事象の発現割合を表 2.7.4.2-20 に、重篤な有害事象の一覧を表 2.7.4.2-21 に示す。重篤な有害事象の詳細な叙述は 2.7.6.18 項及び 2.7.6.19 項に示す。

死亡を含む重篤な有害事象の発現被験者数（発現割合）は、プラセボ群、500 mg bid 群、1000 mg bid 群、1500 mg bid 群の順に 2 名（1.1%）、0 名、8 名（4.4%）、1 名（1.3%）であった。本剤群で発現した重篤な有害事象は、1000 mg bid 群で鎖骨骨折、膀胱癌、前立腺癌、膵の充実性偽乳頭状腫瘍、徐脈、イレウス、脊椎炎性脊髄症が各 1 名、大腿骨骨折及び橈骨骨折が 1 名、1500 mg bid 群で遠隔転移を伴う膵癌が 1 名であった。遠隔転移を伴う膵癌を発現した被験者は死亡し、前立腺癌は未回復であったが、そのほかの事象は回復又は軽快した。いずれの事象も治験薬との因果関係は否定された。重篤な有害事象のうち治験薬の投与中止に至った事象は、1000 mg bid 群の膀胱癌、前立腺癌、脊椎炎性脊髄症、1500 mg bid 群の遠隔転移を伴う膵癌が各 1 名であった。

表 2.7.4.2-20　Summary of Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

System Organ Class Preferred Term	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Any Serious TEAE	2 (1.1%)	0	8 (4.4%)	1 (1.3%)	9 (2.7%)
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)	2 (1.1%)	0	2 (1.1%)	0	2 (0.6%)
Clavicle fracture (鎖骨骨折)	0	0	1 (0.6%)	0	1 (0.3%)
Femur fracture (大腿骨骨折)	0	0	1 (0.6%)	0	1 (0.3%)
Lower limb fracture (下肢骨折)	1 (0.5%)	0	0	0	0
Meniscus injury (半月板損傷)	1 (0.5%)	0	0	0	0
Radius fracture (橈骨骨折)	0	0	1 (0.6%)	0	1 (0.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）)	0	0	3 (1.7%)	1 (1.3%)	4 (1.2%)
Bladder cancer (膀胱癌)	0	0	1 (0.6%)	0	1 (0.3%)
Pancreatic carcinoma metastatic (遠隔転移を伴う膵癌)	0	0	0	1 (1.3%)	1 (0.3%)
Prostate cancer (前立腺癌)	0	0	1 (0.6%)	0	1 (0.3%)
Solid pseudopapillary tumour of the pancreas (膵の充実性偽乳頭状腫瘍)	0	0	1 (0.6%)	0	1 (0.3%)

System Organ Class Preferred Term	Placebo N = 182	Imeglimin 500 mg bid N = 75	Imeglimin 1000 mg bid N = 180	Imeglimin 1500 mg bid N = 75	Imeglimin Total N = 330
Cardiac disorders (心臓障害)	0	0	1 (0.6%)	0	1 (0.3%)
Bradycardia (徐脈)	0	0	1 (0.6%)	0	1 (0.3%)
Gastrointestinal disorders (胃腸障害)	0	0	1 (0.6%)	0	1 (0.3%)
Ileus (イレウス)	0	0	1 (0.6%)	0	1 (0.3%)
Nervous system disorders (神経系障害)	0	0	1 (0.6%)	0	1 (0.3%)
Spondylitic myelopathy (脊椎炎性脊髄症)	0	0	1 (0.6%)	0	1 (0.3%)

- Abbreviations: bid, Twice a day; AE, Adverse event; TEAE, Treatment Emergent AE
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.

表 2.7.4.2-21　Listing of Treatment Emergent Serious Adverse Events in 24-Week Double-blind Period with Monotherapy (PXL008-014, PXL008-018; Safety Population)

