2.6 NONCLINICAL SUMMARY

SECTION 2.6.7—TOXICOLOGY TABULATED SUMMARY

EMTRICITABINE/RILPIVIRINE/TENOFOVIR ALAFENAMIDE FIXED DOSE COMBINATION (FTC/RPV/TAF [F/R/TAF] FDC)

Gilead Sciences

07 May 2015

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

SECTION 2.6.7—TOXICOLOGY TABULATED SUMMARY 1
TABLE OF CONTENTS 2
NOTE TO REVIEWER 5
1. TOXICOLOGY: OVERVIEW 7
2. TOXICOKINETICS: OVERVIEW OF TOXICOKINETICS STUDIES 25
2.1. FTC 25
2.2. RPV 26
2.3. TAF 29
2.4. FTC/TDF 30
3. TOXICOKINETICS: OVERVIEW OF TOXICOKINETICS DATA 31
3.1. FTC 31
3.2. RPV 33
3.3. TAF 37
4. TOXICOLOGY: DRUG SUBSTANCE 39
4.1. FTC 39
4.2. RPV 45
4.3. TAF 53
4.4. Ground FTC/TDF Tablets 55
5. TOXICOLOGY: SINGLE-DOSE TOXICITY 56
5.1. FTC 56
5.2. RPV 57
5.3. TAF 58
6. REPEAT DOSE TOXICITY (NONPIVOTAL STUDIES) 61
6.1. RPV 61
6.2. TDF 72
6.3. TAF 73
7. TOXICOLOGY: REPEAT-DOSE TOXICITY (PIVOTAL STUDIES) 76
7.1. FTC 76
7.2. RPV 90
7.3. TAF 125
7.4. FTC/TDF 154
8. GENOTOXICITY: IN VITRO 156
8.1. FTC: Ames 156
8.2. FTC: Ames 160
8.3. FTC: Ames 162
8.4. FTC: Mouse Lymphoma Assay 164
8.5. RPV: Ames 169
8.6. RPV: Ames 173
8.7. RPV: Ames 176
8.8. RPV: Ames 180
8.9. RPV: Mouse Lymphoma Assay 185
8.10. RPV: Mouse Lymphoma 188
8.11. TAF: Ames 191
8.12. TAF: Mouse Lymphoma Mutation Assay 195

8.13. FTC/TDF: Ames 198
8.14. FTC/TDF: Mouse Lymphoma Assay 201

9. GENOTOXICITY: IN VIVO 204

9.1. FTC: Micronucleus in Mice 204
9.2. RPV: Micronucleus in Mice 205
9.3. TAF: Micronucleus in Mice 207

10. CARCINOGENICITY 208

10.1. FTC: Mouse 208
10.2. FTC: Rat 215
10.3. RPV: Mouse 223
10.4. RPV: Rat 226
10.5. TDF: Mouse 232
10.6. TDF: Rat 238
10.7. TAF 244

11. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY (NONPIVOTAL STUDIES) 245

11.1. FTC 245
11.2. RPV 245
11.3. TAF 247

12. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY: FERTILITY AND EARLY EMBRYONIC DEVELOPMENT TO IMPLANTATION 248

12.1. FTC: Fertility and Early Embryonic Development in Mice 248
12.2. FTC: Male Fertility in Rats 251
12.3. RPV: Male Fertility in Rats 254
12.4. RPV: Female Fertility in the Rat 255
12.5. TAF: Fertility and General Reproduction in Rats 256

13. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY: EFFECTS ON EMBRYO-FETAL DEVELOPMENT 258

13.1. FTC: Embryo/Fetal Development in Mice 258
13.2. FTC: Embryo/Fetal Development in Rabbits 259
13.3. RPV: Developmental Toxicity Study in Rats 260
13.4. RPV: Developmental Toxicity Study in the Rabbit 262
13.5. TAF: Developmental Toxicity in Rat 264
13.6. TAF: Developmental Toxicity in Rabbits 267

14. REPRODUCTIVE AND DEVELOPMENTAL TOXICITY: EFFECTS ON PRE- AND POST-NATAL DEVELOPMENT, INCLUDING MATERNAL FUNCTION 270

14.1. FTC: Pre- and Post-natal Development in Mice 270
14.2. RPV: Pre- and Post-natal Developmental Toxicity and Juvenile Toxicity Dose Range Finding Study in the Rat 273
14.3. RPV: Pre- and Post-natal Developmental Toxicity Study in the Rat 275
14.4. TDF: Developmental and Perinatal/Postnatal Reproduction in Rats 277
14.5. TAF 280

15. STUDIES ON JUVENILE ANIMALS 281

16. LOCAL TOLERANCE 282

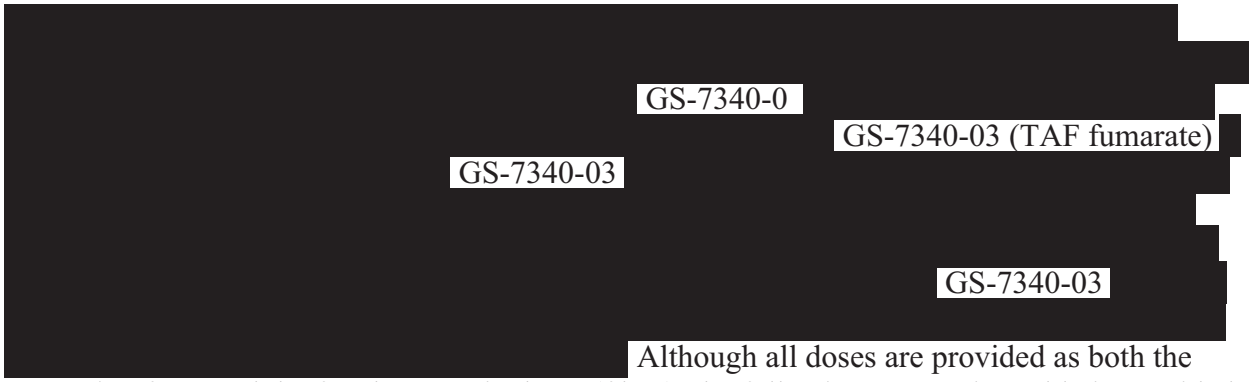
16.1. RPV 282
16.2. TAF 283

17. OTHER TOXICITY STUDIES 284

17.1. FTC 284
17.2. RPV 287
17.3. TAF/TVF 294
17.4. FTC/TDF 298

NOTE TO REVIEWER

This application is being submitted for a fixed dose combination (FDC) that contains nucleoside reverse transcriptase inhibitor (NRTI) emtricitabine (FTC, F, Emtriva®), the nonnucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine (RPV, R, Edurant®) and and the nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir alafenamide: the F/R/TAF FDC (200/25/25 mg) tablet. All nonclinical studies to support the F/R/TAF FDC application are included with no cross referencing to data previously submitted. This comprises all nonclinical tests utilizing FTC, RPV or TAF, including relevant combination studies, eg, FTC/tenofovir disoproxil fumarate (TDF); and other studies necessary to support the proposed product labeling for the treatment of human immunodeficiency virus type 1 (HIV-1) infection. Links to other modules and study reports are in blue text.



Although all doses are provided as both the respective form and the free base equivalents (f.b.e.), the following conversion table is provided as a reference.

GS-7340 Equivalents		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

The following conversions are also provided to aid the reviewer:

- FTC 1 µM = 0.247 µg/mL
- RPV 1 µM = 0.366 µg/mL
- TAF (GS-7340) 1 µM = 0.477 µg/mL
- TFV 1 µM = 0.287 µg/mL

1. TOXICOLOGY: OVERVIEW

Test Articles: FTC, RPV, TAF, TDF

Type of Study/Species/Strain	Method of Administration	Duration of Dosing	Dose (mg/kg)[a]	GLP[b]	Testing Facility	Study No. (CRO Study No.)
Single-Dose Toxicity of FTC						
Mice, Charles River CD-1	Oral Gavage	1 Day	4000	Yes	[redacted] USA	TTEP/93/0020 ([redacted]531)
Mice, Charles River CD-1	IV	1 Day	200	Yes	[redacted] USA	TTEP/93/0023 ([redacted]529)
Rat, Charles River CD	Oral Gavage	1 Day	4000	Yes	[redacted] USA	TTEP/93/0021 ([redacted]532)
Rat, Charles River CD	IV	1 Day	200	Yes	[redacted] USA	TTEP/93/0024 ([redacted]530)
Single-Dose Toxicity of RPV						
Rat, Sprague Dawley	Oral/Gavage	Single dose	Base: 800 (PEG400)	No	J&J PRD	TMC278-EXP5559
Dog, Beagle	Oral/Gavage	Single dose	Base: 40, 80 (PEG400), 80 (PEG400 + CA)	No	J&J PRD	TMC278-EXP5461
Single-Dose Toxicity of TAF						
Rat/Sprague Dawley; 7340-02	Oral Gavage	1 day	0, 6.25, 25, 100[c], 400	No	Gilead Sciences, CO	R990133 (NA)
Rat/Sprague Dawley; 7340-02	Oral Gavage	1 day	0, 100, 300, 1000	Yes	[redacted], Canada	R990185 ([redacted]89186)
Dog/Beagle;7340-02	Oral Gavage	1 day	0, 30[d], 90, 270	Yes	[redacted], Canada	D990181 ([redacted]89187)
Repeat-Dose Toxicity of FTC						
Mouse, Charles River CD-1	Oral Gavage	2 Weeks	0, 120, 600, 3000	Yes	[redacted] UK	TOX001 ([redacted]00701)
Mouse, Charles River CD-1	Oral Gavage	4 Weeks	0, 120, 600, 3000	Yes	[redacted] USA	TOX599

Test Articles: FTC, RPV, TAF, TDF

Type of Study/Species/Strain	Method of Administration	Duration of Dosing	Dose (mg/kg)[a]	GLP[b]	Testing Facility	Study No. (CRO Study No.)
Mouse, Charles River CD-1	Oral Gavage	26 Weeks	0, 167, 500, 1500	Yes	[redacted] UK	TOX022 ([redacted]01001)
Mouse, Charles River CD-1	Oral Gavage	26 Weeks	0, 120, 600, 3000	Yes	[redacted] USA	TOX628
Rat, CD	Oral Gavage	3 Months	0, 120, 600, 3000	Yes	[redacted] USA	TOX097
Monkey, Cynomolgus	Oral Gavage	4 Weeks	0, 80, 400, 2000	Yes	[redacted] USA	TOX600 ([redacted] 309-227)
Monkey, Cynomolgus	Oral Gavage	13 Weeks	0, 40, 200, 1000	Yes	[redacted] USA	TOX627 ([redacted] 309-229)
Monkey, Cynomolgus	Oral Gavage	1 Year	0, 50, 200, 500	Yes	[redacted] USA	TOX032 (6758-114)
Repeat-Dose Toxicity of RPV						
Mouse, Albino Swiss	Oral/Gavage or Diet	2 weeks	**Hydrochloride salt**: 0 (control diet), 40 (diet), 400 (diet), 5000 (diet), 400 (gavage), 2000 (gavage)	No	J&J PRD	TMC278-NC118
Mouse, CB6F1-nonTgrasH2	Oral/Gavage	1 month	**Hydrochloride salt**: 0 (vehicle), 20, 80, 320 (0.5% HPMC)	Yes	[redacted]	TMC278-NC121
Mouse, Albino Swiss	Oral/Gavage	3 months	**Hydrochloride salt**: 0 (vehicle), 20, 80, 320 (0.5% HPMC)	Yes	J&J PRD	TMC278-NC119

Test Articles: FTC, RPV, TAF, TDF

Type of Study/Species/Strain	Method of Administration	Duration of Dosing	Dose (mg/kg)[a]	GLP[b]	Testing Facility	Study No. (CRO Study No.)
Rat, Sprague Dawley	Oral/Gavage	5 days	**Base**: 0 (water), 0 (vehicle), 40, 400 (PEG400)	No	J&J PRD	TMC278-TOX5463
Rat, Sprague Dawley	Oral/Gavage	2 weeks	**Base**: 0 (water), 0 (vehicle), 40, 120, 400 (PEG400 + CA)	Yes	J&J PRD	TMC278-TOX5535
Rat, Sprague Dawley	Oral/Gavage	2 weeks	**Hydrochloride salt**: 0 (vehicle), 400, 1500, 2000 (0.5% HPMC)	No	J&J PRD	TMC278-NC177
Rat, Sprague Dawley	Oral/Gavage or Diet	2 weeks	**Hydrochloride salt**: 0 (control diet), 400 (diet), 1200 (diet), 400 (gavage) **Base**: 400 (diet)	No	J&J PRD	TMC278-NC136
Rat, Sprague Dawley	Oral/Gavage	1 month	**Base**: 0 (vehicle), 10, 400 (PEG400 + CA) **Hydrochloride salt**: 0 (vehicle), 10, 400 (0.5% HPMC)	Yes	J&J PRD	TMC278-NC117
Rat, Sprague Dawley	Oral/Gavage	1 month	**Base**: 0 (water), 0 (vehicle), 10, 40, 160 (PEG400 + CA)	Yes	[redacted]	TMC278-EXP5692

Test Articles: FTC, RPV, TAF, TDF

Type of Study/Species/Strain	Method of Administration	Duration of Dosing	Dose (mg/kg)[a]	GLP[b]	Testing Facility	Study No. (CRO Study No.)
Rat, Sprague Dawley	Oral/Gavage	6 months	**Base**: 0 (vehicle), 40, 120, 400 (PEG400 + CA)	Yes	J&J PRD	TMC278-NC101
Rabbit, New Zealand White	Oral/Gavage	5 days	**Base**: 0 (vehicle), 100, 300, 1000 (0.5% HPMC)	No	J&J PRD	TMC278-NC126
Dog, Beagle	Oral/Gavage	7 days	**Base**: 0 (water), 0 (vehicle), 20, 40, 80 (PEG400 + CA)	Yes	J&J PRD	TMC278-EXP5534
Dog, Beagle	Oral/Gavage	1 month	**Base**: 0 (water), 0 (vehicle), 5, 10, 40 (PEG400 + CA)	Yes	J&J PRD	TMC278-EXP5650
Dog, Beagle	Oral/Gavage	1 month	**Base**: 0 (vehicle), 5, 40 (PEG400 + CA) **Hydrochloride salt**: 0 (vehicle), 5, 40 (0.5% HPMC)	Yes	J&J PRD	TMC278-NC116
Dog, Beagle	Oral/Gavage	6 months	**Base**: 0 (vehicle), 5, 10, 40 (PEG400 + CA)	Yes	J&J PRD	TMC278-NC115
Dog, Beagle	Oral/Gavage	12 months	**Base**: 0 (vehicle), 5, 10, 40 (PEG400 + CA)	Yes	[redacted]	TMC278-NC107

Test Articles: FTC, RPV, TAF, TDF

Type of Study/Species/Strain	Method of Administration	Duration of Dosing	Dose (mg/kg)[a]	GLP[b]	Testing Facility	Study No. (CRO Study No.)
Monkey, Cynomolgus	Oral/Gavage	8 weeks	**Hydrochloride salt**: 0 (vehicle), 200, 500 bid (1% HPMC + 0.5% polysorbate 20)	Yes	[redacted]	TMC278-NC248
Repeat-Dose Toxicity of TAF						
Mouse/CD:CD1(ICR); GS-7340-02	Oral Gavage	2 weeks	0, 100, 500, 1000	No	[redacted]	TX-120-2006 ([redacted] 8235665)
Mouse/CD:CD1(ICR); GS-7340-02	Oral Gavage	13 weeks	0[g], 10, 30, 100	Yes	[redacted]	TX-120-2007 ([redacted] 8241074)
Rat/Sprague-Dawley (Crl): GS-7340-02	Oral Gavage	6 days	0, 100, 400	No	Gilead Sciences, Inc. Boulder, CO	R2000044 (NA)
Rat/Sprague Dawley; GS-7340-02	Oral Gavage	7 days	0, 6.25, 25, 100, 400	No	Gilead Sciences, Inc. Boulder, CO	R000139 (NA)
Rat/(Crl:CD (SD) BR); GS-7340-02	Oral Gavage	4 weeks	0, 1.5[d], 6.25, 25, 100, 400	Yes	[redacted], Canada	R990182 ([redacted] 89176)
Rat/(Crl:CD (SD) BR); GS-7340-02	Oral Gavage	26 weeks	0, 5, 25, 100	Yes	[redacted], Canada	TOX-120-001 ([redacted] 89686)
Rabbit/NZW; GS-7340-02	Oral Gavage	7 days	0, 20, 50, 75	No	[redacted], Canada	TX-120-2003 ([redacted] 902246)
Dog/Beagle; GS-7340-02	Oral Gavage	4 weeks	0, 0.1, 0.3, 1[d], 3, 10	Yes	[redacted], Canada	D990175 [redacted] 89128)

Test Articles: FTC, RPV, TAF, TDF

Type of Study/Species/Strain	Method of Administration	Duration of Dosing	Dose (mg/kg)[a]	GLP[b]	Testing Facility	Study No. (CRO Study No.)
Dog/Beagle; GS-7340-02	Oral Gavage	39 weeks	0, 2, 6. 18/12	Yes	[redacted], Canada	TOX-120-002 ([redacted] 89647)
Monkey/cynomolgus; GS-7340-02	Nasogastric Gavage	4 weeks	0, 3, 30	Yes	[redacted]	P2000114 [redacted] 1050-11)
Repeat-Dose Toxicity of FTC/TDF						
Dog, Beagle	Oral Gavage	4 Weeks	FTC/TDF: 20/0, 0/30, 2/3, 20/30	Yes	[redacted] USA	TX-164-2004 (6511-155)
Genotoxicity of FTC						
In Vitro/*S. typhimurium* and *E. coli*	In Vitro	NA	100 to 5000 µg/plate	Yes	[redacted]	[redacted] 18637-0-409R
In Vitro/*S. typhimurium*	In Vitro	NA	6.67 - 5000 µg/plate	Yes	[redacted]	MUT203 (15437-0-401)
In Vitro/*S. typhimurium* and *E. coli*	In Vitro	NA	313 - 5000 µg/plate	Yes	[redacted] Japan	K01-3154
In Vitro/Mouse Lymphoma/L5178Y $TK^{+/-}$ Cells	In Vitro	NA	1000 to 5000 µg/mL	Yes	[redacted]	TOX012 [redacted]. 702)
In Vivo/Micronucleus/Mouse/ ICR	Oral Gavage	1 Day	0, 500, 1000, 2000	Yes	[redacted]	TOX011 ([redacted]. 123M)
Genotoxicity of RPV						
In vitro nonmammalian cell system	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA102	In vitro	**Base**: 0, 7.81, 15.63, 31.25, 62.50, 125, 250 and 500 µg/plate	Yes	J&J PRD	TMC278-Exp5540
Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA102	In vitro	—	**Base**: 0, 7.81, 15.63, 31.25, 62.50, 125, 250 and 500 µg/plate	Yes	J&J PRD	TMC278-Exp5693

Test Articles: FTC, RPV, TAF, TDF

Type of Study/Species/Strain	Method of Administration	Duration of Dosing	Dose (mg/kg)[a]	GLP[b]	Testing Facility	Study No. (CRO Study No.)
Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA102	In vitro	—	**Base**: 0, 3, 7.81, 10, 15.63, 25, 31.25, 50, 62.5, 100, 125, 200, 250, 400 and 500 µg/plate	Yes	J&J PRD	TMC278-NC279
Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA102	In vitro	—	**Hydrochloride salt**: 0, 3.91, 7.81, 15.63, 31.25, 62.5, 125, 250 and 500 µg/plate	Yes	J&J PRD	TMC278-NC335
Mouse Lymphoma cells L5178Y	In vitro	—	**Base**: 0, 0.5, 1, 2, 2.5, 4, 5, 6, 8, 10, 15, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 250, 500 µg/mL	Yes	J&J PRD	TMC278-Exp5539
Mouse Lymphoma cells L5178Y	In vitro	—	**Hydrochloride salt**: 0, 2.5, 5, 10, 12.5, 15, 20, 25, 30, 35, 40 and 50 µg/mL	Yes	[redacted]	TMC278-NC336
In Vivo micronucleus	Mouse, Albino Swiss	Oral/Gavage Single dose	**Base**: 0 (vehicle), 100, 400, 1600 (PEG400 + CA)	Yes	J&J PRD	TMC278-5538
Genotoxicity of TAF						
In Vitro/*S. typhimurium, E. coli:* GS-7340-02	In vitro	52h	100, 333, 1000, 3330, 5000 µg/plate	Yes	[redacted]	V990212 ([redacted] 20900-0-409OECD)

Test Articles: FTC, RPV, TAF, TDF

Type of Study/Species/Strain	Method of Administration	Duration of Dosing	Dose (mg/kg)[a]	GLP[b]	Testing Facility	Study No. (CRO Study No.)
In Vitro/L5178Y mouse lymphoma forward mutation assay/GS-7340-02	In vitro	24h	125 to 1500 µg/mL	Yes	[redacted]	V990213 ([redacted] 20900-0-431 ICH)
In Vivo/Micronucleus/ Mouse/Crl:CD-1 (ICR) BR; GS-7340-02	Oral Gavage	1 day	500, 1000, 2000	Yes	[redacted]	M2000113 ([redacted] 21816-0-455OECD)
Genotoxicity of FTC/TDF						
In Vitro/*S. typhimurium* and *E. coli*	In Vitro	NA	Fixed ratio of 2 parts FTC to 3 parts TDF up to 5000 µg/plate	Yes	[redacted]	TX-164-2002 [redacted]
In Vitro/Mouse Lymphoma/L5178Y $TK^{+/-}$ Cells	In Vitro	NA	Fixed ratio of 2 parts FTC to 3 parts TDF, 15 to 500 µg/mL	Yes	[redacted]	TX-164-2003 [redacted]
Carcinogenicity of FTC						
Mouse/CD-1 (ICR)	Oral Gavage	2 Years	0, 80, 250, 750	Yes	[redacted]	TOX109 (814-005)
Rat/CD (Sprague Dawley)	Oral Gavage	2 Years	0, 60, 200, 600	Yes	[redacted]	TOX108 (814-006)
Carcinogenicity of RPV						
Mouse, CD-1	Oral/Gavage	2 years	**Hydrochloride salt**: 0 (vehicle), 20, 60, 160 (0.5% HPMC)	Yes	[redacted]	TMC278-NC120
Rat, Sprague Dawley	Oral/Gavage	2 years	**Hydrochloride salt**: 0 (vehicle), 40, 200, 500, 1500 (0.5% HPMC)	Yes	[redacted]	TMC278-NC123

Test Articles: FTC, RPV, TAF, TDF

Type of Study/Species/Strain	Method of Administration	Duration of Dosing	Dose (mg/kg)[a]	GLP[b]	Testing Facility	Study No. (CRO Study No.)
Carcinogenicity of TDF						
Mouse/CD-1 (ICR)	Oral Gavage	2 Years	0, 100, 300 600	Yes	[redacted] Canada	M990205 (89284)
Rat/CD (Sprague Dawley)	Oral Gavage	2 Years	0, 30, 100, 300	Yes	[redacted] Canada	R990204 (89282)
Reproductive and Developmental Toxicity of FTC						
Fertility and Early Embryonic Development/Mouse/ CD-1	Oral Gavage	F: 2 wks to +6 days M: 4 wks to +6 wks	0, 250, 500, 1000	Yes	[redacted]	TOX036 ([redacted])
Fertility and Early Embryonic Development/Rat/CD Sprague-Dawley (males only)	Oral Gavage	M: 73 days + throughout mating	0, 150, 750, 3000	Yes	[redacted]	TOX679 (TTEP/95/0 028)
Embryo-fetal Development/ Mouse/CD-1	Oral Gavage	GD 6–15	0, 250, 500, 1000	Yes	[redacted]	TOX033 ([redacted] 345001)
Embryo-fetal Development\ Mouse/CD-1	Oral Gavage	GD 6–15	0, 250, 500, 1000	Yes	[redacted]	TOX037 ([redacted] 345003)
Embryo-fetal Development/ Rabbit/New Zealand White	Oral Gavage	GD 7–19	0, 250, 500, 1000	Yes	[redacted]	TOX034 ([redacted] 345002)
Embryo-fetal Development/ Rabbit/New Zealand White	Oral Gavage	GD 7–19	0, 100, 300, 1000	Yes	[redacted]	TOX038 ([redacted] 345004)
Pre-and Post-natal Development Including Maternal Function/ Mouse/CD-1	Oral Gavage	F_0 F dosed only from GD 6 to LD 20	0, 250, 500, 1000	Yes	[redacted]	TOX039 ([redacted])
Reproductive and Developmental Toxicity of RPV						

Test Articles: FTC, RPV, TAF, TDF

Type of Study/Species/Strain	Method of Administration	Duration of Dosing	Dose (mg/kg)[a]	GLP[b]	Testing Facility	Study No. (CRO Study No.)
Fertility and Early Embryonic Development/ Rat, Sprague Dawley	Oral/Gavage	10 weeks prior to mating and 4 weeks after the mating period	**Hydrochloride salt**: 0 (vehicle), 100, 400, 1600 (0.5% HPMC)	Yes	[redacted]	TMC278-NC124
Fertility and Early Embryonic Development/ Rat, Sprague Dawley	Oral/Gavage	2 weeks prior to pairing and up to day 7 of pregnancy	**Hydrochloride salt**: 0 (vehicle), 40, 120, 400 (0.5% HPMC)	Yes	J&J PRD	TMC278-NC125
Embryo-fetal Development/ Rat, Sprague Dawley	Oral/Gavage	GD6–17	**Base**: 0 (vehicle), 40, 120, 400 (PEG400 + CA)	No	J&J PRD	TMC278-NC127
Rat, Sprague Dawley	Oral/Gavage	GD6–17	**Base**: 0 (vehicle), 40, 120, 400 (PEG400 + CA)	Yes	J&J PRD	TMC278-NC105
Rabbit, New Zealand White	Oral/Gavage	GD6–19	**Base**: 0 (vehicle), 25, 75, 150 (0.5% HPMC)	No	J&J PRD	TMC278-NC128

Test Articles: FTC, RPV, TAF, TDF

Type of Study/Species/Strain	Method of Administration	Duration of Dosing	Dose (mg/kg)[a]	GLP[b]	Testing Facility	Study No. (CRO Study No.)
Embryo-fetal Development Rabbit, New Zealand White	Oral/Gavage	GD6–19	**Base**: 0 (vehicle), 5, 20, 60 (0.5% HPMC)	No	J&J PRD	TMC278-NC129
Rabbit, New Zealand White	Oral/Gavage	GD6–19	**Base**: 0 (vehicle), 5, 10, 20 (0.5% HPMC)	Yes	J&J PRD	TMC278-NC130
Prenatal & Postnatal Development and Juvenile Toxicity/Rat, Sprague Dawley	Oral/Gavage	GD6–LD7 (dams), Day 12 to Day 25 of age (pups)	**Hydrochloride salt**: 0 (vehicle), 40, 120, 400 (0.5% HPMC)	No	[redacted]	TMC278-NC168
Prenatal & Postnatal Development/ Rat, Sprague Dawley	Oral/Gavage	GD6–LD20	**Hydrochloride salt**: 0 (vehicle), 40, 120, 400 (0.5% HPMC)	Yes	[redacted]	TMC278-NC131
Reproductive and Developmental Toxicity of TDF						
Pre-& Post-natal Development/ Rat/Crl: CD (SD)	Oral Gavage	GD 7–LD 20 or GD 7–24	0, 50, 150, 450, 600	Yes	[redacted]	R990202 (707-016)
Reproductive and Developmental Toxicity of TAF						
Fertility/Rat, Crl:CD(SD)/GS-7340-03	Oral Gavage	M: 4 weeks premating, 10 weeks total F: 2 weeks premating - GD 13	0, 20, 80[h], 160[i] base eq	Yes	[redacted]	TX-120-2012 ([redacted] 8264528)
Dose Range Finding Embryo-Fetal Development/ Rat, Crl:CD(SD); GS-7340-02	Oral Gavage	GD 6-17	0, 5, 100[j], 200[k]	Yes	[redacted] Canada	TOX-120-001 ([redacted] 902244)

Test Articles: FTC, RPV, TAF, TDF

Type of Study/Species/Strain	Method of Administration	Duration of Dosing	Dose (mg/kg)[a]	GLP[b]	Testing Facility	Study No. (CRO Study No.)
Embryo-Fetal Development/ Rat, Crl:CD (SD); GS-7340-02	Oral Gavage	GD 6-17	0, 25, 100[jk], 250	Yes	[redacted] Canada	TX-120-2002 ([redacted] 902245)
Dose Range Finding Developmental DRF/Rabbit, Hra: (NZW) SPF; GS-7340-02	Oral Gavage	GD 7-20	0, 5, 25, 50[dj], 100[ch]	Yes	[redacted] Canada	TX-120-2004 ([redacted] 902247)
Embryo-Fetal Developmental/Rabbit, Hra: (NZW) SPF; GS-7340-02	Oral Gavage	GD 7-20	0, 10, 30[j], 100[dk]	Yes	[redacted] Canada	TX-120-2005 ([redacted] 902248)
Local Tolerance of RPV						
Bovine corneal opacity - permeability eye irritation test	Bovine corneas	In Vitro	**Hydrochloride salt**: 20% w/w in 0.9% NaCl (vehicle)	No	J&J PRD	TMC278-NC202
Phototoxicity	Balb/c mouse fibroblast	In vitro	**Hydrochloride salt**: 0.001 to 2.16 mg/L	No	J&J PRD	TMC278-NC188
Primary skin irritation	Rabbit, New Zealand White	Dermal application 4 hours	**Hydrochloride salt**: 0.5 g	No	[redacted]	TMC278-NC159
Local lymph node assay	Mouse, CBA/Ca/Ola/Hsd	Dermal application 3 days	**Hydrochloride salt**: 5, 10 and 35% in Acetone/Olive Oil (4:1)	No	[redacted]	TMC278-NC199
Local Tolerance of TAF						
In Vitro Tests/Bovine Corneal Opacity and Permeability Assay; (BCOP); GS-7340-03	Topical	4 hr	20% (w/w) in 0.9% sodium chloride solution	Yes	[redacted], UK	TX-120-2013 ([redacted], UK EUN0017)

Test Articles: FTC, RPV, TAF, TDF

Type of Study/Species/Strain	Method of Administration	Duration of Dosing	Dose (mg/kg)[a]	GLP[b]	Testing Facility	Study No. (CRO Study No.)
In Vivo Tests/Rabbit Dermal Irritation/Hra: (NZW)SPF; GS-7340-02	Topical	4 hr	0.5g/rabbit	Yes	[redacted]	TX-120-2011 ([redacted] 8253834)
Other Toxicity Studies with FTC						
Immunotoxicity/Rat/ Sprague Dawley	Oral Gavage	4 Weeks	0, 60, 240, 1000	Yes	[redacted]	TOX146 (503791)
Impurities/Mouse/CD-1	Oral Gavage	4 Weeks	50/1, 150/3 and 450/9	Yes	[redacted]	TOX153 ([redacted] 345018)
Impurities/Mouse/CD-1	Oral Gavage	4 Weeks	0, 50, 150, 450	Yes	[redacted]	TX-162-2001 ([redacted] 345019)
Other/Reverse Mutation/*S. typhimurium., E. coli*	In Vitro	NA	1.5 to 5000 µg/plate and 1% TP-0296, up to 50 µg/plate	Yes	[redacted]	TOX151 ([redacted])
Other/Chromosome Aberration, CHO (±S9)	In Vitro	NA	313 to 5000 µg/mL, 1% TP-0296	Yes	[redacted]	TOX152 ([redacted])
Other Studies with RPV						
Endocrinology						
In Vitro Guinea Pig Adrenal Cell Test for the evaluation of the cortisol biosynthesis	In vitro	—	**Base**: 10^{-9} to 10^{-5}M (0.00037 to 3.7 µg/mL)	No	J&J PRD	TMC278-EXP5653
A study on the effect of R278474 on the biosynthesis of cortisol in crude subcellular fractions of dog adrenal cortex	In vitro	—	**Base**: 0.03 to 75 µM (0.011 to 27.75 µg/mL)	No	J&J PRD	TMC278-FK4790

Test Articles: FTC, RPV, TAF, TDF

Type of Study/Species/Strain	Method of Administration	Duration of Dosing	Dose (mg/kg)[a]	GLP[b]	Testing Facility	Study No. (CRO Study No.)
Single Dose Oral Endocrinology Study in the Beagle Dog	Oral/Gavage	Single dose	**Base**: 0 (vehicle), 20, 80 (PEG400 + CA)	No	J&J PRD	TMC278-EXP5627
Impurities						
In vitro bacterial reverse mutation test with R314585 (TMC278.HCl) spiked with 4% 不純物A* (不純物A'*.HCl) in *Salmonella typhimurium/ Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA102	In vitro	—	**Hydrochloride salt**: 0, 3.91, 7.81, 15.63, 31.25, 62.5, 125 and 250 µg/plate spiked with 4% 不純物A*	Yes	J&J PRD	TMC278-NC308
In vitro bacterial reverse mutation test with R314585 (TMC278.HCl) spiked with 4% 不純物B* (不純物B'*.HCl) in *Salmonella typhimurium Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA102	In vitro	—	**Hydrochloride salt**: 0, 3.91, 7.81, 15.63, 31.25, 62.5, 125 and 250 µg/plate spiked with 4% 不純物B*	Yes	J&J PRD	TMC278-NC309
Mutation at the thymidine kinase (tk) locus of mouse lymphoma L5178Y (MLA) using the Microtitre fluctuation technique/Mouse Lymphoma cells L5178Y	In vitro	—	**Hydrochloride salt**: up to 75 µg/mL spiked with 4% 不純物A*	Yes	[redacted]	TMC278-NC311

Test Articles: FTC, RPV, TAF, TDF

Type of Study/Species/Strain	Method of Administration	Duration of Dosing	Dose (mg/kg)[a]	GLP[b]	Testing Facility	Study No. (CRO Study No.)
Mutation at the thymidine kinase (tk) locus of mouse lymphoma L5178Y cells (MLA) using the Microtitre fluctuation technique/Mouse Lymphoma cells L5178Y	In vitro	—	**Hydrochloride salt**: up to 75 µg/mL spiked with 4% 不純物B*	Yes	[redacted]	TMC278-NC312
1-Month Repeated Dose Oral Impurity Qualification Study for TMC278.HCL in the Sprague Dawley Rat	Oral/Gavage	1-month	**Hydrochloride salt**: 0 (vehicle), 10, 10 spiked with 4% 不純物A*, 10 spiked with 4% 不純物B* (0.5% HPMC)	Yes	J&J PRD	TMC278-NC314
In Vitro Bacterial Reverse Mutation Test with *Salmonella typhimurium/Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA102	In vitro	—	不純物H*: 0 (vehicle), 78.13, 156.25, 312.5, 625, 1250, 2500 and 5000 µg/plate	Yes	J&J PRD	TMC278-NC179
In Vitro Bacterial Reverse Mutation Test with *Salmonella typhimurium/ Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA102	In vitro	—	不純物H*: 0 (vehicle), 78.13, 156.25, 312.5, 625, 1250, 2500 and 500 µg/ plate	No	J&J PRD	TMC278-NC165

Test Articles: FTC, RPV, TAF, TDF

Type of Study/Species/Strain	Method of Administration	Duration of Dosing	Dose (mg/kg)[a]	GLP[b]	Testing Facility	Study No. (CRO Study No.)
In Vitro Bacterial Reverse Mutation Test with *Salmonella typhimurium*	In vitro	—	不純物H*: Exp 1 (2): 0 (vehicle), 78.13 (93.75), 156.25 (187.5), 312.5 (375), 625 (750), 1250 (1500), 2500 (3000) and 5000 µg/plate	Yes	J&J PRD	TMC278-1646_00164 51
Screening Chromosome Aberration Test in Human Lymphocyes In Vitro	In vitro	4 or 24 hours	不純物H*: 0, 65.22, 130.44, 260.88 and 521.75 µg/mL	No	[redacted]	TMC278-NC184
In Vitro Bacterial Reverse Mutation Test with *Salmonella typhimurium*	In vitro	—	不純物E*: Experiment 1 (2): 0 (vehicle), 78.13 (93.75), 156.25 (187.5), 312.5 (375), 625 (750), 1250 (1500), 2500 (3000) and 5000 µg/plate	Yes	J&J PRD	TMC278-1646_00152 98

Test Articles: FTC, RPV, TAF, TDF

Type of Study/Species/Strain	Method of Administration	Duration of Dosing	Dose (mg/kg)[a]	GLP[b]	Testing Facility	Study No. (CRO Study No.)
In Vitro Bacterial Reverse Mutation Test with *Salmonella typhimurium*	In vitro	—	不純物F*: Experiment 1 (2): 0 (vehicle), 78.13 (93.75), 156.25 (187.5), 312.5 (375), 625 (750), 1250 (1500), 2500 (3000) and 5000 µg/plate	Yes	J&J PRD	TMC278-1646_00152 99
Other Toxicity Studies with TAF						
LLNA/Mouse, CBA/Ca; GS-7340-03	Topical	3 days	10, 25, 50% (w/v)	Yes	[redacted] UK	TX-120-2014 ([redacted] UK EUN0018)
Impurity Qualification in Rat; GS-7340-02	Oral Gavage	2 weeks	0, 5, 50	Yes	[redacted]	TX-120-2008 ([redacted] 8246754)
Impurity Qualification in Rat; GS-7340-03	Oral Gavage	4 weeks	0, 25, 50	Yes	[redacted]	TX-120-2021 ([redacted] 8298810)
Bone Metabolism in Rat (Sprague Dawley); GS-7340-02	Oral Gavage	6 days	0, 400	No	Gilead Sciences Boulder, CO	R990177 (NA)
Bone Metabolism in Rat (Sprague Dawley); GS-7340-02	Oral Gavage	6 days	100, 400	No	Gilead Sciences Boulder, CO	R2000044 (NA)
Renal Effect in Rat (Sprague Dawley); GS-7340-02	Oral Gavage	1 day	0, 100, 1000	Yes	[redacted], Canada	R990186 ([redacted] 56520)
Bone marker Assessment Dog (Beagle); GS-7340-02	Oral gavage	5 days	37.5, 75	Yes	[redacted]	D990142 ([redacted] 9529.3)

Test Articles: FTC, RPV, TAF, TDF

Type of Study/Species/Strain	Method of Administration	Duration of Dosing	Dose (mg/kg)[a]	GLP[b]	Testing Facility	Study No. (CRO Study No.)
Other Toxicity Studies with FTC/TDF						
Impurities/Rat/SD	Oral Gavage	14 Days	TDF/FTC: 30/20, <u>100/67</u>, 300/200	Yes	[redacted] Canada	TX-164-2001 (800392)
Impurities/Rat/SD	Oral Gavage	14 Days	TDF/FTC: 0, 30/20, 100/67, 300/200, 30/20, 100/67, <u>300/200</u>	Yes	[redacted], Canada	TX-164-2005 (805427)

a Unless otherwise specified, the highest No-Observed-Adverse-Effect Level (NOAEL) is underlined.
b 'Yes', indicates study includes a GLP Compliance statement.
c NOAEL greater than
d NOEL
e Due to animal deaths in the high dose group at 300 mg/kg/day, the high dose animals were not dosed on Dosing Phase Day 2. Beginning on Dosing Phase Day 3, the high dose level was reduced to 200 mg/kg/day
f NOAEL: < 50 mg/kg/day COBI
g NOAEL could not be determined
h Male and female
i Early embryonic toxicity
j Maternal
k Embryo-fetal
l For both lots (# [redacted] and # [redacted]).
m GS-9350, Lot # [redacted].
n GS-9350, Lot # [redacted] (spiked with impurities)
o GS-9350/GS-9137 non-degraded crushed tablets, Lot # [redacted].
p GS-9350/GS-9137 degraded crushed tablets, Lot # [redacted].