Study	Treatment Group	Patient	Age (years)/ Sex/ CKD/ Hepatic	Preferred Term	Period/ Start Day/ End Day/ Duration (days)	Relationship/ Action Taken	Severity/ Serious	Outcome
014	Placebo	[redacted]-010	5[redacted]/ M/ Stage 2/ No	Meniscus injury (半月板損傷)	DB/ 31/ 189/ 159	NOT RELATED TO STUDY DRUG/ Drug Interrupted	Moderate/ Yes	Recovered/Resolved
	Imeglimin 1000 mg bid	[redacted]-001	7[redacted]/ F/ Stage 2/ No	Bradycardia (徐脈)	DB/ 58/ 71/ 14	NOT RELATED TO STUDY DRUG/ Dose Not Changed	Severe/ Yes	Recovered/Resolved
	Imeglimin 1000 mg bid	[redacted]-006	4[redacted]/ F/ Stage 2/ No	Solid pseudopapillary tumour of the pancreas (膵の充実性偽乳頭状腫瘍)	DB/ 153/ 210/ 58	NOT RELATED TO STUDY DRUG/ Drug Interrupted	Severe/ Yes	Recovered/Resolved
	Imeglimin 1000 mg bid	[redacted]-001	6[redacted]/ M/ Stage 2/ No	Prostate cancer (前立腺癌)	DB/ 61/ ./ .	NOT RELATED TO STUDY DRUG/ Drug Withdrawn	Severe/ Yes	Not Recovered/Not Resolved
	Imeglimin 1000 mg bid	[redacted]-004	6[redacted]/ F/ Stage 2/ No	Clavicle fracture (鎖骨骨折)	DB/ 31/ 211/ 181	NOT RELATED TO STUDY DRUG/ Dose Not Changed	Moderate/ Yes	Recovered/Resolved
	Imeglimin 1500 mg bid	[redacted]-002	7[redacted]/ M/ Stage 2/ No	Pancreatic carcinoma metastatic (遠隔転移を伴う膵癌)	DB/ 121/ 184/ 64	NOT RELATED TO STUDY DRUG/ Drug Withdrawn	Severe/ Yes	Fatal
018	Placebo	018-[redacted]-010	7[redacted]/ F/ Stage 2/ No	Lower limb fracture (下肢骨折)	DB/ 78/ 149/ 72	NOT RELATED/ Dose Not Changed	Severe/ Yes	Recovered/Resolved
	Imeglimin 1000 mg bid	018-[redacted]-005	7[redacted]/ F/ Stage 2/ No	Femur fracture (大腿骨骨折)	DB/ 147/ 196/ 50	NOT RELATED/ Dose Not Changed	Severe/ Yes	Recovered/Resolved
	Imeglimin 1000 mg bid	018-[redacted]-005	7[redacted]/ F/ Stage 2/ No	Radius fracture (橈骨骨折)	DB/ 147/ 196/ 50	NOT RELATED/ Dose Not Changed	Severe/ Yes	Recovered/Resolved
	Imeglimin 1000 mg bid	018-[redacted]-002	5[redacted]/ M/ Stage 2/ No	Spondylitic myelopathy (脊椎炎性脊髄症)	DB/ 123/ ./ .	NOT RELATED/ Drug Withdrawn	Severe/ Yes	Recovering/Resolving
	Imeglimin 1000 mg bid	018-[redacted]-002	6[redacted]/ M/ Stage 2/ No	Ileus (イレウス)	DB/ 122/ 127/ 6	NOT RELATED/ Drug Interrupted	Moderate/ Yes	Recovered/Resolved
	Imeglimin 1000 mg bid	018-[redacted]-003	7[redacted]/ M/ Stage 2/ No	Bladder cancer (膀胱癌)	DB/ 29/ ./ .	NOT RELATED/ Drug Withdrawn	Moderate/ Yes	Recovering/Resolving

- Abbreviations: bid, Twice a day; M, Male; F, Female; CKD, Chronic Kidney Disease; Hepatic, Hepatic parameter abnormality; DB, Double-blind
- All adverse events were coded using MedDRA dictionary version 20.1.

- Duration (days): (End Day) - (Start Day) +1
- End Day and Duration were set to missing if the stop date of the event was missing.

2.7.4.2.1.4.2　単独及び血糖降下薬との併用療法：長期投与（52 週）：019 試験

重篤な有害事象の発現割合を表 2.7.4.2-22 に、重篤な有害事象の一覧を表 2.7.4.2-23 に示す。重篤な有害事象の詳細な叙述は 2.7.6.24 項に示す。