JTK-303 = GS-9137, elvitegravir (EVG); GS-9350 = cobicistat (COBI); NA = not applicable; RTV = ritonavir; ATV = atazanavir; DRF = dose range-finding; GD = gestation day; LD = lactation day; PPD = post-partum day; PND = post natal day; w/w = weight/weight; w/v = weight/volume; CA = citric acid; SC = subcutaneous; IV = intravenous; F = female; M = male; GS-8374 = investigational HIV protease inhibitor; bid =twice daily; qd = every day; q2d = every two days; q7d = every 7 days

2. TOXICOKINETICS: OVERVIEW OF TOXICOKINETICS STUDIES

2.1. FTC

Test Article: FTC

Type of Study	Test System	Method of Administration	Dose (mg/kg)	GLP[a]	Gilead Study No.
4-Week Repeat Dose	Mouse	Oral Gavage	0, 120, 600, 3000	Yes	TOX599 Appendix 5
26-Week Repeat Dose	Mouse	Oral Gavage	0, 167, 500, 1500	Yes	TOX022 Addendum
26-Week Repeat Dose	Mouse	Oral Gavage	0, 120, 600, 3000	Yes	TOX628 Appendix F
Carcinogenicity	Mouse	Oral Gavage	0, 80, 250, 750	Yes	TOX109
13-Week Repeat Dose	Rat	Oral Gavage	0, 120, 600, 3000	Yes	TOX097 Appendix N
Carcinogenicity	Rat	Oral Gavage	0, 60, 200, 600	Yes	TOX108
4-Week Repeat Dose	Monkey	Oral Gavage	0, 80, 400, 2000	Yes	TOX600 Appendix 12
13-Week Repeat Dose	Monkey	Oral Gavage	0, 40, 200, 1000	Yes	TOX627 Appendix 14
52-Week Repeat Dose	Monkey	Oral Gavage	0, 50, 200, 500	Yes	TOX032 Appendix 6
Embryo/Fetal Development	Rabbits	Oral Gavage	0, 100, 300, 1000	Yes	TOX038

a Yes', indicates study includes a GLP Compliance statement.

2.2. RPV

Test Article: RPV

Type of Study	Test System	Method of Administration	Dose (mg/kg)	GLP[a]	Gilead Study No.
Single Dose Toxicity	Rat, Sprague Dawley	Oral/Gavage	Base: 800 (PEG400)	No	TMC278-EXP5559 (FK4278)
Single Dose Toxicity	Dog, Beagle	Oral/Gavage	Base: 40, 80 (PEG400) 80 (PEG400 + CA)	No	TMC278-EXP5461 (FK4102)
2-Week Repeat Dose Toxicity	Mouse, Albino Swiss	Oral/Gavage or diet	Hydrochloride salt: 0 (control diet), 40 (diet), 400 (diet), 5000 (diet), 400 (gavage), 2000 (gavage)	No	TMC278-NC118
1-Month Repeat Dose Toxicity	Mouse, CB6F1-nonTgrasH2	Oral/Gavage	Hydrochloride salt: 0 (vehicle), 20, 80, 320 (0.5% HPMC)	Yes	TMC278-NC121
3-Month Repeat Dose Toxicity	Mouse, Albino Swiss	Oral/Gavage	Hydrochloride salt: 0 (vehicle), 20, 80, 320 (0.5% HPMC)	Yes	TMC278-NC119
5-Day Repeat Dose Toxicity	Rat, Sprague Dawley	Oral/Gavage	Base: 0 (vehicle), 40, 400 (PEG400)	No	TMC278-EXP5463 (FK4103)
2-Week Repeat Dose Toxicity	Rat, Sprague Dawley	Oral/Gavage	Base: 0 (water), 0 (vehicle), 40, 120, 400 (PEG400 + CA)	Yes	TMC278-EXP5535 (FK4243)
2-Week Repeat Dose Toxicity	Rat, Sprague Dawley	Oral/Gavage	Hydrochloride salt: 0 (vehicle), 400, 1500, 2000 (0.5% HPMC)	No	TMC278-NC177
2-Week Repeat Dose Toxicity	Rat, Sprague Dawley	Oral/Gavage or diet	Hydrochloride salt: 0 (control diet), 400 (diet), 1200 (diet), 400 (gavage) Base: 400 (diet)	No	TMC278-NC136

Test Article: RPV

Type of Study	Test System	Method of Administration	Dose (mg/kg)	GLP[a]	Gilead Study No.
1-Month Repeat Dose Toxicity	Rat, Sprague Dawley	Oral/Gavage	Base: 0 (vehicle),10, 400 (PEG400 + CA) Hydrochloride salt: 0 (vehicle), 10, 400 (0.5% HPMC)	Yes	TMC278-NC117
1-Month Repeat Dose Toxicity and Immunotoxicity Evaluation	Rat, Sprague Dawley	Oral/Gavage	Base: 0 (water), 0 (vehicle),10, 40, 160 (PEG400 + CA))	Yes	TMC278-EXP5692
6-Month Repeat Dose Toxicity	Rat, Sprague Dawley	Oral/Gavage	Base: 0 (vehicle), 40, 120, 400 (PEG400 + CA)	Yes	TMC278-NC101
5-Day Repeat Dose Toxicity	Rabbit, New Zealand White	Oral/Gavage	Base: 0 (vehicle), 100, 300, 1000 (0.5% HPMC)	No	TMC278-NC126
7-Day Repeat Dose Toxicity	Dog, Beagle	Oral/Gavage	Base: 0 (water), 0 (vehicle), 20, 40,80 (PEG400 + CA)	Yes	TMC278-EXP5534 (FK4244)
1-Month Repeat Dose Toxicity	Dog, Beagle	Oral/Gavage	Base: 0 (water), 0 (vehicle), 5, 10, 40 (PEG400 + CA)	Yes	TMC278-EXP5650
1-Month Repeat Dose Toxicity	Dog, Beagle	Oral/Gavage	Base: 0 (vehicle), 5, 40 (PEG400 + CA) Hydrochloride salt: 0 (vehicle), 5, 40 (0.5% HPMC)	Yes	TMC278-NC116
6-Month Repeat Dose Toxicity	Dog, Beagle	Oral/Gavage	Base: 0 (vehicle), 5, 10, 40 (PEG400 + CA)	Yes	TMC278-NC115
12-Month Repeat Dose Toxicity	Dog, Beagle	Oral/Gavage	Base: 0 (vehicle), 5, 10, 40 (PEG400 + CA)	Yes	TMC278-NC107

Test Article: RPV

Type of Study	Test System	Method of Administration	Dose (mg/kg)	GLP[a]	Gilead Study No.
8-Week Repeat Dose Toxicity	Monkey, Cynomolgus	Oral/Gavage	Hydrochloride salt: 0 (vehicle), 200, 500 bid (1% HPMC + 0.5% polysorbate 20)	Yes	TMC278-NC248
Genotoxicity - In vivo (Micronucleus assay)	Mouse, Albino Swiss	Oral/Gavage	Base: 0 (vehicle), 100, 400, 1600 (PEG400 + CA)	Yes	TMC278-Exp5538 (FK4259)
Carcinogenicity	Mouse, CD-1	Oral/Gavage	Hydrochloride salt: 0 (vehicle), 20, 60, 160 (0.5% HPMC)	Yes	TMC278-NC120
Carcinogenicity	Rat, Sprague Dawley	Oral/Gavage	Hydrochloride salt: 0 (vehicle), 40, 200, 500, 1500 (0.5% HPMC)	Yes	TMC278-NC123
Developmental Toxicity	Rat, Sprague Dawley	Oral/Gavage	Base: 0 (vehicle), 40, 120, 400 (PEG400 + CA)	Yes	TMC278-NC105
Developmental Toxicity	Rabbit, New Zealand White	Oral/Gavage	Base: 0 (vehicle), 5, 10, 20 (0.5% HPMC)	Yes	TMC278-NC130
Per- and Post-natal Developmental study with Juvenile Exposure	Rat, Sprague Dawley	Oral/Gavage	Hydrochloride salt: 0 (vehicle), 40, 120, 400 (0.5% HPMC)	No	TMC278-NC168

CA = citric acid, GLP = Good Laboratory Practice, HPMC = hydroxylpropyl methylcellulose , PEG400 = polyethylene glycol 400

a unless otherwise stated

2.3. TAF

Test Article: TAF

Type of Study	Test System	Method of Administration	Dose (mg/kg) GS-7340-02	GLP[a]	Gilead Study No.
2-Week Repeat Dose	Mouse	Oral Gavage	0, 100, 500, 1000	No	TX-120-2006
13-Week Repeat Dose	Mouse	Oral Gavage	0, 10, 30, 100	Yes	TX-120-2007
4 -Week Repeat Dose	Rat	Oral Gavage	0, 1.5, 6.25, 25, 100, 400	Yes	R990182
26-Week Repeat Dose	Rat	Oral Gavage	0, 5, 25, 100	Yes	TOX-120-2001
4-Week Repeat Dose	Dog	Oral Gavage	0, 0.1, 0.3, 1, 3, 10	Yes	D990175
39-Week Repeat Dose	Dog	Oral Gavage	0, 2, 6, 18/12	Yes	TOX-120-002
4-Week Repeat Dose	Monkey	Oral Gavage	0, 3, 30	Yes	P2000114
Dose Range Finding Embryo/Fetal Development	Rat	Oral Gavage	0, 5, 100, 200	Yes	TX-120-2001
Embryo/Fetal Development	Rat	Oral Gavage	0, 25, 100, 250	Yes	TX-120-2002
7-Day Tolerability Study	Rabbit	Oral Gavage	0, 20, 50, 75	No	TX-120-2003
Dose Range Finding Embryo/Fetal Development	Rabbit	Oral Gavage	0, 5, 25, 50, 100	Yes	TX-120-2004
Embryo/Fetal Development	Rabbit	Oral Gavage	0, 10, 30, 100	Yes	TX-120-2005
Qualification of Impurities	Rat	Oral Gavage	0, 5, 50	Yes	TX-120-2008
Qualification of Impurities	Rat	Oral Gavage	0, 25, 50	Yes	TX-120-2021

a 'Yes' indicates study includes a GLP Compliance statement.

2.4. FTC/TDF

Test Article: FTC/TDF

Type of Study	Test System	Method of Administration	Dose (mg/kg)	GLP[a]	Gilead Study No.
4-Week Repeat Dose with FTC/TDF	Dog	Oral Gavage	20/0, 0/30, 2/3, 20/30	Yes	TX-164-2004

a 'Yes', indicates study includes a GLP Compliance statement.

3. TOXICOKINETICS: OVERVIEW OF TOXICOKINETICS DATA

3.1. FTC

Test Article: FTC

Steady State AUC (µg·h/mL)							
Species	**Mouse**		**Rat**		**Monkey**		**Rabbit**
Method of Administration	**Oral Gavage**		**Oral Gavage**		**Oral Gavage**		**Oral Gavage**
Gender (M/F)	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Female**
Dose (mg/kg/day)							
40					13.1[n], 12.2[o]	14.4[n], 13.4[o]	
50					16.1[p], 17.0[q], 18.1[r]	18.1[p], 22.9[q], 33.2[r]	
60			29.9[j], 42.9[k]	30.9[j], 52.5[k]			
80	25.5[f], 27.5[g]	27.6[f], 23.7[g]			37.1[l], 31.6[m]	37.8[l], 33.6[m]	
100							87.3[s]
120	169.7[e], 103[a], 78[b]	115.4[e], 74[a], 83[b]	61.6[h], 65.6[i]	55.6[h], 69.3[i]			
167	63.8[c], 82.3[d]	67.9[c], 93.1[d]					
200			97.3[j], 137[k]	156[j], 171[k]	64.8[n], 71.0[o], 74.9[p], 102.9[q], 97.2[r]	54.6[n], 51.9[o], 99.9[p], 119.9[q], 97.8[r]	
250	91.0[f], 90.9[g]	65.0[f], 91.78[g]					
300							315[s]
400					170[l], 196[m]	170[l], 164[m]	
500	181.4[c], 248.4[d]	209.6[c], 284.4[d]			265.5[p], 341.7[q], 274[r]	195.7[p], 321.1[q], 238[r]	
600	586[e], 499[a], 410[b]	491[e], 304[a], 326[b]	296[h], 329[i] 280[j], 327[k]	260[h], 362[i] 260[j], 404[k]			
750	235[f], 287[g]	209[f], 323[g]					
1000					403[n], 331[o]	274[n], 233[o]	1258[s]
1500	513[c], 732[d]	569[c], 899[d]					
2000					631[l], 730[m]	765[l], 732[m]	

Test Article: FTC

Steady State AUC (µg·h/mL)							
Species	**Mouse**		**Rat**		**Monkey**		**Rabbit**
Method of Administration	**Oral Gavage**		**Oral Gavage**		**Oral Gavage**		**Oral Gavage**
Gender (M/F)	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Female**
Dose (mg/kg/day)							
3000	2026[e], 1936[a] 1800[b]	1549[e], 1516[a] 1711[b]	1413[h], 1276[i]	1357[h], 1646[i]			

a TOX599 (Week 4) b TOX599 (Day 3) c TOX022 (Week 13) d TOX022 (Week 26) e TOX628 (Week 26) f TOX109 (Week 2)
g TOX109 (Week 26) h TOX097 (Day 2) i TOX097 (Day 90) j TOX108 (Week 2) k TOX108 (Week 26) l TOX600 (Day 3)
m TOX600 (Week 4) n TOX627 (Week 12) o TOX627 (Day 3) p TOX032 (Week 13) q TOX032 (Week 26), r TOX032 (Week 52)
s TOX038 (GD 19)

Note: In a combination study (FTC + TDF) in dogs, AUCs for FTC were 25.3 and 32.3 µg•h/mL, respectively, for 20 mg/kg/day FTC alone or in combination with 30 mg/kg/day TDF (TX-164-2004).

3.2. RPV

Test Article: RPV

C_{max} at steady state (µg/mL)											
Daily Dose(mg/kg/day)		Study Duration (days)	Mouse		Rat		Rabbit	Dog		Monkey
TM C278	Formulation		M	F	M	F	F	M	F	F
5	base [a]	363						1.1	1.5	
5 (pregnant)	base [b]	14 (GD19)					6.7			
10	base [a]	363						1.3	2.2	
10 (pregnant)	base [b]	14 (GD19)					10			
20	HCl [c]	Week 28	9.8	9.9						
20 (pregnant)	base [b]	14 (GD19)					15			
40	HCl [d]	Week 39			0.82	2.1				
40 (juvenile)	HCl [e]	14			2.6	5.8				
40	base [a]	363						4.1	5.5	
40 (pregnant)	base [f]	11 (GD16)				5.6				
40	base [g]	175			1.7	6.6				
60	HCl [c]	Week 28	22	29						
120 (juvenile)	HCl [e]	14			3.7	3.6				
120 (pregnant)	base [f]	11 (GD16)				7.2				
120	base [g]	175			3	8.8				
160	HCl [c]	Week 28	36	58						
200	HCl [d]	Week 39			1.3	4.7				
200	HCl [h]	55								0.18
400 (juvenile)	HCl [e]	14			9.1	7.3				
400 (juvenile)	HCl [e]	14			6.4	4.9				

Test Article: RPV

C_{max} at steady state (µg/mL)											
Daily Dose(mg/kg/day)		Study Duration (days)	Mouse		Rat		Rabbit	Dog		Monkey
TMC278	Formulation		M	F	M	F	F	M	F	F
400 (pregnant)	base [f]	11 (GD16)				13				
400	base [g]	175			6.2	16				
500	HCl [d]	Week 39			1.8	8.5				
500	HCl [h]	55								0.31
1500	HCl [d]	Week 39			2.2	9.4				

Only the long-term and main studies in mice, rats, rabbits and dogs and cynomolgus monkeys after oral administration of TMC278 are presented in this table. a: NC107; b: NC130; c: NC120; d: NC123; e: NC168; f: NC105; g: NC101 (doses were split and given twice daily with a 1.5-hour interval from Day 84 onwards); h: NC248 (500 mg/kg/day was given as 250 mg/kg/day twice daily with 6-hour interval).

GD = Gestation Day

Test Article: RPV

AUC_{0-24h} at steady state (µg·h/mL)

Daily Dose (mg/kg/day)		Study Duration (days)	Mouse		Rat		Rabbit	Dog		Monkey
TMC278	Formulation		M	F	M	F	F	M	F	F
5	base [a]	363						17	19	
5 (pregnant)	base [b]	14 (GD19)					105			
10	base [a]	363						24	36	
10 (pregnant)	base [b]	14 (GD19)					170			
20	HCl [c]	Week 28	76	51						
20 (pregnant)	base [b]	14 (GD19)					232			
40	HCl [d]	Week 39			6.3	14				
40 (juvenile)	HCl [e]	14			12	18				
40	base [a]	363						65	61	
40 (pregnant)	base [f]	11 (GD16)				37				
40	base [g]	175			12	50				
60	HCl [c]	Week 28	230	278						
120 (juvenile)	HCl [e]	14			34	28				
120 (pregnant)	base [f]	11 (GD16)				63				
120	base [g]	175			35	116				
160	HCl [c]	Week 28	505	766						
200	HCl [d]	Week 39			8.2	41				
200	HCl [h]	55								2.7
400 (juvenile)	HCl [e]	14			50	53				
400 (juvenile)	HCl [e]	14			43	39				
400 (pregnant)	base [f]	11 (GD16)				152				
400	base [g]	175			73	244				
500	HCl [d]	Week 39			14	46				
500	HCl [h]	55								4.6
1500	HCl [d]	Week 39			18	84				

Only the long-term and main studies in mice, rats, rabbits and dogs and cynomolgus monkeys after oral administration of TMC278 were presented in this table.

a: NC107; b: NC130; c: NC120; d: NC123; e: NC168; f: NC105; g: NC101 (doses were split and given twice daily with a 1.5-hour interval from Day 84 onwards); h: NC248 (500 mg/kg/day was given as 250 mg/kg/day twice daily with 6-hour interval).
GD = Gestation Day

3.3. TAF

Test Article: TAF

	Steady State Tenofovir (R-PMPA) AUC (µg•h/mL)							
Species	**Mouse**		**Rat**		**Rabbit**	**Dog**		**Monkey**
Method of Administration	**Oral Gavage**		**Oral Gavage**		**Oral Gavage**	**Oral Gavage**		**Oral Gavage**
Gender (M/F)	**M**	**F**	**M**	**F**	**F**	**M**	**F**	**M & F**
Dose (mg/kg/day)								
0.1						NC[e]	NC[e]	
0.15			0.05[c@]	0.06 [c@]				
0.3						NC[e]	NC[e]	
1						NC[e]	NC[e]	
2						1.30[f*]	1.07[f*]	
3						NC[e]	NC[e]	0.35[a*]
5			0.7 [d*] 0.02[k$] 0.07[k§]	0.7 [d*] 0.41[g]	1.6[i]			
6						3.89[f*]	5.01[f*]	
6.25			0.4 [c@]	0.3 [c@]				
10	0.19[b]	0.24[b]			2.0[j]	5.26[e*]	5.26[e*]	
18/12						14.90[*]	12.57[f*]	
20					2.3[l]			
25			2.5[c@] 3.8[d*] 2.4[n*∞] 3.0[n*∂] 2.6[n*ß]	2.8[c@] 3.8[d*] 2.8[h]	6.0[i]			
30	1.56[b]	1.45[b]			5.0[j]			5.87[a*]
50			2.0[k$] 2.5[k§] 6.8[n*∞] 6.0[n*∂] 6.0[n*ß]		11.8[i] 5.7[l]			
75					10.1[l]			
100	5.97[m] 7.80[b]	5.51[m] 6.55[b]	12.2[c@] 15.5[d*]	14.6 [c@] 15.5[d*] 20.6[g] 17.4[h]	23.5[i] 27.3[j]			
200				35.7 g				
250				55.7h				
270								
400			62.7 c@	75.1 c@				
500	27.2m	30.8m	500	27.2m				

a P2000114 (Day 28)
b TX-120-2007 (Week 13)
c R990182 (Day 28)
d TOX-120-001 (Week 26)
e D990175 (Day 28)
f TOX-120-002 (Week 39) *(dose reduced from 18 to 12 mg/kg/day on Days 45 and 51 for males and females, respectively)*
g TX-120-2001 (Day 17)

h TX-120-2002 (Day 17)
i TX-120-2004 (Day 20)
j TX-120-2005 (Day 20)
k TOX-120-2008 (Day 14)
l TOX-120-2003 (Day 7)
m TX-120-2006 (Day 14)
n TX-120-2021 (Day 28)

NA = not applicable; NC = not calculable; DR = dose reduced from 18 to 12 mg/kg/day on Days 45 and 51, for males and females respectively

Other than as indicated all AUC values are specified as AUC0-t; @ = AUC0-last; * = males and females combined; $ = 97.7% purity; § = 83.1% purity; ∞ = 99.3% purity;

∂ = 98.0% purity; ß = 987.9% purity

4. TOXICOLOGY: DRUG SUBSTANCE

4.1. FTC

Test Article: FTC

Lot No.	Purity (%)		Individual Impurities (%)				Total Impurities	Type of Toxicity Study
	[redacted] (TP-0274)	HPLC (w/w)	不純物FE*	不純物FF* (TP-0352)	不純物FG* (TP-0297)	Individual Unspecified Impurities		
SPECIFICATION	**≤ 1.5[a]**	**≥ 98.0 & ≤ 102.0**	**≤ 0.50**	**≤ 0.30**	**≤ 0.70**	**≤ 0.10**	**≤ 1.00**	
[redacted]	1.1[b]	97.7	NA[b]	NA[c]	NA[c]	NR	NR	Genetic[i]
[redacted]	2.0[b]	95.6[e]	ND	0.33	0.36	0.08% TP-0270; <0.05% TP-0296; <0.05% RRT 0.67; 0.05% RRT 1.21; 0.1% RRT 1.27; 0.05% RRT 1.77; <0.05% RRT 1.99; 0.05% RRT 2.27; 0.08% RRT 2.78; 0.08% RRT 3.25	1.19	Repeat Dose[j]

Test Article: FTC

Lot No.	Purity (%) [redacted] (TP-0270)	Purity (%) HPLC (w/w)	Individual Impurities (%) 不純物FE*	Individual Impurities (%) 不純物FF* (TP-0352)	Individual Impurities (%) 不純物FG* (TP-0297)	Individual Impurities (%) Individual Unspecified Impurities	Total Impurities	Type of Toxicity Study
SPECIFICATION	**≤ 1.5[a]**	**≥ 98.0 & ≤ 102.0**	**≤ 0.50**	**≤ 0.30**	**≤ 0.70**	**≤ 0.10**	**≤ 1.00**	
[redacted]	1.0[b]	93.0[e]	ND	ND	0.26	0.07% TP-0296; 0.09% RRT 0.52; 0.12% RRT 0.53; 0.10% RRT 0.54; 0.06% RRT 0.58; <0.05% RRT 0.59; 0.05% RRT 0.72; 0.10% RRT 0.74; 0.16% RRT 0.92; <0.05% RRT 0.93; 0.83% RRT 1.01; 0.13% RRT 1.06; 0.06% RRT 1.13; 0.09% RRT 1.45; 0.10% RRT 1.49; 0.05% RRT 1.51; 0.24% RRT 1.99; 0.19% RRT 2.27; 0.06% RRT 2.29; 0.07% RRT 2.39; 0.09% RRT 2.42; 0.09% RRT 2.47	3.04[e]	Repeat Dose[j]
[redacted]	1.0[b]	96.6	ND	ND	0.12	0.05% TP-0270; 0.07% TP-0296; <0.05% RRT 0.92; <0.05% RRT 0.97; <0.05% RRT 1.06; 0.13% RRT 1.27; <0.05% RRT 1.45; 0.13% RRT 1.51; <0.05% RRT 1.57; 0.07% RRT 2.27	0.57	Repeat Dose[j]

Test Article: FTC

Lot No.	Purity (%) [redacted] (TP-0270)	Purity (%) HPLC (w/w)	Individual Impurities (%) 不純物FE*	Individual Impurities (%) 不純物FF* (TP-0352)	Individual Impurities (%) 不純物FG* (TP-0297)	Individual Impurities (%) Individual Unspecified Impurities	Total Impurities	Type of Toxicity Study
SPECIFICATION	**≤ 1.5[a]**	**≥ 98.0 & ≤ 102.0**	**≤ 0.50**	**≤ 0.30**	**≤ 0.70**	**≤ 0.10**	**≤ 1.00**	
[redacted]	1.0[b]	97.3	ND	ND	0.43	<0.05% TP-0270; 0.05% TP-0296; 0.06% RRT 0.92; <0.05% RRT 0.97; <0.05% RRT 1.06; <0.05% RRT 1.27; <0.05% RRT 1.52; 0.06% RRT 2.27	0.60	Repeat Dose[j]
[redacted]	1.4[b]	94.3[e]	ND	ND	0.24	0.07% TP-0296; <0.05% RRT 0.51; 0.10% RRT 0.54; <0.05% RRT 0.72; 0.06% RRT 0.74; 0.16% RRT 0.92; <0.05% RRT 0.93; 0.96% RRT 1.02; 0.11% RRT 1.06; <0.05% RRT 1.45; 0.05% RRT 1.50; <0.05% RRT 1.51; 0.29% RRT 1.99; 0.14% RRT 2.27; 0.06% RRT 2.30; 0.09% RRT 2.42 <0.05% RRT 2.47	2.34[e]	Repeat Dose[k]

Test Article: FTC

Lot No.	Purity (%) [redacted] (TP-0274)	Purity (%) HPLC (w/w)	Individual Impurities (%) 不純物FE*	Individual Impurities (%) 不純物FF* (TP-0352)	Individual Impurities (%) 不純物FG* (TP-0297)	Individual Impurities (%) Individual Unspecified Impurities	Total Impurities	Type of Toxicity Study
SPECIFICATION	**≤ 1.5[a]**	**≥ 98.0 & ≤ 102.0**	**≤ 0.50**	**≤ 0.30**	**≤ 0.70**	**≤ 0.10**	**≤ 1.00**	
[redacted]	1.7[b]	92.9[e]	ND	ND	0.26	0.08% TP-0296; 0.09% RRT 0.52; 0.12% RRT 0.53; 0.10% RRT 0.54; 0.06% RRT 0.58; 0.05% RRT 0.59; 0.05% RRT 0.72; 0.11% RRT 0.74; 0.17% RRT 0.92; <0.05% RRT 0.93; 0.83% RRT 1.01; 0.14% RRT 1.06; 0.10% RRT 1.45; 0.10% RRT 1.50; 0.05% RRT 1.51; 0.25% RRT 1.99; 0.19% RRT 2.27; 0.06% RRT 2.29; 0.07% RRT 2.40; 0.10% RRT 2.42; 0.09% RRT 2.46	3.13[e]	Reproductive[l]
[redacted]	0.7[b]	98.1	NA[c]	NA[c]	0.2[f] (RRT 0.83)	0.1% RRT 0.58; 0.1% RRT 0.60; 0.1% RRT 1.17; 0.1% RRT 1.24; 0.2% RRT 1.27[g]; 0.1% RRT 1.63	0.9	Repeat Dose[m]
[redacted]	1.3[b]	95.2	ND	ND	0.21	0.07% RRT 2.00; 0.25% RRT 2.27[h]; 0.09% RRT 2.30; <0.05% RRT 2.42 <0.05% RRT 2.47	0.63	Repeat Dose[m]
[redacted]	1.4[b]	97.0	ND	ND	0.29	0.06% RRT 1.99; 0.07% RRT 2.27 0.06% RRT 2.42	0.48	Repeat Dose[m]

Test Article: FTC

Lot No.	Purity (%) [redacted] (TP-0274)	Purity (%) HPLC (w/w)	Individual Impurities (%) 不純物FE*	Individual Impurities (%) 不純物FF* (TP-0352)	Individual Impurities (%) 不純物FG* (TP-0297)	Individual Impurities (%) Individual Unspecified Impurities	Total Impurities	Type of Toxicity Study
SPECIFICATION	**≤ 1.5[a]**	**≥ 98.0 & ≤ 102.0**	**≤ 0.50**	**≤ 0.30**	**≤ 0.70**	**≤ 0.10**	**≤ 1.00**	
[redacted]	1.8[b]	97.1	ND	ND	0.41	<0.05% RRT 0.74; <0.05% RRT 1.45; 0.05% RRT 1.50; 0.07% RRT 1.52; 0.10% RRT 1.99; 0.15% RRT 2.27[c]; 0.06% RRT 2.30; <0.05% RRT 2.42 0.05% RRT 2.47	0.89	Repeat Dose[m]
[redacted]	1.1[b]	98.0	ND	ND	0.19	0.10% RRT 2.27; <0.05% RRT 2.30 <0.05% RRT 2.42	0.29	Reproductive[n]
[redacted]	0.5[b]	99.0	ND	ND	0.21	0.06% RRT 0.67; <0.05% RRT 1.45 <0.05% RRT 1.50	0.28	Repeat Dose[o]
[redacted]	0.7	99.6	ND	ND	0.07	Trace	0.1	Impurity Qualification[p]
[redacted]	0.3	99.5	ND	ND	0.1	0.1%	0.2	Immunotoxicity[q]
[redacted]	0.5	99.8	ND	ND	0.1	ND	0.1	Other Toxicity[r]
[redacted]	NT	87.0	0.35	0.07	ND	0.09% 5-FC; 0.15% 不純物FA*; 0.88% 不純物FI* ; 0.08% RRT 1.50	1.6	Impurity Qualification[s]
[redacted]	NT	100.0	ND	ND	0.1	0.1% RRT 1.445	0.2	Carcinogenicity[t]
[redacted]	0.3	99.5	ND	ND	0.1	0.1%	0.2	Carcinogenicity[t]
[redacted]	0.0	100.1	0.17	ND	ND	ND	0.2	Repeat Dose[u]
[redacted]	0.0	99.6	0.05	ND	ND	ND	0.1	Genetic[v]
[redacted]	0.0	99.7	0.10	ND	ND	ND	0.1	Genetic[w]
[redacted]	0.0	99.1	0.12	ND	ND	ND	0.1	Repeat Dose[u], Genetic[w]

a Specification has limit of NLT 98.5% 不純物FI*. In Canada, the specification in NMT 1.0%
b Chiral purity reported on Certificate of Analysis as %(-)FTC; value reported in table is [100% - (value reported on Certificate of Analysis)].
c Not a "Specified Impurity" at time of release testing

d Assay and chromatographic purity data generated during re-analysis using current analytical method; data will differ from Certificate of Analysis for this batch.
e Value is w/w percent from re-analysis; batch met AUC specification in place for this attribute at time of release.
f Drug product impurity at RRT ~ 0.84 is TP-0297 (FTC-不純物FG*) which is a drug substance manufacturing impurity, not a drug degradation product.
g Batch met Individual Unspecified Impurity Limit in place at time of release testing (NMT 0.50% for each).
h Batch met Individual Unspecified Impurity Limit in place at time of release testing (NMT 0.30% for each).
i Used for study number(s): TOX011; TOX012.
j Used for study number(s): TOX022.
k Used for study number(s): TOX022, TOX032.
l Used for study number(s): TOX036, TOX037, TOX033, TOX034, TOX038, TOX039, TOX022.
m Used for study number(s): TOX032.
n Used for study number(s): TOX038, TOX103.
o Used for study number(s): TOX097.
p Used for study number(s): TOX153.
q Used for study number(s): TOX146.
r Used for study number(s): TOX151, TOX152.
s Used for study number(s): TX-162-2001.
t Used for study number(s): TOX108, TOX109.
u Used for study number(s): TX-164-2004.
v Used for study number(s): TX-164-2002, TX-164-2003.
w Used for study number(s): K01-3154; Note: material was a mixture of lots [redacted] and [redacted]

NA = not applicable; NMT = not more than; ND = none detected (<0.05%); NR = not reported; NT = not tested; RRT = relative retention time

4.2. RPV

Test Article: RPV

Batch No.	Purity (%)	Specified Impurities (%)				Total Impurities	Study No.	Type of Study
		不純物C*	不純物A'*	不純物B'*	Individual Unspecified Impurities			
SPECIFICATION:	**≥ 98.0 & ≤ 102.0**	**≤ [redacted] %**	**≤ [redacted] %**	**≤ [redacted] %**	**≤ 0.10**	**≤ 1.0**		
[redacted]	/	/	/	/			TMC278-Exp5463	Five-Day Repeated Dose Oral Toxicity Study in the Rat.
							TMC278-Exp5461	Single Dose Escalation Oral Toxicity Study Followed by a 5-Day Repeated Dose Oral Toxicity Study in the Beagle Dog (tolerance study).
[redacted]	/	/	/	/			TMC278-Exp5461	Single Dose Escalation Oral Toxicity Study Followed by a 5-Day Repeated Dose Oral Toxicity Study in the Beagle Dog (tolerance study).
[redacted]	/	/	/	/			TMC278-Exp5627	Single Dose Oral Endocrinology Study in the Beagle Dog.

Test Article: RPV

Batch No.	Purity (%)	Specified Impurities (%)				Total Impurities	Study No.	Type of Study
		不純物C*	不純物A'*	不純物B'*	Individual Unspecified Impurities			
[redacted]	99.3	0.36	0.06	0.06			TMC278-NC136	2-Week Repeated Dose Oral Toxicity Study in the Rat.
							TMC278-NC117	1-Month Repeated Dose Oral Toxicity Study in the Rat.
							TMC278-NC116	1-Month Repeated Dose Oral Toxicity Study in the Beagle Dog.
							TMC278-NC101	6-Month Repeated Dose Oral Toxicity Study with 1-Month Recovery in the Rat.
							TMC278-NC115	6-Month Repeated Dose Oral Toxicity Study with 3-Month Interim Kill in the Beagle Dog.
							TMC278-NC126	5-Day Repeated Dose Oral Toxicity Study in the Female Rabbit.

Test Article: RPV

Batch No.	Purity (%)	Specified Impurities (%)				Total Impurities	Study No.	Type of Study
		不純物C*	不純物A'*	不純物B'*	Individual Unspecified Impurities			
							TMC278-NC127	Pilot Oral Developmental Toxicity Study in the Rat.
							TMC278-NC105	Oral Developmental Toxicity Study in the Rat.
							TMC278-NC128	Pilot Oral Developmental Toxicity Study in the Rabbit.
							TMC278-NC129	Pilot Oral Developmental Toxicity Study in the Rabbit.
							TMC278-NC130	Oral Developmental Toxicity Study in the Rabbit.
[redacted]	98.0	0.62	0.06	ND			TMC278-NC107	52-Week Oral (Gavage) Toxicity Study in the Beagle Dog.
[redacted]	98.2	0.21	0.20	0.31			TMC278-NC279	In Vitro Bacterial Reverse Mutation Test of TMC278 in *Salmonella typhimurium* with Human Liver S9-Mix.