- 単独療法群では、死亡を含む重篤な有害事象の発現被験者数（発現割合）は 4 名（3.0%）で、虫垂炎、くも膜下出血、処置後出血、心房細動が各 1 名に発現した。いずれの事象も治験薬との因果関係は否定された。くも膜下出血を発現した被験者は死亡したが、そのほかの事象は回復した。
- SU 併用療法群では、死亡を含む重篤な有害事象の発現被験者数（発現割合）は 11 名（8.7%）で、鎖骨骨折、結腸癌第 1 期、直腸癌、不安定狭心症、急性心筋梗塞、挫傷、硬膜下血腫、外傷性気胸、子宮平滑筋腫、下部消化管出血、滑膜炎が各 1 名に発現した。いずれの事象も治験薬との因果関係は否定された。結腸癌第 1 期及び直腸癌は未回復で、急性心筋梗塞は回復したが後遺症を伴った。そのほかの事象は回復又は軽快した。重篤な有害事象のうち治験薬の投与中止に至った事象は、結腸癌第 1 期及び直腸癌が各 1 名であった。
- GLIN 併用療法群では、死亡を含む重篤な有害事象の発現被験者数（発現割合）は 1 名（1.6%）で、精巣癌が 1 名に発現した。治験薬との因果関係は否定され、転帰は軽快であった。治験薬の投与は中止された。
- BIG 併用療法群では、死亡を含む重篤な有害事象の発現被験者数（発現割合）は 4 名（6.3%）で、心筋梗塞、胆管細胞癌、虫垂炎、大腸ポリープが各 1 名に発現した。いずれの事象も治験薬との因果関係は否定された。胆管細胞癌は未回復であったが、そのほかの事象は回復した。重篤な有害事象のうち治験薬の投与中止に至った事象は、胆管細胞癌が 1 名であった。
- AGI 併用療法群では、死亡を含む重篤な有害事象の発現被験者数（発現割合）は 4 名（6.3%）で、卵巣嚢胞、不安定狭心症、熱中症が各 1 名に、胆嚢炎及び薬物性肝障害が 1 名に発現した。いずれの事象も治験薬との因果関係は否定され、転帰は回復であった。
- TZD 併用療法群では、死亡を含む重篤な有害事象の発現被験者数（発現割合）は 4 名（6.2%）で、腸膀胱瘻、頭蓋脳損傷、炎症、細菌性肺炎が各 1 名に発現した。いずれの事象も治験薬との因果関係は否定された。腸膀胱瘻は未回復であったが、そのほかの事象は回復した。重篤な有害事象のうち治験薬の投与中止に至った事象は、腸膀胱瘻が 1 名であった。
- DPP4-I 併用療法群では、死亡を含む重篤な有害事象の発現被験者数（発現割合）は 3 名（4.8%）で、多発骨折、大腸ポリープ、子宮内膜癌第 3 期が各 1 名に発現した。いずれの事象も治験薬との因果関係は否定された。子宮内膜癌第 3 期は未回復であったが、そのほかの事象は回復又は軽快した。重篤な有害事象のうち治験薬の投与中止に至った事象は、多発骨折が 1 名であった。
- GLP1-RA 併用療法群では、死亡を含む重篤な有害事象の発現被験者数（発現割合）

は 5 名（7.1%）で、腰部性急患狭窄症、浸潤性乳管癌、皮様嚢腫、冠動脈狭窄が各 1 名に、冠動脈狭窄及び脳梗塞が 1 名に発現した。いずれの事象も治験薬との因果関係は否定され、転帰は回復又は軽快であった。重篤な有害事象のうち治験薬の投与中止に至った事象は、浸潤性乳管癌が 1 名であった。

- SGLT2-I 併用療法群では、死亡を含む重篤な有害事象の発現被験者数（発現割合）は 4 名（6.3%）で、ラクナ梗塞、大腸ポリープ、脊椎骨折が各 1 名に、心不全及び肺炎が 1 名に発現した。いずれの事象も治験薬との因果関係は否定された。ラクナ梗塞は回復したが後遺症を伴った。そのほかの事象は回復又は軽快した。