ND = not detected or <0.05 w/w%; / = not determined; 不純物C* is the free base of 不純物C* (HCl salt); 不純物A'*= 不純物A'* is the free base of 不純物A* (HCl salt); 不純物B'*= 不純物B'* is the free base of 不純物B* (HCl salt)

Test Article: RPV

Batch No. / PROPOSED SPECIFICATION:	Purity (%)	Specified Impurities (%) 不純物C* ≤[redacted] %	不純物A'* ≤[redacted] %	不純物B'* ≤[redacted] %	Study No.	Type of Study
[redacted]	98.5	0.61	0.14	0.16	TMC278-Exp5693	In Vitro Bacterial Reverse Mutation Test with *Salmonella Typhimurium.*
					TMC278-Exp5692	4-Week Oral (gavage) Immunotoxicity Study in the Rat.
					TMC278-Exp5650	1-Month Repeated Dose Oral Toxicity Study in the Beagle Dog with 1-Month Recovery.
					TMC278-FK4790	A Study on the Effect of R278474 on the Biosynthesis of Cortisol in Crude Subcellular Fractions of Dog Adrenal Cortex.
[redacted]	96.8	1.4	1.56	ND	TMC278-Exp5535	2-Week repeated Dose Oral Toxicity Study in the Rat.
					TMC278-Exp5559	Single Dose Oral Toxicity Study in the Rat.
					TMC278-Exp5534	7-Day Repeated Dose Oral Toxicity Study in the Beagle Dog.
					TMC278-Exp5539	In Vitro Mammalian Forward Mutation Test with L5178Y Mouse Lymphoma Cells (TK-locus) using the Microtiter® Fluctuation Technique.
					TMC278-Exp5540	In Vitro Bacterial Reverse Mutation Test with *Salmonella Typhimurium*.
					TMC278-Exp5538	In Vivo Micronucleus Test on Bone Marrow Cells of Mice.
					TMC278-Exp5653	In Vitro Guinea Pig Adrenal Cell Test for the Evaluation of Cortisol Biosynthesis.

ND = not detected or <0.05 w/w%

Test Article: RPV

Batch No. / PROPOSED SPECIFICATION:	Purity (%)	Specified Impurities (%) 不純物C* ≤ [redacted] %	不純物A'* ≤ [redacted] %	不純物B'* ≤ [redacted] %	Study No.	Type of Study
[redacted]	100.3	0.37	0.09	0.05	TMC278-NC118	2-Week Repeated Dose Oral Toxicity Study in the Swiss Mouse.
					TMC278-NC136	2-Week Repeated Dose Oral Toxicity Study in the Rat.
					TMC278-NC177	2-Week Repeated Dose Oral Toxicity Study of R314585 in the Rat.
					TMC278-NC117	1-Month Repeated Dose Oral Toxicity Study in the Rat.
					TMC278-NC116	1-Month Repeated Dose Oral Toxicity Study in the Beagle Dog.
					TMC278-NC121	4-Week Toxicity Study by Oral Route (Gavage) in CB6F1-nonTgrasH2 mice.
					TMC278-NC119	3-Month Repeated Dose Oral Toxicity Study in the Mouse.
					TMC278-NC125	Oral Female Fertility Study in the Rat.
					TMC278-NC168	Oral (Gavage) Pre and Post-natal Developmental Toxicity and Juvenile Toxicity Dose Range Finding Study in the Rat.
					TMC278-NC124	Oral (Gavage) Male Fertility Study in the Rat.
[redacted]	97.8	0.27	ND	ND	TMC278-NC124	Oral (Gavage) Male Fertility Study in the Rat.
[redacted]	98.8	0.70	0.21	0.11	TMC278-NC131	Oral (Gavage) Pre and Post-Natal Developmental Toxicity Study in the Rat.
					TMC278-NC188	In Vitro Phototoxicity Testing of R314585 by the Neutral Red Uptake Assay Using Balb/c 3T3 Mouse Fibroblasts.
					TMC278-NC202	In Vitro Bovine Corneal Opacity-Permeability Eye Irritation Test.
					TMC278-NC199	Local Lymph Node Assay (LLNA).

ND = not detected or <0.05 w/w%

Test Article: RPV

Batch No. / PROPOSED SPECIFICATION:	Purity (%)	Specified Impurities (%) 不純物C* ≤ [redacted] %	不純物A'* ≤ [redacted] %	不純物B'* ≤ [redacted] %	Study No.	Type of Study
[redacted]	99.7	0.17	0.32	0.22	TMC278-NC159	Primary Skin Irritation Study in Rabbits (4-Hour Semi-Occlusive Application).
					TMC278-NC120	Carcinogenicity Study by Oral Gavage Administration to CD-1 Mice For 104 Weeks.
					TMC278-NC123	Carcinogenicity Study by Oral Gavage Administration to CD-Rats for 104 Weeks.
[redacted]	99.7	0.17	0.32	0.22	TMC278-NC159	Primary Skin Irritation Study in Rabbits (4-Hour Semi-Occlusive Application).
					TMC278-NC120	Carcinogenicity Study by Oral Gavage Administration to CD-1 Mice For 104 Weeks.
					TMC278-NC123	Carcinogenicity Study by Oral Gavage Administration to CD-Rats for 104 Weeks.

Test Article: RPV

Batch No. / PROPOSED SPECIFICATION:	Purity (%)	Specified Impurities (%) 不純物C* ≤ [redacted] %	不純物A'* ≤ [redacted] %	不純物B'* ≤ [redacted] %	Study No.	Type of Study
[redacted]	99.6	0.18	0.12	ND	TMC278-NC335	In Vitro Bacterial Reverse Mutation Test with R314585 (TMC278.HCl) in *Salmonella typhimurium*.
					TMC278-NC336	Mutation at the Thymidine Kinase (tk) Locus of Mouse Lymphoma L5178Y Cells (MLA) Using the Microtitre Fluctuation Technique.
					TMC278-NC311	Mutation at the Thymidine Kinase (tk) Locus of Mouse Lymphoma L5178Y (MLA) Using the Microtitre Fluctuation Technique.
					TMC278-NC309	In Vitro Bacterial Reverse Mutation Test with R314585 (TMC278.HCl) spiked with 4% 不純物B* (不純物B'*.HCl) in *Salmonella typhimurium*.
					TMC278-NC308	In Vitro Bacterial Reverse Mutation Test with R314585 (TMC278.HCl) spiked with 4% 不純物A* (不純物A'*.HCl) in *Salmonella typhimurium*.
					TMC278-NC314	1-Month Repeated Dose Oral Impurity Qualification Study for TMC278.HCl in the Rat
					TMC278-NC312	Mutation at the thymidine kinase (*tk*) locus of mouse lymphoma L5178Y cells (MLA) using the Microtitre^{R} fluctuation technique.
[redacted]	98.8	0.42	0.28	0.14	TMC278-NC120	Carcinogenicity Study by Oral Gavage Administration to CD-1 Mice For 104 Weeks.
					TMC278-NC123	Carcinogenicity Study by Oral Gavage Administration to CD rats for 104 weeks.
[redacted]	98.6	0.88	0.23	0.15	TMC278-NC120	Carcinogenicity Study by Oral Gavage Administration to CD-1 Mice For 104 Weeks.
					TMC278-NC123	Carcinogenicity Study by Oral Gavage Administration to CD Rats for 104 Weeks.
[redacted]	100.4	ND	0.13	0.05	TMC278-NC120	Carcinogenicity Study by Oral Gavage Administration to CD-1 Mice For 104 Weeks.

Test Article: RPV

Batch No. / PROPOSED SPECIFICATION:	Purity (%)	Specified Impurities (%) 不純物C* ≤[redacted]%	不純物A'* ≤[redacted]%	不純物B'* ≤[redacted]%	Study No.	Type of Study
					TMC278-NC123	Carcinogenicity Study by Oral Gavage Administration to CD Rats for 104 Weeks.
[redacted]	99.7	0.18	0.11	ND	TMC278-NC248	Endocrinological Oral (gavage) 8-Week Study in the Female Sexually Immature Cynomolgus Monkey.

ND = not detected or <0.05 w/w%

4.3. TAF

Batch No.	Purity* (%)	TAF Impurities (%)										Type of Study
		PMPA	不純物TA*	Monophenyl PMPA	不純物TB*	不純物TC*	不純物TD*	GS-7339	不純物TE*	不純物TF*#	不純物TG*	
Specification	[redacted]	≤ [redacted]	≤ [redacted]	≤ [redacted]	≤ [redacted]	≤ [redacted]	≤ [redacted]	≤ [redacted]	≤ [redacted]	≤ [redacted]	≤ [redacted]	
[redacted]	[redacted]	—	—	—	—	—	—	—	—	—	NT	a
[redacted]	[redacted]	—	—	—	—	—	—	[redacted]	—	—	NT	b
[redacted]	[redacted]	—	—	—	—	—	—	[redacted]	—	—	NT	c
[redacted]	[redacted]	—	—	—	—	—	—	[redacted]	—	—	NT	d
[redacted]	[redacted]	—	—	—	—	—	—	[redacted]	—	—	NT	e
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NT	f
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	g
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	—	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	h
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	i
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	—	—	[redacted]	[redacted]	—	[redacted]	j
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	—	[redacted]	—	—	NT	k

Batch No.	Purity (%)	Observed Impurities (%)												Type of Study
		PMPA	不純物TA*	Mono phenyl PMPA	不純物TB*	GS-695144 #	GS-695139 #	GS-645374 #	GS-645376 #	GS-648417 #	GS-648418 #	不純物TC*	GS-645380 #	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	—	—	[redacted]	[redacted]	—	—	[redacted]	—	k
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	—	—	[redacted]	[redacted]	[redacted]	[redacted]	k

Batch No.	Observed Impurities (%)													
	Phenol	GS-645502	GS-645503	GS-7339	GS-645504	GS-645506	GS-645505	GS-645507	GS-648419 #	GS-659142 Isomer 1 #	GS-659142 Isomer 2 #	# 不純物TF *	不純物TG *	Type of Study
[redacted]	[redacted]	—	—	[redacted]	—	—	—	—	[redacted]	[redacted]	[redacted]	—	[redacted]	k
[redacted]	—	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	—	—	—	—	[redacted]	k

* These two batches of drug substance were used to qualify known and/or potential impurities. They were prepared by spiking process impurities and therefore have a different impurity profile to other batches.

\# Not specified in 3.2.S.4.1

@ Coeluted with GS-645502

* These two batches of drug substance were used to qualify known and/or potential impurities. They were prepared by spiking process impurities and therefore have a different impurity profile to other batches.

—: < DL
Detection limit (DL) = [redacted]% for all impurities

Tr: trace < [redacted] (quantitation limit (QL) = [redacted]%) NT = not tested

a Used for study numbers V990212, V990213(Genetic toxicity)

b Used for study numbers R990133, R990185, D990181, R990139, R990182, D990142, D990175, R990177, R990186 (Single Dose; Repeat Dose; Other)

c Used for study number TOX-120-001 (Repeat Dose)

d Used for study number TOX-120-002 (Repeat Dose)

e Used for study numbers P2000114, R2000044, M2000113 (Repeat Dose; Genetic toxicity)

f Used for study numbers TX-120-2001, TX-120-2002, TX-120-2004, TX-120-2005, TX-120-2006, TX-120-2007, TX-120-2008, TX-120-2003 (Reprotox; Repeat Dose; Impurity Qualification)

g Used for study number TX-120-2011 (Local Tolerability)

h Used for study number TX-120-2008 (Impurity Qualification)

i Used for study number TX-120-2012 (Reprotox)

j Used for study numbers TX-120-2013, TX-120-2014 (Worker Safety)

k Used for study number TX-120-2021 (Impurity Qualification)

4.4. Ground FTC/TDF Tablets

Lot No.	% Purity (HPLC)		Impurity Content TDF (%)										Impurity Content FTC (%)						Type of Toxicity Study
	TDF	FTC	[redacted]	不純物XA*	不純物XB*	不純物XC*	不純物XD*	不純物XE*	不純物XF*	不純物XG*	不純物XH*	[redacted]	[redacted]	GS-9039	5-FC	GS-9237, 不純物FB*	GS-492127 不純物FC*	Unspecified Impurities	
SPECIFICATION	≥ 90.0% ≤ 105.0%	≥ 90.0% ≤ 105.0%	≤ 6.0%	% ≤	% ≤	% ≤	% ≤	% ≤	% ≤	% ≤	% ≤	% ≤ 0.20%	≤ 3.0%	% ≤	% ≤	% ≤	% ≤	≤ 0.20%.	
[redacted]	95.1	95.9	1.3	0.35			0.10					See below[b]	0.1		0.06			1.06	Impurity Qual.[c]
[redacted]	89.8	80.6	4.9	2.67	0.15	0.26	0.12	0.11	0.08	0.18	0.04	See below[a]	7.7	7.51	0.14	5.96	1.64	Dioxolane 0.04	Impurity Qual.[c]
[redacted]	99.8	101.5	0.7	0.56	tr							不純物XI* 0.11	0.1			0.07	tr		Impurity Qual.[d]
[redacted]	91.3	87.2	5.4	3.25	0.55	0.28	0.35	0.14	0.10	0.24	0.15	See below[e]	11.5	3.18	0.06	6.36	1.69	Trans-(+)-FTC 0.18	Impurity Qual.[d]

a 0.09% RRT 0.18; 0.05% RRT 0.35; 0.09% RRT 0.36; 0.05% RRT 0.45; 0.06% RRT 0.47; 0.06% 不純物XJ* ; 0.12% RRT 0.86; 0.11 不純物XK*; 0.06% RRT 1.21.
b 0.05 RRT 0.68; 0.11 不純物XK*; 0.04 RRT 1.21.
c Used for study number: TX-164-2001.
d Used for study number: TX-164-2005.
e 0.05% PMPA; 0.07% RRT 0.759; 0.10% 不純物XI* ; 0.05% 不純物XK*; 0.06% RRT 0.628
RRT = relative retention time; tr = trace (observed level < 0.05%)

5. TOXICOLOGY: SINGLE-DOSE TOXICITY

5.1. FTC

Test Article: FTC

Species / Strain	Method of Administration (Vehicle)	Dose (mg/kg)	Gender / No. per Group	NOAEL (mg/kg)	Noteworthy Findings	Gilead Study No.
Mice, Charles River CD-1	Oral Gavage	4000	5 M 5 F	4000	No clinical signs of toxicity were noted. No effects on body weight were noted. No gross pathology findings were noted.	TTEP/93/0020
Mice, Charles River CD-1	Intravenous	200	5 M 5 F	200	No clinical signs of toxicity were observed. No effects on body weight were noted. No gross pathology findings were noted.	TTEP/93/0023
Rat, Charles River CD	Oral Gavage	4000	5 M 5 F	4000	No clinical signs of toxicity were observed. No effects on body weight were noted. No gross pathology findings were noted.	TTEP/93/0021
Rat, Charles River CD	Intravenous	200	5 M 5 F	200	No clinical signs of toxicity were observed. No effects on body weight were noted. No gross pathology findings were noted. The approximate lethal dose in rats dosed intravenously was > 200 mg/kg.	TTEP/93/0024

NOAEL = No-Observed-Adverse-Effect Level; M = male; F = female

5.2. RPV

Test Article: RPV

Species/ Strain	Route/Method of Administration (Vehicle/ Formulation)	Batch no.	Doses (mg/kg)	Gender and No. per Group	NOAEL (mg/kg)	Noteworthy Findings	Study Number
Rat/Sprague Dawley	Oral/Gavage (PEG400)	[redacted]	800 mg/kg	2M + 2F 4M + 4F (TK)	ND	No mortality. Clinical signs: Salivation in all males and 2/6 females. C_{max} = 18 (F) and 8.0 (M) µg/mL and $AUC_{0-\infty}$ = 233 (F) and 86 (M) µg·h/mL.	TMC278-Exp5559
Dog/Beagle	Oral/Gavage (PEG400) or (PEG400 + CA)	[redacted]	SD: 40 mg/kg (PEG400), 80 mg/kg (PEG400) 80 mg/kg (PEG400 + CA) RD (5-day): 80 mg/kg/day (PEG400 + CA)	1M + 1F/group	ND	No mortality. SD/PEG 40 mg/kg: No effects C_{max} = 1.1 (M) and 0.95 (F) µg/mL and AUC_{0-24h} = 21 (M) and 19 (F) µg·h/mL. 80 mg/kg: Vomiting (1 and 2 days after dosing, male), soft feces (3 days after dosing (male) and 2 or 3 days after dosing (female)). C_{max} = 0.88 (M) and 0.81 (F) µg/mL and AUC_{0-24h} = 17 (M) and 16 (F) µg·h/mL SD/PEG +CA 80 mg/kg: No effects C_{max} = 2.1 (M) and 2.2 (F) µg/mL and AUC_{0-24h} = 42 (M) and 49 (F) µg·h/mL RD/PEG + CA 80 mg/kg: Salivation 4th day (male), vomiting 3rd day (male), gastrointestinal irritation. On day 5, C_{max} = 13 (M) and 8.0 (F) µg/mL and AUC_{0-24h} = 262 (M) and 154 (F) µg.h/mL.	TMC278-Exp5461

5.3. TAF

Test Article: TAF

Species / Strain	Method of Administration (Vehicle)	Duration of Dosing	Dose (mg/kg)	Gender and No. / Group	NOAEL (mg/kg)	Noteworthy Findings	Gilead Study No. (CRO Study No.)
Rat/Sprague-Dawley (Harlan)	Oral Gavage (50 mM citrate buffer)	1 day (with 13 day observation period)	0, 6.25, 25, 100, 400	4/sex/ group	100	Slight reductions in lymphocyte counts and significantly decreased (14%) absolute and relative liver weights were observed in females at 400 mg/kg. Histologic evaluation of tissues including lymphoid tissues and liver revealed no treatment related gross or microscopic findings.	R990133 (NA)
Rat/Sprague-Dawley (Crl)	Oral Gavage (25 mM citric acid)	1 day (with 14 day observation period)	0, 100, 300, 1000	5/sex/ group	1000	Salivation was noted immediately following dose administration in both males and females at all dose levels, with the exception of females at a dose of 100 mg/kg, and was most severe in animals treated at 1000 mg/kg. Slight reduction in BW gain was seen at 1000 mg/kg, although BW gain in these animals was comparable to the controls over Days 8 to 14 of the observation period.	R990185[a] ([redacted] 89186)

Test Article: TAF

Species / Strain	Method of Administration (Vehicle)	Duration of Dosing	Dose (mg/kg)	Gender and No. / Group	NOAEL (mg/kg)	Noteworthy Findings	Gilead Study No. (CRO Study No.)
Dog/Beagle	Oral Gavage (25 mM citric acid)	1 day (with 14 day observation)	0, 30, 90, 270	1/sex/ group	30 (NOEL)	Vomiting, retching and salivation observed at 270 mg/kg. This was more pronounced in the male that also showed signs of reduced activity, weakness, tremors and incoordination. Salivation was also noted at 90 mg/kg. BW was variable between groups, with the most marked loss seen in the 270 mg/kg male. FC was also variable with markedly lower consumption in the male at 270 mg/kg. An increase in BUN was also noted in the male treated at 270 mg/kg, and in females at 30, 90 and 270 mg/kg on Day 2. Differences were no longer apparent by Day 14. Increases in kidney and spleen weight relative to BW were noted for males at 30, 90 and 270 mg/kg, with an increase in relative spleen weight also observed in females at 30 or 270 mg/kg. Treatment-related renal tubular changes characterized by basophilia and karyomegaly were seen in the male and female at 270 mg/kg, and also the female at 90 mg/kg. Moderate atrophy of the	D990181[a] ([redacted] 89187)

a Indicates GLP compliant
NOEL = No-Observed-Effect Level; NOAEL = No-Observed-Adverse-Effect Level; M = male; F = female; NA = not applicable; BW = body weight; FC = food consumption; BUN = blood nitrogen urea

6. REPEAT DOSE TOXICITY (NONPIVOTAL STUDIES)

6.1. RPV

Species/Strain No. and Gender/Group	Route/Method of Administration (Vehicle/ Formulation)	Duration	Batch no.	Doses[a] (mg/kg)	NOAEL (mg/kg)	Noteworthy Findings	Study Number
Mouse/Swiss Main animals: 5M/5F Satellite animals: 3M/3F	Admixed to diet	2-week	[redacted]	0, 40, 400, 5000 mg/kg/day TMC 278.HCl	/	**40 mg/kg:** C_{max}: 8.9-8.3 µg/mL; AUC_{0-24h}:150-148 µg·h/mL (M-F) **400 mg/kg:** C_{max}: 57-63 µg/mL; AUC_{0-24h}: 1066-1320 µg·h/mL (M-F) ↓ BWG (M: 22%, F: 17%), ↑ FC (M: 46%, F: 39%), ↓ RBC (M: 8%), Hb (M: 7%), Hct (M: 8%), eosinophils (F: 48%), ↑ reticulocytes (M: 11%, F: 23%), ↑ bilirubin (M: 3-fold, F: 3-fold), ALP (M: 2-fold, F: 3-fold), AST (M: 1-fold, F: 3-fold), albumin (M: 13%), cholesterol (F: 22%), ↓ triglycerides (M: 50%, F: 73%). **5000 mg/kg**: All animals died.	TMC 278-NC118
	Oral gavage (0.5% w/v HPMC)			400, 2000 mg/kg/day TMC 278.HCl	/	**400 mg/kg:** ↓ BWG (M:13%, F: 29%), ↑ reticulocytes (M: 17%, F: 23%), ↑ bilirubin (F: 2-fold), ALP (M: 3-fold, F: 2-fold), ALT (M: 1-fold, F: 3-fold), AST (F: 2-fold), albumin (M: 22%), cholesterol (F: 48%), calcium (M: 8%, F: 5%), protein (M: 13%), urea (M: 19%, F: 40%), ↓ triglycerides (F: 63%). C_{max}: 63-94 µg/mL; AUC_{0-24h}: 687−123 µg·h/mL (M-F) **2000 mg/kg:** All animals died.	

a dose of HCl salt is presented as base equivalents; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BWG: body weight gain; F: female; FC: food consumption; Hb: hemoglobin; Hct: hematocrit. HPMC: hydroxypropyl methyl cellulose; M: male; RBC: Red blood cells; WBC: white blood cells; / = not determined.