表 2.7.4.2-22　Summary of Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term in 52-Week Long-term Period with Monotherapy and Combination Therapy (PXL008-019; Long-term Safety Population)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Any Serious TEAE	4 (3.0%)	11 (8.7%)	1 (1.6%)	4 (6.3%)	4 (6.3%)	4 (6.2%)	3 (4.8%)	5 (7.1%)	4 (6.3%)	36 (6.2%)	40 (5.6%)
Injury, poisoning and procedural complications (傷害、中毒および処置合併症)	2 (1.5%)	4 (3.1%)	0	0	1 (1.6%)	1 (1.5%)	1 (1.6%)	0	1 (1.6%)	8 (1.4%)	10 (1.4%)
Clavicle fracture (鎖骨骨折)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Contusion (挫傷)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Craniocerebral injury (頭蓋脳損傷)	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Heat illness (熱中症)	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
Multiple fractures (多発骨折)	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Pneumothorax traumatic (外傷性気胸)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Post procedural haemorrhage (処置後出血)	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Spinal fracture (脊椎骨折)	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)
Subarachnoid haemorrhage (くも膜下出血)	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Subdural haematoma (硬膜下血腫)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Cardiac disorders (心臓障害)	1 (0.7%)	2 (1.6%)	0	1 (1.6%)	1 (1.6%)	0	0	2 (2.9%)	1 (1.6%)	7 (1.2%)	8 (1.1%)
Angina unstable (不安定狭心症)	0	1 (0.8%)	0	0	1 (1.6%)	0	0	0	0	2 (0.3%)	2 (0.3%)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Coronary artery stenosis (冠動脈狭窄)	0	0	0	0	0	0	0	2 (2.9%)	0	2 (0.3%)	2 (0.3%)
Acute myocardial infarction (急性心筋梗塞)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Atrial fibrillation (心房細動)	1 (0.7%)	0	0	0	0	0	0	0	0	0	1 (0.1%)
Cardiac failure (心不全)	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)
Myocardial infarction (心筋梗塞)	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）)	0	3 (2.4%)	1 (1.6%)	1 (1.6%)	0	0	1 (1.6%)	1 (1.4%)	0	7 (1.2%)	7 (1.0%)
Cholangiocarcinoma (胆管細胞癌)	0	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Colon cancer stage I (結腸癌第１期)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Endometrial cancer stage III (子宮内膜癌第３期)	0	0	0	0	0	0	1 (1.6%)	0	0	1 (0.2%)	1 (0.1%)
Invasive ductal breast carcinoma (浸潤性乳管癌)	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Rectal cancer (直腸癌)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Testis cancer (精巣癌)	0	0	1 (1.6%)	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Uterine leiomyoma (子宮平滑筋腫)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Gastrointestinal disorders (胃腸障害)	0	1 (0.8%)	0	1 (1.6%)	0	1 (1.5%)	1 (1.6%)	0	1 (1.6%)	5 (0.9%)	5 (0.7%)
Large intestine polyp (大腸ポリープ)	0	0	0	1 (1.6%)	0	0	1 (1.6%)	0	1 (1.6%)	3 (0.5%)	3 (0.4%)
Enterovesical fistula (腸膀胱瘻)	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Lower gastrointestinal haemorrhage (下部消化管出血)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Infections and infestations (感染症および寄生虫症)	1 (0.7%)	0	0	1 (1.6%)	0	1 (1.5%)	0	0	1 (1.6%)	3 (0.5%)	4 (0.6%)
Appendicitis (虫垂炎)	1 (0.7%)	0	0	1 (1.6%)	0	0	0	0	0	1 (0.2%)	2 (0.3%)
Pneumonia (肺炎)	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)
Pneumonia bacterial (細菌性肺炎)	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Musculoskeletal and connective tissue disorders (筋骨格系および結合組織障害)	0	1 (0.8%)	0	0	0	0	0	1 (1.4%)	0	2 (0.3%)	2 (0.3%)
Lumbar spinal stenosis (腰部脊柱管狭窄症)	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Synovitis (滑膜炎)	0	1 (0.8%)	0	0	0	0	0	0	0	1 (0.2%)	1 (0.1%)
Nervous system disorders (神経系障害)	0	0	0	0	0	0	0	1 (1.4%)	1 (1.6%)	2 (0.3%)	2 (0.3%)
Cerebral infarction (脳梗塞)	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Lacunar infarction (ラクナ梗塞)	0	0	0	0	0	0	0	0	1 (1.6%)	1 (0.2%)	1 (0.1%)

System Organ Class Preferred Term	Imeglimin N = 134	Imeglimin + SU N = 127	Imeglimin + GLIN N = 64	Imeglimin + BIG N = 64	Imeglimin + AGI N = 64	Imeglimin + TZD N = 65	Imeglimin + DPP4-I N = 63	Imeglimin + GLP1-RA N = 70	Imeglimin + SGLT2-I N = 63	Combination Total N = 580	Imeglimin Total N = 714
Congenital, familial and genetic disorders (先天性、家族性および遺伝性障害)	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
Dermoid cyst (皮様嚢腫)	0	0	0	0	0	0	0	1 (1.4%)	0	1 (0.2%)	1 (0.1%)
General disorders and administration site conditions (一般・全身障害および投与部位の状態)	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Inflammation (炎症)	0	0	0	0	0	1 (1.5%)	0	0	0	1 (0.2%)	1 (0.1%)
Hepatobiliary disorders (肝胆道系障害)	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
Cholecystitis (胆嚢炎)	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
Drug-induced liver injury (薬物性肝障害)	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
Reproductive system and breast disorders (生殖系および乳房障害)	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)
Ovarian cyst (卵巣嚢胞)	0	0	0	0	1 (1.6%)	0	0	0	0	1 (0.2%)	1 (0.1%)

- Abbreviations: AE, Adverse event; TEAE, Treatment Emergent AE; SU, Sulphonylurea; GLIN, Glinide; BIG, Biguanide; AGI, Alpha glucosidase inhibitor; TZD, Thiazolidinedione; DPP4-I, Dipeptidyl peptidase-4 inhibitor; GLP1-RA, Glucagon-like peptide 1 receptor agonist; SGLT2-I, Sodium glucose cotransporter 2 inhibitor
- "Imeglimin" in this table means "Imeglimin 1000 mg twice daily".
- "Combination Total" is the sum of the subjects excluding monotherapy "Imeglimin".
- "Imeglimin Total" is the sum of all subjects in Imeglimin treatment groups.
- All adverse events were coded using MedDRA dictionary version 20.1.
- Within each subject, multiple reports of adverse events mapped to a common System Organ Class and Preferred Term are counted only once.
- Percentages are based on Population N.