Species/Strain No. and Gender/Group	Route/Method of Administration (Vehicle/ Formulation)	Duration	Batch no.	Doses[a] (mg/kg)	NOAEL (mg/kg)	Noteworthy Findings	Study Number
Mouse/CB6F1-nonTgrasH2 Main animals: 10M/10F Satellite animals: 15M/15F	Oral/gavage (0.5% w/v HPMC)	1-month	[redacted]	0, 20, 80, 320 mg/kg /day TMC278. HCl	/	**20 mg/kg:** Liver: hypertrophy, Uterus: atrophy C_{max}: 14-15 µg/mL; AUC_{0-24h}: 64-54 µg·h/mL (M-F) **80 mg/kg:** ↑ liver (M: 24%, F: 29%). Liver: hypertrophy, Kidney: degenerative/necrotic nephropathy. C_{max}: 30-37 µg/mL; AUC_{0-24h}: 250–240 µg·h/mL (M-F) **320 mg/kg**: 2 mortalities. ↓ BW and ↑ FC. ↓ RBC (M: 4%), Hb (M: 4%, F: 4%), Hct (F: 6%), reticulocytes (F: 56%), ↑ platelets (M: 14%, F: 24%), calcium (F: 72%), IP (F: 42%), bilirubin (F: 3-fold), urea (M: 72%, F: 58%), protein (M:9%, F: 18%), albumin (M: 17%), cholesterol (M: 46%, F: 110%), ALP (M: 3-fold,F: 2-fold). ↑ liver (M: 2-fold, F: 2-fold), kidney (F: 14%), spleen (F: 40%), ↓ ovaries (50%), thymus (F: 2!%). Liver: hypertrophy, Kidney: degenerative/necrotic nephropathy, Thymus: lymphoid depletion, Bone marrow: myeloid cell hyperplasia, Spleen: erythro/myelopoiesis, Uterus: atrophy. C_{max}: 66–69 µg/mL; AUC_{0-24h}: 1090–942 µg·h/mL (M-F)	TMC278-NC121[b]
Rat/Sprague Dawley 5M	Oral/gavage (PEG400)	5-day	[redacted]	0 (water), 0 (vehicle), 40, 400 mg/kg /day TMC278 base	40 (NOEL)	**40 mg/kg:** No effects C_{max}: 1.4 µg/mL; AUC_{0-24h}: 14 µg·h/mL **400 mg/kg**: ↑ potassium (7%), No histopathology changes C_{max}: 1.8 µg/mL; AUC_{0-24h}: 28 µg·h/mL	TMC278-TOX5463

a dose of HCl salt is presented as base equivalents; b: GLP compliant study; ALP: alkaline phosphatase; AUC_{0-24h} : area under the concentration vs time curve untill 24 hours after dosing; BW: body weight; C_{max}: maximum concentration; F: female; FC: food consumption; Hb: hemoglobin; Hct: hematocrit. HPMC: hydroxypropyl methyl cellulose; IP: inorganic phosphate; M: male; RBC: red blood cells; WBC: white blood cells; / = not determined

Species/Strain No. and Gender/Group	Route/Method of Administration (Vehicle/ Formulation)	Duration	Batch no.	Doses [a] (mg/kg)	NOAEL (mg/kg)	Noteworthy Findings	Study Number
Rat/Sprague Dawley Main groups: 5M/5F Satellite groups: 4M/4F	Oral/gavage (PEG400 + CA)	14-day	[redacted]	0 (water), 0 (vehicle), 40, 120, 400 mg/kg/day TMC278 base	/	**40 mg/kg:** ↓ T_4 (M: 10%, F: 32%). Thyroid: hypertrophy (M). C_{max} = 2.2-5.7 µg/mL (M-F). AUC_{0-24h} = 16-42 µg·h/mL (M-F) **120 mg/kg**: ↑TSH (M: 94%, F: 40%); ↓ T_4 (M: 27%, F: 50%). Thyroid: hypertrophy C_{max} = 3.6-7.8 µg/mL (M-F); AUC_{0-24h} = 35-88 µg·h/mL (M-F) **400 mg/kg**: ↑ protein (M: 3%); ↑ albumin (M: 7%). ↑TSH (M: 120%, F: 51%); ↓ T_4 (M: 29%, F: 66%). ↑ thyroid weight (36%, F). Thyroid: hypertrophy. C_{max} = 8.4-15 µg/mL (M-F); AUC_{0-24h} = 84-152 µg·h/mL (M-F)	TMC278-TOX5535 [b]

a dose of HCl salt is presented as base equivalents; b: GLP compliant study; ALT: alanine aminotransferase; AUC_{0-24h} : area under the concentration vs time curve till 24 h after dosing; CA: citric acid; C_{max}: maximum concentration; F: female; Hb: hemoglobin; Hct: hematocrit. HPMC: hydroxypropyl methyl cellulose, M: male; PEG400: polyethylene glycol 400; T_4: tetraiodothyronine/thyroxine; TSH: thyroid stimulating hormone; WBC: white blood cells; / = not determined.

Species/Strain No. and Gender/Group	Route/Method of Administration (Vehicle/ Formulation)	Duration	Batch no.	Doses [a] (mg/kg)	NOAEL (mg/kg)	Noteworthy Findings	Study Number
Rat/Sprague Dawley Main groups: 5M/5F Satellite groups:6 M/6F	Admixed to diet	14-day	[redacted] and [redacted]	0 (control diet), 400, 1200 mg/kg/day TMC278. HCl or 400 mg/kg/day TMC278 base	/	**400 mg/kg (TMC278.HCl-diet):** ↓WBC (F: 13%); ↑ ALT (M: 33%); ↑ thyroid weight (M: 20%, F: 54%). Thyroid: hypertrophy C_{max}: 5.2-7.2 µg/mL; $AUC_{0-24\ h}$= 82-137 µg·h/mL (M-F). **400 mg/kg (TMC278 base-diet):** ↓WBC (M: 18%, F: 23%); Hb (M: 6%); Hct (M: 6%); ↑ thyroid weight (M: 27%, F: 39%). Thyroid: hypertrophy C_{max}: 3.7-4.3 µg/mL; $AUC_{0-24\ h}$= 57-86 µg·h/mL (M-F) **1200 mg/kg (TMC278.HCl-diet):** ↓WBC (F: 9%); Hb (M: 6%); Hct (M: 6%); ↑ALT (M: 44%); ↑liver weight (M: 30%, F: 18%); ↑thyroid weight (M: 60%, F: 77%). Liver: hypertrophy, Thyroid: hypertrophy. C_{max}: 11-13 µg/mL; AUC_{0-24h} = 180-266 µg·h/mL (M-F)	TMC278-NC136
	Oral/Gavage (0.5% w/v HPMC)		[redacted]	400 mg/kg/day TMC278. HCl		**400 mg/kg (TMC278.HCl-gavage):** ↓WBC (F: 19%); ↓cholesterol (M: 29%); ↑ALT (M: 19%); ↑ thyroid weight (M: 33%, F: 39%). Thyroid: hypertrophy C_{max}: 7.3-12 µg/mL; AUC_{0-24h} = 51-103 µg·h/mL (M-F)	

a dose of HCl salt is presented as base equivalents; ALT: alanine aminotransferase; AUC_{0-24h} : area under the concentration vs time curve till 24 h after dosing; CA: citric acid; C_{max}: maximum concentration; F: female; Hb: hemoglobin; Hct: hematocrit. HPMC: hydroxypropyl methyl cellulose, M: male; PEG400: polyethylene glycol 400; T_4: tetraiodothyronine/thyroxine; TSH: thyroid stimulating hormone; WBC: white blood cells; / = not determined.

Species/Strain No. and Gender/Group	Route/Method of Administration (Vehicle/ Formulation)	Duration	Batch no.	Doses [a] (mg/kg)	NOAEL (mg/kg)	Noteworthy Findings	Study Number
Rat/Sprague Dawley Main groups: 5M/5F Satellite groups:3 M/3F	Oral/Gavage (0.5% w/v HPMC)	2-week	[redacted]	0 (vehicle), 400, 1500, 2000 mg/kg/day TMC278. HCl	/	**400 mg/kg:** ↑ thyroid weight (F: 42%). Thyroid: hypertrophy (F). C_{max} = 5.2-12 µg/mL (M-F); AUC_{0-24h}= 42-96 µg·h/mL (M-F) **1500 mg/kg:** ↑ APTT (M: 19%), PT (M: 20%); ↓ chloride (F: 3%); glucose (F: 18%); urea nitrogen (F: 33%); creatinine (F: 23%). ↑ thyroid weight (F: 62%). Thyroid: hypertrophy. C_{max} = 9.5-12 µg/mL (M-F); AUC_{0-24h}= 86-115 µg·h/mL (M-F) **2000 mg/kg:** ↑ APTT (M: 14%), PT (M: 15%); ↓ chloride (F: 3%); cholesterol (M: 30%); glucose (F: 14%). urea nitrogen (F: 33%); creatinine (F: 17%). ↑ thyroid weight (F: 55%). Thyroid: hypertrophy. C_{max} = 7.7-14 µg/mL (M-F); AUC_{0-24h}= 77-147 µg·h/mL (M-F)	TMC278-NC177

a dose of HCl salt is presented as base equivalents; ALT: alanine aminotransferase; APTT: activated partial thromboplastine time; AUC_{0-24h} : area under the concentration vs time curve till 24 h after dosing; C_{max}: maximum concentration; F: female; HPMC: hydroxypropyl methyl cellulose, M: male; PT: Prothrombin time; T_4: tetraiodothyronine/thyroxine; TSH: thyroid stimulating hormone; WBC: white blood cells; / = not determined.

Species/Strain No. and Gender/Group	Route/Method of Administration (Vehicle/ Formulation)	Duration	Batch no.	Doses[a] (mg/kg)	NOAEL (mg/kg)	Noteworthy Findings	Study Number
Rat/Sprague Dawley Main groups: 10M/10F Satellite groups:6 M/6F	Oral/gavage (PEG400 + CA)	1-month	[redacted]	0 (vehicle), 10, 400 mg/kg/day TMC278 base	/	**10 mg/kg:** Thyroid: hypertrophy. C_{max} = 0.74-1.4 µg/mL (M-F); AUC_{0-24h} = 5.4-8.6 µg·h/mL (M-F) **400 mg/kg:** ↓ Hct (3%); potassium (13%); chloride (F: 2%); cholesterol F: (22%); urea nitrogen (F: 15%); ↑ albumin (M: 7%); protein (M: 5%); ↑ TSH (M: 51%, F: 15%); T_3 (M: 57%); ↓ T_4.(M: 61%, F: 52%). ↑ liver weight (M: 24%, F: 15%); ↑ thyroid weight (F: 60%). Liver: hypertrophy, Thyroid: hypertrophy. C_{max} = 7.7-13 µg/mL (M-F); AUC_{0-24h} = 90-149 µg·h/mL (M-F)	TMC278-NC117[b]
	Oral/gavage (0.5% w/v HPMC)		[redacted]	0 (vehicle), 10, 400 mg/kg/day TMC278. HCl	/	**10 mg/kg:** Thyroid: hypertrophy C_{max} = 0.76-1.7 µg/mL (M-F); AUC_{0-24h}= 4.5-7.8 µg·h/mL (M-F) **400 mg/kg:** ↑ RBC (F: 4%); albumin (M: 5%); ↓ cholesterol (F: 10%); triglycerides (F: 35%); urea nitrogen (M: 18%, F: 11%); ↑ TSH (M: 49%, F: 38%), T_3 (M: 56%); ↓ T_4 (M: 37%, F: 44%); ↑ thyroid weight (F: 29%). Liver: hypertrophy, Thyroid: hypertrophy C_{max} = 4.8-9.0 µg/mL (M-F); AUC_{0-24h}= 33-86 µg·h/mL (M-F)	

a dose of HCl salt is presented as base equivalents; b: GLP compliant study; AUC_{0-24h} : area under the concentration vs time curve till 24 h after dosing; CA: citric acid; C_{max}: maximum concentration; F: female; Hct: hematocrit; HPMC: hydroxypropyl methyl cellulose; M: male; PEG400: polyethylene glycol 400; RBC: red blood cells; T_3: triiodothyronine; T_4: tetraiodothyronine, thyroxine; TSH: thyroid stimulating hormone; / = not determined.

Species/Strain No. and Gender/Group	Route/Method of Administration (Vehicle/ Formulation)	Duration	Batch no.	Doses (mg/kg)	NOAEL (mg/kg)	Noteworthy Findings	Study Number
Rabbit/Albino New Zealand White 5F/group	Oral/gavage (0.5% HPMC)	5-day	[redacted]	0 (vehicle), 100, 300, 1000 mg/kg/day TMC278 base	/	**100 mg/kg:** ↓ body weight (8%), food consumption (23%). C_{max}: 57.3 µg/mL; AUC_{0-24h}: 1120 µg·h/mL **300 mg/kg:** ↓ body weight (14%), food consumption (62%). ↓ reticulocytes (61%); ↑ creatinine (51%). C_{max}: 124 µg/mL; AUC_{0-24h}: 2695 µg·h/mL **1000 mg/kg:** ↓ body weight (22%), food consumption (92%). ↓ reticulocytes (78%); ↑ creatinine (63%). C_{max}: 138 µg/mL; AUC_{0-24h}: 2971 µg·h/mL	TMC278-NC126

AUC_{0-24h} : area under the concentration vs time curve till 24 h after dosing; C_{max}: maximum concentration; F: female; HPMC: hydroxypropyl methyl cellulose; / = not determined.

Species/Strain No. and Gender/Group	Route/Method of Administration (Vehicle/ Formulation)	Duration	Batch no.	Doses (mg/kg)	NOAEL (mg/kg)	Noteworthy Findings	Study Number
Dog/Beagle 4M/group	Oral/gavage PEG400 + CA	7-day	[redacted]	0 (water), 0 (vehicle), 20, 40, 80 mg/kg/day TMC278 base	/	**0 (water):** Vomiting, salivation, soft feces. **0 (vehicle):** Vomiting, salivation, soft feces. Focal congestion in the small intestine. **20 mg/kg:** Vomiting, salivation, soft feces. ↓ cortisol (44%); Small intestines: Focal congestion and mucosal hemorrhages. Adrenal glands: Multifocal inflammatory cell infiltration and multifocal vacuolated cells in the zona fasciculata C_{max}: 3.7 µg/mL; AUC_{0-24h}: 39 µg·h/mL **40 mg/kg:** Vomiting, salivation, soft feces. ↑ bilirubin (2-fold), glucose (7%) and cholesterol (17%); ↓ cortisol (72%); Small intestines: Focal congestion and mucosal hemorrhages. Adrenal glands: Multifocal inflammatory cell infiltration and multifocal vacuolated cells in the zona fasciculata. C_{max}: 7.7 µg/mL; AUC_{0-24h}: 159 µg·h/mL **80 mg/kg:** Vomiting, salivation, soft feces. ↑ glucose (10%), cholesterol (12%) and bilirubin (2-fold); ↓ cortisol (56%); Small intestines: Focal congestion and mucosal hemorrhages. Adrenal glands: Multifocal inflammatory cell infiltration and multifocal vacuolated cells in the zona fasciculata. C_{max}: 7.8 µg/mL; AUC_{0-24h}: 147 µg·h/mL	TMC278-TOX5534

AUC_{0-24h}: area under the concentration vs time curve till 24 h after dosing; CA: citric acid; C_{max}: maximum concentration; M: male; PEG400: polyethylene glycol 400; / = not determined.

Species/Strain No. and Gender/Group	Route/Method of Administration (Vehicle/ Formulation)	Duration	Batch no.	Doses (mg/kg)	NOAEL (mg/kg)	Noteworthy Findings	Study Number

Species/Strain No. and Gender/Group	Route/Method of Administration (Vehicle/ Formulation)	Duration	Batch no.	Doses (mg/kg)	NOAEL (mg/kg)	Noteworthy Findings	Study Number
Dog/Beagle 3M/3F	Oral/gavage (PEG400 + CA)	1-month	[redacted]	0 (vehicle), 5, 40 mg/kg/day TMC278 base	/	**5 mg/kg**: Uterus: increased glandular development. C_{max} = 1.4-1.1 µg/mL (M-F); AUC_{0-24h} = 23-14 µg·h/mL (M-F) **40 mg/kg**: ↓ RBC (F: 7%, F), Hct (M: 12%, F: 5%), reticulocytes (M: 61%). ↓ IP (F: 11%), triglycerides (M: 53%), ↑ bilirubin (M: 39%, F: 62%), ALP (M: 1-fold, F: 2-fold), ALT (M: 5-fold, F: 2-fold), γGT (M: 3-fold); ↑ ACTH (M: 77%, F: 92%), progesterone (M: 10-fold), 17α-OH-progesterone (M: 34-fold), ↓ cortisol (M: 47%, F: 34%); Liver: Centrilobular and periportal inflammation, brown pigmented macrophages, single cell death and oval cell proliferation, Adrenal glands: Swollen cells with densely	TMC278-NC116[a]

a GLP compliance; ACTH: adrenocorticotropic hormone; ALT: alanine aminotransferase, ALP: alkaline phosphatase; AUC_{0-24h} : area under the concentration vs time curve till 24 h after dosing; CA: citric acid; C_{max}: maximum concentration; F: female; γGT: gamma glutamyltransferase; Hct: hematocrit; IP: inorganic phosphate; M: male; PEG400: polyethylene glycol 400; RBC: red blood cell; / = not determined.

Species/Strain No. and Gender/Group	Route/Method of Administration (Vehicle/ Formulation)	Duration	Batch no.	Doses (mg/kg)	NOAEL (mg/kg)	Noteworthy Findings	Study Number
Dog/Beagle 3M/3F	Oral/gavage (0.5% w/v HPMC)	1-month	[redacted]	0 (vehicle), 5, 40 mg/kg/day TMC278.HCl	/	**5 mg/kg:** ↓ IP (F: 10%). Uterus: ↑ in glandular development C_{max} = 0.89-0.70 µg/mL (M-F); AUC_{0-24h} = 13-7.5 µg·h/mL (M-F) **40 mg/kg:** Hct (M: 15%, F: 7%), reticulocytes (M: 43%). ↓ IP (F: 8%), ↑ bilirubin (M: 17%, F:100%), ALP (M: 3-fold, F: 3-fold), AST (F: 1-fold), ALT (M: 1-fold, F: 6-fold), γGT (F: 6-fold), ↑ ACTH (M: 59%, F: 54%), cortisol (M: 54%), progesterone (M: 10-fold), 17α-OH-progesterone (M: 29-fold). Liver: Centrilobular and periportal inflammation, brown pigmented macrophages, single cell death and oval cell proliferation. Adrenal glands: Swollen cells with densely stained cytoplasm in zona reticularis and fasciculata and presence of foamy cells in the zona fasciculata. Ovaries: ↑ in cystic luteinized follicles or tertiary follicles. Uterus: ↑ in glandular development. Testes: Prominent Leydig cells. C_{max} = 4.1-5.8 µg/mL (M-F); AUC_{0-24h} = 76-81 µg·h/mL L (M-F)	TMC278-NC116[b]

a dose of HCl salt is presented as base equivalents; b: GLP compliant study; ACTH: adrenocorticotropic hormone; ALT: alanine aminotransferase, ALP: alkaline phosphatase; AST: aspartate aminotransferase; AUC_{0-24h} : area under the concentration vs time curve till 24 h after dosing; C_{max}: maximum concentration; F: female; γGT: gamma glutamyltransferase; Hct: hematocrit; HPMC: hydroxypropyl methyl cellulose; M: male; / = not determined.

6.2. TDF

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Gender and No. per Group	NOAEL[a] /NOEL[b] (mg/kg)	Noteworthy Findings	Study Number
Mouse, ICR CD-1	Oral gavage	13 days	0, 100, 300, 1000	5 M & 5 F	< 100 mg/kg[b]	Marked ↓ of platelet counts in 2/8 F at 1000 mg/kg. Dose-related ↑ in ALT activity; ↑ ALP activity and phosphorus concentration at 300 and 1000 mg/kg. Minimal ↑ in incidence of single cell necrosis and centrilobular hypertrophy in the liver and minimal renal proximal tubular epithelial karyomegaly in the 1000 mg/kg group.	M990191
Rat, Sprague Dawley	Oral gavage	5 days	0, 25, 100, 400	4 M	≥ 100 mg/kg < 400 mg/kg[b]	Slight ↓ in terminal (Day 8) mean body weights at 400 mg/kg.	96-TOX-4331-002
Dog, Beagle	Oral gavage	5 days	0, 9, 45, 180	2 M	9 mg/kg[b]	NOEL: 9 mg/kg/d Non-formed, mucoid, liquid or no feces, emesis, and ↓ body wgts and food consumption at 45 and 180 mg/kg/d. Mild to marked ↑ BUN and creatinine (45 mg/kg/d also), marked ↑ phosphorus and potassium, and marked ↓ calcium and chloride at 180 mg/kg/d. Renal tubular cell degeneration/regeneration and cell necrosis were noted at 45 and 180 mg/kg/d. Bone marrow hypocellularity, lymphocytic depletion of spleen, gut associated lymphoid tissues, and lymph nodes, and cryptal epithelial cell necrosis of small and large intestines were noted at 180 mg/kg/d.	96-TOX-4331-001

a No Observed Adverse Effect Level; b No Observed Effect Level

6.3. TAF

Test Article: TAF

Species / Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Dose (mg/kg/ day)	Gender and No. per Group	NOAEL (mg/kg/ day)	Noteworthy Findings	Gilead Study No. (CRO Name and Study No.)
Mouse/Crl:CD 1(ICR)	Oral Gavage (0.1% (v/v) Tween 20 and 0.1% (w/v) hydroxypropylmethylcellulose (HPMC) K100LV in reverse osmosis water)	2 weeks	0, 100, 500, 1000	10/sex/group	100	Early deaths occurred at 500 and 1000 mg/kg/day. Test article-related effects included minimal to moderate clinical pathology changes at 500 or 1000 mg/kg/day and anatomic pathology findings for all animals given GS-7340-02. NOAEL; 100 mg/kg/day	TX-120-2006 ([redacted] 8235665)

Test Article: TAF

Species / Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Dose (mg/kg/ day)	Gender and No. per Group	NOAEL (mg/kg/ day)	Noteworthy Findings	Gilead Study No. (CRO Name and Study No.)
Rat/Sprague-Dawley (Crl)	Oral Gavage (50 mM citric acid)	6 days	100, 400	8 males/group	NA	Reduced body weight gain at 400 mg/kg/day. Significant, dose-dependent reductions in 1,25-dihydroxyvitamin D3 and serum phosphate. Significant, nondose-dependent reductions in serum calcium were also observed. Urinary excretion of calcium was decreased on Day 1 for both treatment groups; however by Day 6, urinary excretion of calcium was increased ~ 213% at 400 mg/kg.	R2000044 (NA)

Test Article: TAF

Species / Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Dose (mg/kg/ day)	Gender and No. per Group	NOAEL (mg/kg/ day)	Noteworthy Findings	Gilead Study No. (CRO Name and Study No.)
Rat/Sprague Dawley	Oral Gavage	7 days	0, 6.25, 25, 100, 400	4/sex/group	NA	Significant effects at 400 mg/kg/day: decrease in: body weight gain, kidney weights WBC and splenic extramedullary hematopoiesis. Dose-dependent increase in PTH and a non-dose dependent reduction in 1,25-dihydroxycholecalciferol at all dose levels. The NOEL for this study was determined to be < 6.25 mg	R990139 (NA)
Rabbit/ NZW	Oral Gavage	7 days	0, 20, 50, 75	3 males/ group	75	Slight decrease in cumulative body weight gain at 50 and 75 mg/kg/day	TX-120-2003 (902246)

7. TOXICOLOGY: REPEAT-DOSE TOXICITY (PIVOTAL STUDIES)

7.1. FTC

7.1.1. 2-Week Oral Toxicity Study in Mice

Test Article: FTC

Report Title: 14-Day Oral (Gavage) Toxicity Study in Mice Given FTC		**Gilead Study No.: TOX001 ([redacted] 00701)**
Species/Strain: Mouse / Charles River CD-1	**Duration of Dosing:** 14 Days	
Initial Age: Approximately 3-4 Weeks Old	**Duration of Postdose:** 14 Days	**GLP Compliance:** Yes
Date of First Dose: [redacted] 19[redacted]	**Vehicle/Formulation:** 0.5% methylcellulose	**Lot No.:** [redacted]
No Observed Adverse-Effect Level: 3000 mg/kg	**Method of Administration:** Oral, divided doses spaced by approximately six hours	

Dose (mg/kg)	**0 (Vehicle)**		**120**		**600**		**3000**	
Number of Animals	**M: 15**	**F: 15**	**M: 15**	**F: 15**	**M: 15**	**F: 15**	**M: 15**	**F: 15**
Plasma Conc. 45 Min Post-Dose: (µg/mL; Mean ± SD) Day 2	NA	NA	12.2 ± 1.87	11.7 ± 1.39	62.7 ± 9.69	63.0 ± 2.83	318 ± 4.3	358 ± 108.2
Day 14	NA	NA	13.6 ± 3.37	14.7 ± 10.01	66.9 ± 2.48	55.4 ± 2.04	389 ± 85.4	405 ± 59.2
Noteworthy Findings								
Died or Sacrificed Moribund[a]	1	0	0	0	0	0	0	1
Clinical Observations	No treatment related findings.							
Body Weight (%)	No treatment related findings.							
Food consumption (%)	No treatment related findings.							
Ophthalmic Examinations	No treatment related findings.							
Hematology and Chemistry	No treatment related findings.							
Organ Weights (%)	No treatment related findings.							
Gross and Histopathology	No treatment related findings.							
Additional Examinations	Proof of Absorption – An additional 3 groups of 8 M/F mice received 120, 600, and 3000 mg/kg/day FTC, daily by oral gavage, split over two doses, for 2 or 14 days. Blood samples were obtained from 3 M/F from these groups approximately 45 minutes after the first dose on that day. An additional 5 M/F mice in groups 1-4 were used for a pre-study blood screen.							
Postdose Evaluation	5 M/F per group continued without dosing for 14 days to investigate recovery: No FTC-related findings were noted.							

a Two mice died during the study; both were considered to be a result of gavage error.
NA = not applicable

7.1.2. 4-Week Toxicity Study in Mice

Test Article: FTC

Report Title: A Thirty-Day Oral Toxicity Study in Mice Given 524W91		**Gilead Study No.:** TOX599
Species/Strain: Mouse / Charles River CD-1	**Duration of Dosing:** 30-32 Days	
Initial Age: Approximately 48 day males and 52 day females	**Duration of Postdose:** 13 Days	**GLP Compliance:** Yes
Date of First Dose: [redacted] 19[redacted]	**Method of Administration:** Oral	**Lot No.:** [redacted]
Special Features: Electron microscopy	**Vehicle/Formulation:** Vehicle control: 0.5% aqueous methylcellulose	

No Observed Adverse-Effect Level: 600 mg/kg

Dose (mg/kg)	**0 (Vehicle)**		**120**		**600**		**3000**	
Number of Animals	**M: 14**	**F: 14**	**M: 14**	**F: 14**	**M: 14**	**F: 14**	**M: 14**	**F: 14**
Toxicokinetics:								
C_{max} ss (µg/mL) Day 3	NA	NA	40.8	52.2	200	196	749	623
Day 32	NA	NA	52.2	38.8	219	211	742	675
AUCss µg·h/mL) Day 3	NA	NA	78.1	83.1	410	326	1800	1711
Day 32	NA	NA	103	73.9	499	304	1680	1320
Noteworthy Findings								
Died or Sacrificed Moribund[a]	0	0	0	1	0	0	4	2
Clinical Observations	No treatment related findings.							
Body Weight (%)	No treatment related findings.							
Food Consumption (%)	No treatment related findings.							
Ophthalmic Examinations	No treatment related findings.							
Hematology	The once-daily administration of 3000 mg/kg for 30–32 days resulted in decreased total erythrocyte count, hemoglobin, and hematocrit and increased mean corpuscular volume, mean corpuscular hemoglobin, and red cell distribution width. The no-effect level for hematological changes was 600 mg/kg/day.							

Test Article: FTC

Report Title: A Thirty-Day Oral Toxicity Study in Mice Given 524W91							**Gilead Study No.: TOX599**	
Dose (mg/kg)	**0 (Vehicle)**		**120**		**600**		**3000**	
Number of Animals	**M: 14**	**F: 14**	**M: 14**	**F: 14**	**M: 14**	**F: 14**	**M: 14**	**F: 14**
Hematocrit	-	-	-	-	-	-	-	D* t
Hemoglobin	-	-	-	-	-	-	-	D t
Total erythrocyte count	-	-	-	-	-	-	D*	D* t
Mean corpuscular volume	-	-	-	-	-	-	I*	I t
Mean corpuscular hemoglobin	-	-	-	-	-	-	I*	I* t
Red cell distribution width	-	-	-	-	-	-	I*	I* t
Serum Chemistry	No treatment related findings.							
Urinalysis	No treatment related findings.							
Organ Weights (%)	In females, mean relative organ weight (for pituitary, heart, spleen, ovary) increased at 3000 mg/kg/day. In males, mean relative spleen weight increased at 3000 mg/kg/day and decreased for testes and thymus at 3000 mg/kg/day. The weight changes were unaccompanied by any histopathological alterations.							
Changes in organ weights	-	-	-	-	-	-	D-Thymus	I-Pituitary
(no histopathological changes)	-	-	-	-	-	-	D-Testes	I-Heart
	-	-	-	-	-	-	I-Spleen	I-Ovary
	-	-	-	-	-	-	-	I-Spleen
Gross and Histopathology	No treatment related findings.							
Electron Microscopy	No drug related ultrastructural changes noted in heart and skeletal muscle sampled from 5 mice/sex/group and from 5 males and 5 females from the control and 3000 mg/kg/day groups.							
Postdose Evaluation:	Four mice/sex/group held 13 days for post-dose recovery.							

a Seven animals died, one animal in the 120 mg/kg/day group and 6 in the 3000 mg/kg/day group. Cause of death was either mis-dosing, or probable mis-dosing in 5 animals. The cause of death was undetermined in 2 high-dose mice (3000 mg/kg/day), and a relationship to drug treatment could not be ruled out.

NA = not applicable; D = decrease; I = increase; p = permanent; t = transitory; * = $p < 0.05$ or < 0.01

7.1.3. 26-Week Toxicity Study in Mice

Test Article: FTC

Report Title: Six Month Oral (Gavage) Toxicity Study in Mice Given FTC with a 3-Month Interim Sacrifice		**Gilead Study No. TOX022** ([redacted]01001)
Species/Strain: Mouse / Charles River CD-1	**Duration of Dosing:** 13 Weeks	
Initial Age: 4 – 5 Weeks	**Duration of Postdose:** 1 Month	**GLP Compliance:** Yes
Date of First Dose: [redacted] 19[redacted]	**Method of Administration:** Oral Gavage	**Lot No.:** [redacted]
No Observed Adverse-Effect Level: 500 mg/kg/day	**Vehicle/Formulation:** 0.5% aqueous methylcellulose	

Dose (mg/kg)	**0 (Vehicle)**		**167**		**500**		**1500**	
Number of Animals	**M: 30**	**F: 30**	**M: 30**	**F: 30**	**M: 30**	**F: 30**	**M: 30**	**F: 30**
Toxicokinetics:								
C_{max} (µg/mL) 3 months	NA	NA	44.0	37.2	128.0	88.8	225.0	187.1
6 months	NA	NA	41.7	48.6	87.3	111.7	310.9	306.0
AUC_{0-24} (µg·h/mL) 3 months	NA	NA	63.8	67.9	181.4	209.6	513.4	569.5
6 months	NA	NA	82.3	93.1	248.4	284.4	732.1	899.4
Noteworthy Findings								
Died or Sacrificed Moribund[a]	2	0	0	0	0	0	0	0
Clinical Observations	No treatment related findings.							
Body Weight (%)	No treatment related findings.							
Food consumption (%)	No treatment related findings.							
Ophthalmoscopy	No treatment related findings.							
Hematology	Mean corpuscular volume and mean cell hemoglobin showed a small increase at 1500 mg/kg/day at week 27. This was more notable in females and was still slightly elevated in females at the end of the recovery period.							
Serum Chemistry	No treatment related findings.							
Organ Weights (%)	No treatment related findings.							

Test Article: FTC

Report Title: Six Month Oral (Gavage) Toxicity Study in Mice Given FTC with a 3-Month Interim Sacrifice					**Gilead Study No. TOX022** ([redacted]01001)			
Dose (mg/kg)	**0 (Vehicle)**		**167**		**500**		**1500**	
Number of Animals	**M: 30**	**F: 30**	**M: 30**	**F: 30**	**M: 30**	**F: 30**	**M: 30**	**F: 30**
Gross Pathology	No treatment related findings.							
Histopathology	No treatment related findings.							
Postdose Evaluation	Changes in mean cell volume and hemoglobin still evident at end of recovery period.							

a There were 4 deaths during the study. One control male was sacrificed on Day 7 (had shown convulsions, piloerection, and unsteady gait on day 6; no notable findings at necropsy); and a further control male was killed on Day 128 for (animal was prostrate, subdued, had weight loss, and had lost the use of the hindlimbs; no notable findings at necropsy but at histopathological evaluation had evidence of a possible spinal injury). A group 6 male was found dead (following a convulsion and also showed weight loss) on day 85 and 1 group 7 male was found dead on day 25 (no clinical signs). Deaths were considered unrelated to FTC treatment.

NA = not applicable

7.1.4. 6-Month Oral Toxicity Study in Mice

Test Article: FTC

Report Title: A Six Month Oral Toxicity Study (With a Three Month Interim Sacrifice) in Mice Given 524W91		**Gilead Study No. TOX628**
Species/Strain: Mouse / Charles River CD-1	**Duration of Dosing:** 6 Months	
Initial Age: Approx. M: 62 days; **F:** 67 days	**Duration of Postdose:** 3 Weeks	**GLP Compliance:** Yes
Date of First Dose: [redacted] 19[redacted]	**Method of Administration:** Oral Gavage	
Special Features: Electron microscopy	**Vehicle/Formulation:** 0.5% aqueous methylcellulose	

No Observed Adverse-Effect Level: 600 mg/kg/day

Dose (mg/kg)	**0 (Vehicle)**		**120**		**600**		**3000**	
Number of Animals	**M: 25**	**F: 25**	**M: 25**	**F: 25**	**M: 25**	**F: 25**	**M: 25**	**F: 25**
Toxicokinetics:								
C_{max} (µg/mL)	NA	NA	69.0	44.8	152	188	635	503
AUC[a] (µg·h/mL)	NA	NA	170	115	586	491	2026	1549
Noteworthy Findings								
Died or Sacrificed Moribund[b]	1	0	0	0	0	0	1	1
Clinical Observations	No treatment related findings.							
Body Weight (%)	No treatment related findings.							
Food Consumption (%)	No treatment related findings.							
Ophthalmic Examinations	No treatment related findings.							
Hematology	Very slight and reversible changes in total erythrocyte count (RBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and red cell distribution width (RDW) relative to control values were observed in male and female mice given 3000 mg/kg/day. These changes were present after approximately 3 months of dosing and were no greater in severity after 6 months of dosing.							

Test Article: FTC

Report Title: A Six Month Oral Toxicity Study (With a Three Month Interim Sacrifice) in Mice Given 524W91							**Gilead Study No. TOX628**	
Dose (mg/kg)	**0 (Vehicle)**		**120**		**600**		**3000**	
Number of Animals	**M: 25**	**F: 25**	**M: 25**	**F: 25**	**M: 25**	**F: 25**	**M: 25**	**F: 25**
Total erythrocyte count	-	-	-	-	-	-	D t ns	D t ns
Mean corpuscular volume	-	-	-	-	-	-	I t ns	I t ns
Mean corpuscular hemoglobin	-	-	-	-	-	-	I t ns	I t ns
Red cell distribution width	-	-	-	-	-	-	I t ns	I t ns
Serum Chemistry	No treatment related findings.							
Urinalysis	A very slight reversible increase in urine quantity was noted on dose day 179 in male and female mice given 3000 mg/kg/day. However, no treatment-related microscopic changes were observed in the kidney to correlate with this finding.							
Organ Weights (%)	There was a reversible increase in absolute and relative thyroid weights in female mice given 3000 mg/kg/day. Values were within control ranges and there were no histological changes to correlate with this finding.							
Gross Pathology	No treatment related findings.							
Histopathology	No treatment related findings.							
Electron Microscopy	Liver, heart, and skeletal muscle (from terminal sacrifice control and high-dose mice; first 3/sex/group) – No treatment related changes.							
Postdose Evaluation	Findings were noted to be reversible during the recovery period.							

a Drug plasma concentrations were evaluated in 3 additional groups: 28 males, 28 females in each group. Three animals/group/sex were bled at 4 time points (0.5, 4, 12 and 24 hours) after dosing on days 175 and 176. Body weights and observations for clinical signs of toxicity were also evaluated in these animals.
C_{max} and AUC increased with dose. Females had statistically significantly lower ($p < 0.05$) plasma AUC values than did males at all dose levels.

b 6 animals died during the study. Based on the clinical signs, gross and/or histopathological findings, the deaths were considered unrelated to treatment. Two additional deaths occurred in the toxicokinetic groups. The cause of death was undetermined in these 2 males (120 mg/kg/day, 600 mg/kg/day) and the deaths were considered unrelated to treatment since no treatment-related deaths occurred at 3000 mg/kg/day in the toxicokinetic groups.

NA = not applicable; d = decrease; I = increase; p = permanent; t = transitory; ns = not significant

7.1.5. 3-Month Oral Toxicity Study in Rats

Test Article: FTC

Report Title: A 3-Month Oral Gavage Study for Bioassay Dose Selection in CD Rats		**Gilead Study No. TOX097**
Species/Strain: Rat / CD	**Duration of Dosing:** 90 Days	
Initial Age: Approximately 6 Weeks Old	**Duration of Postdose:** None	**GLP Compliance:** Yes
Date of First Dose: [redacted]	**Method of Administration:** Oral	**Lot No.:** [redacted]
No Observed Adverse-Effect Level: 600 mg/kg/day	**Vehicle/Formulation:** 0.5% aqueous methylcellulose	

Dose (mg/kg)	**0 (Vehicle)**		**120**		**600**		**3000**	
Number of Animals	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**	**M: 10**	**F: 10**
Toxicokinetics: C_{max} (µg/mL) Day 2	NA	NA	15.3	18.1	59.2	73.2	211	225
Day 90	NA	NA	17.5	21.0	77.9	120	222	323
AUC_{0-24} (µg·h/mL) Day 2	NA	NA	61.6	55.6	296	260	1413	1357
Day 90	NA	NA	65.6	69.3	329	362	1275	1646
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0
Clinical Observations	No treatment-related findings.							
Body Weight (%)	No treatment-related findings.							
Food Consumption (%)	No treatment-related findings.							
Hematology	Slightly decreased RBC counts and hemoglobin values were observed in both sexes at 3000 mg/kg/day, which reached statistical significance for females only.							
Serum Chemistry	No treatment-related findings.							
Urinalysis	No treatment-related findings.							
Organ Weights (%)	Pituitary and thyroid/parathyroid gland weights were decreased at 3000 mg/kg/day.							
Gross Pathology/Histopathology	No treatment-related findings.							

NA = not applicable; M = male; F = female

7.1.6. 1-Month Oral Toxicity Study in Monkeys

Test Article: FTC

Report Title: A 30-Day Oral Toxicity Study in Cynomolgus Monkeys Given 524W91		**Gilead Study No. TOX600**
Species/Strain: Monkey/Cynomolgus (Macaca fascicularis)	**Duration of Dosing:** At least 28 Days	
Initial Age: Approximately 2.5–7 year males and 6–17 year females	**Duration of Postdose:** 3 Weeks	**GLP Compliance:** Yes
Date of First Dose: [redacted] 19[redacted]	**Method of Administration:** Oral, divided doses spaced by approximately six hours	**Lot No.:** [redacted]
Vehicle/Formulation: 0.5% aqueous methylcellulose		
No Observed Adverse-Effect Level: 400 mg/kg/day	**Special Features:** Electron microscopy, CSF, Neurophysiology	

Dose (mg/kg)	**0 (Vehicle)**		**80**		**400**		**2000**	
Number of Animals	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**
Toxicokinetics:								
C_{max} (µg/mL) Day 3	NA	NA	14.6	15.8	58.3	66.0	194	204
Day 27	NA	NA	12.4	12.9	63.8	63.0	202	191
AUC^{a}_{0-6} (µg·h/mL) Day 3	NA	NA	37.1	37.8	170	170	631	765
Day 27	NA	NA	31.6	33.6	196	164	730	732
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0
Clinical Observations	Increased incidence of soft feces in females given 2000 mg/kg/day.							
Body Weight (%)	No treatment-related findings.							
Food Consumption (%)	No treatment-related findings.							
Ophthalmoscopy[b]	No treatment-related findings.							
Electrocardiography[c]	No treatment-related findings.							
Hematology/Serum Chemistry	No treatment-related findings.							
Urinalysis	No treatment-related findings.							
Organ Weights (%)[d]	No treatment-related findings.							
Gross Pathology Necropsy[d]	No treatment-related findings.							
Histopathology[d]	No treatment-related findings.							

Test Article: FTC

Report Title: A 30-Day Oral Toxicity Study in Cynomolgus Monkeys Given 524W91							**Gilead Study No. TOX600**	
Dose (mg/kg)	**0 (Vehicle)**		**80**		**400**		**2000**	
Number of Animals	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**
Additional Examinations								
Electronic microscopy[e]	Focal areas of "moth-eaten" mitochondria were seen in control (Group 1) cardiac muscle specimens. Moth-eaten mitochondria were also seen in cardiac muscle in the 2000 mg/kg/day group (Group 4) but some of the Group 4 samples exhibited normal mitochondria. Since no drug-related ultrastructural changes were seen in cardiac muscle in a 90 day study in monkeys given FTC, these mitochondrial findings were not considered to be drug-related. No drug-related electron microscopic changes were observed in skeletal muscle at any dose level.							
CSF concentration	4.3% of plasma levels for 80 mg/kg/day; 3.7% of plasma levels for 400 mg/kg/day; 3.7% of plasma levels for 2000 mg/kg/day groups. CSF levels increased as plasma levels increased.							
Neurophysiology	No treatment-related findings.							
Neuropathology	No treatment-related findings.							
Postdose Evaluation	No treatment-related findings.							

a Drug plasma concentrations – No gender-specific differences were noted in any of the pharmacokinetic parameters measured. Also, no significant differences in pharmacokinetic parameters were determined between Days 3 and Day 27. C_{max} and the AUC values increased in proportion to the dose. No significant drug accumulation occurred over the dosing period.
b Ophthalmic examination (pupillary dilation was achieved with 1% tropicamide ophthalmic solution and ketamine HCl for immobilization).
c Electrocardiography (unanesthetized monkeys).
d At the termination of dosing 3 monkeys/sex/group were sacrificed, examined grossly, selected organs were weighed, and tissues were taken for histopathological examination.
e Electronic microscopy – samples of skeletal and cardiac muscle from the control and 2000 mg/kg/day group were taken for ultrastructural examination.
NA = not analyzed

7.1.7. 3-Month Oral Toxicity Study in Monkeys

Test Article: FTC

Report Title: A 3-Month Oral Toxicity Study in Cynomolgus Monkeys Given 524W91		**Gilead Study No. TOX627** ([redacted] 309-229)
Species/Strain: Monkey/Cynomolgus (Macaca fascicularis)	**Duration of Dosing:** 3 Months	
Initial Age: Approximately 2–5.5 Years	**Duration of Postdose:** 3 Weeks	**GLP Compliance:** Yes
Date of First Dose: [redacted] 19[redacted]	**Method of Administration:** Oral, divided doses spaced by approximately six hours	**Lot No.:** [redacted]
Special Features: Electron microscopy, Neurophysiology		
No Observed Adverse-Effect Level: 1000 mg/kg/day	**Vehicle/Formulation:** Vehicle control: 0.5% aqueous methylcellulose	

Dose (mg/kg)	**0 (Vehicle)**		**40**		**200**		**1000**	
Number of Animals	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**
Toxicokinetics: C_{max} (µg/mL)								
Day 3	NA	NA	5.19	6.06	28.9	22.9	101	92.5
Day 87	NA	NA	5.27	5.96	26.0	23.1	117	94.4
AUC_{0-6} (µg·h/mL)[a]								
Day 3	NA	NA	12.2	13.4	71.0	51.9	331	233
Day 87	NA	NA	13.1	14.5	64.8	54.6	403	274
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0
Clinical Observations	No treatment-related findings.							
Body Weight (%)	No treatment-related findings.							
Food Consumption (%)	No treatment-related findings.							
Ophthalmic Examinations[b]	No treatment-related findings.							
Electrocardiography[c]	No treatment-related findings.							
Hematology/ Serum Chemistry	No treatment-related findings.							
Urinalysis	No treatment-related findings.							
Organ Weights (%)[d]	No treatment-related findings.							
Gross Pathology Necropsy[d]	No treatment-related findings.							

Test Article: FTC

Report Title: A 3-Month Oral Toxicity Study in Cynomolgus Monkeys Given 524W91					**Gilead Study No. TOX627** ([redacted] 309-229)			
Dose (mg/kg)	**0 (Vehicle)**		**40**		**200**		**1000**	
Number of Animals	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**
Histopathology[d]	No treatment-related findings.							
Additional Examinations								
Neurophysiology	No treatment-related findings.							
Neuropathology	No treatment-related findings.							
Electronmicroscopy[e]	No treatment-related findings.							
Postdose Evaluation	No treatment-related findings.							

a Drug plasma concentrations – C_{max} and AUC increased with the dose and there was no evidence of accumulation: Systemic exposure to FTC was similar between sexes and between days 3 and 87.
b Ophthalmic examination (pupillary dilation was achieved with 1% tropicamide ophthalmic solution and ketamine HCl for immobilization).
c Electrocardiography (unanesthetized monkeys)
d At the termination of dosing 3 monkeys/sex/group were sacrificed, examined grossly, selected organs were weighed and tissues were taken for histopathologic examination.
e Electronmicroscopy – samples of liver, skeletal and cardiac muscle for 3 monkeys/sex/group were taken for ultrastructural examination.
NA = not applicable

7.1.8. 52-Week Oral Toxicity Study in Monkeys

Test Article: FTC

Report Title: 52-Week Oral Toxicity Study of TP-0006 (FTC) in Cynomolgus Monkeys with a 4-Week Recovery Period		**Gilead Study No. TOX032** ([redacted] 6758-114)
Species/Strain: Monkey / Cynomolgus (Macaca fascicularis)	**Duration of Dosing:** 52 Weeks	
Initial Age: Approx. 3–7 Years	**Duration of Postdose:** 4 Weeks	**GLP Compliance:** Yes
Date of First Dose: [redacted] 19[redacted]	**Method of Administration:** Oral, divided doses spaced by approximately six hours	**Lot No.:** [redacted]
Vehicle/Formulation: 0.5% aqueous methylcellulose		
No Observed Adverse-Effect Level: 200 mg/kg/day	**Special Features:** Neurophysiology	

Dose (mg/kg)		**0 (Vehicle)**		**50**		**200**		**500**	
Number of Animals		**M: 8**	**F: 8**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 8**	**F: 8**
Toxicokinetics:									
C_{max} (µg/mL)	Week 13	NA	NA	3.7	2.9	11.1	16.9	41.5	26.9
	Week 26	NA	NA	3.7	4.8	15.6	24.8	51.2	39.3
	Week 52	NA	NA	4.3	7.3	17.4	21.3	50.6	37.6
AUC_{0-24} (µg·h/mL)[a]	Week 13	NA	NA	16.1	18.1	74.9	100	266	196
	Week 26	NA	NA	17.0	22.9	103	120	342	321
	Week 52	NA	NA	18.1	33.3	97.2	97.8	274	238

Test Article: FTC

Report Title: 52-Week Oral Toxicity Study of TP-0006 (FTC) in Cynomolgus Monkeys with a 4-Week Recovery Period					**Gilead Study No. TOX032** ([redacted] 6758-114)			
Dose (mg/kg)	**0 (Vehicle)**		**50**		**200**		**500**	
Number of Animals	**M: 8**	**F: 8**	**M: 4**	**F: 4**	**M: 4**	**F: 4**	**M: 8**	**F: 8**
Died or Sacrificed Moribund	0	0	0	0	0	0	0	0
Body Weight (%)	No treatment-related findings.							
Clinical Observations	No treatment-related findings.							
Ophthalmic Examinations	No treatment-related findings.							
Electrocardiography	No treatment-related findings.							
Hematology	Slightly decreased mean erythrocyte counts, increased mean corpuscular volume and increased mean corpuscular hemoglobin in females treated with 500 mg/kg/day.							
Serum Chemistry	The activity of alanine aminotransferase was increased in several individuals (including controls). No treatment related patterns were identified.							
Urinalysis	No treatment-related findings.							
Organ Weights (%)	No treatment-related findings.							
Gross Pathology Necropsy	No treatment-related findings.							
Histopathology	No treatment-related findings.							
Additional Examinations								
Neurophysiology	No treatment-related findings.							
Postdose Evaluation	No treatment-related findings.							

a FTC was rapidly and well absorbed with peak plasma concentrations occurring between 0.5 to 2 hours post dosing. Plasma half-life was 2–4 hours for all dose levels. Half-life may have been underestimated because of the short (6 hour) sampling period. A longer half-life was expected, based on the measurable pre-dose drug concentrations and the slightly higher plasma FTC concentrations after repeated dosing. No major differences in plasma FTC exposure between male and female monkeys. Plasma C_{max}, AUC_{0-6}, and estimated steady-state AUC_{0-24} (Weeks 13, 26, and 52) increased linearly over the dose range of 50 to 500 mg/kg/day.

7.2. RPV

7.2.1. Three-Month Repeated Dose Oral Toxicity Study in the Mouse

Test Article: RPV

Report Title: 3-Month Repeated Dose Oral Toxicity Study in the Mouse		**Study no.:** TMC278-NC119
Species/strain: Mouse/SPF Swiss	**Administration route/method:** Oral/gavage	
Age at first dose: 42 days	**Doses:** 0 (vehicle) 20, 80 and 320 mg base eq./kg/day TMC278.HCl	**GLP compliance:** Yes
Duration of dosing: 91 days	**Test article batch:** [redacted]	**Date of First Dose:** [redacted]
Duration of postdose: /	**Vehicle/formulation:** 0.5% w/v HPMC	
No Observed Adverse Effect Level: 20 mg base eq./kg/day		

Toxicokinetics:

Dose (mg base eq./kg/day)	**0 (vehicle)**		**20**		**80**		**320**	
No. of animals	**M:12**	**F:12**	**M:15**	**F:15**	**M:15**	**F:15**	**M:15**	**F:15**
Day 1								
C_{max} (µg/mL)	-	-	14	13	28	32	63	55
$AUC_{0-\infty}$ (µg·h/mL)	-	-	71	59	236	250	1010	707
Day 31								
C_{max} (µg/mL)	-	-	14	18	38	37	63	84
AUC_{0-24} (µg·h/mL)	-	-	61[b]	74	263	313	860	1170
Day 87								
C_{max} (µg/mL)	-	-	18	19	34	42	61	90
AUC_{0-24} (µg·h/mL)	-	-	80	61	210	313	665	1360

Test Article: RPV

Report Title: 3-Month Repeated Dose Oral Toxicity Study in the Mouse	**Study no.:** TMC278-NC119

Noteworthy Findings:

Dose (mg base eq./kg/day)	**0 (vehicle)**		**20**		**80**		**320**	
	M:10	**F:10**	**M:10**	**F:10**	**M:10**	**F:10**	**M:10**	**F:10**
Died or Sacrified Moribund	0	0	0	0	0	0	0	0
Body Weight[a]								
Week 13 / Day 91	35.3	29.1	-	-	-	-	1.110**	1.110**
Body Weight Gain[a]								
Week 13 / Day 91	6.6	6.2	-	-	-	-	1.545***	1.532**
Food Consumption[a]								
Total Food Consumption	473	489	-	-	1.131**	-	1.199***	1.223**
Clinical Observations								
Abdominal Distension	0	0	-	-	-	-	5*	7**
Waste of food	-	0	-	-	-	-	-	3

a At the end of dosing period. For vehicle, group means are shown. For treated groups, multiples of control/baseline are shown. Statistical significance is based on actual data (not on the multiples of control/baseline); - = No noteworthy findings; * - $p<0.05$, ** - $p<0.01$, *** - $p<0.001$.

b = $AUC_{0\text{-}24h}$ was more than 25% extrapoled; $AUC_{0\text{-}8h}$ = 61 µg.h/mL; HPMC: hydroxypropyl methylcellulose.

Test Article: RPV

Report Title: 3-Month Repeated Dose Oral Toxicity Study in the Mouse (continued)	**Study no.:** TMC278-NC119

Noteworthy Findings:

Dose (mg base eq./kg/day)	**0 (vehicle)**		**20**		**80**		**320**	
No. of animals	**M:10**	**F:10**	**M:10**	**F:10**	**M:10**	**F:10**	**M:10**	**F:10**
Hematology[a]								
White blood cells (10^3/µL)	7.6	-	-	-	-	-	0.526***	-
Red blood cells (10^6/µL)	9.54	9.54	-	-	-	-	0.917**	0.907**
Hemoglobin (g/dL)	14.2	14.5	-	-	-	-	0.923**	0.924**
Hematocrit (%)	46.3	47.3	-	-	-	-	0.940**	0.926***
Reticulocytes (10^3/µL)	-	256.1	-	-	-	-	-	1.369*
Thrombocytes (10^3/µL)	-	1387	-	-	-	-	-	0.882*
Neutrophils (10^3/µL)	1.28	-	-	-	-	-	0.695*	-
Lymphocytes (10^3/µL)	5.89	-	-	-	-	-	0.494***	-
Eosinophils (10^3/µL)	0.21	-	-	-	-	-	0.524*	-
Serum Chemistry[a]								
Calcium (mg/dL)	9.0	9.1	-	-	-	-	1.067*	1.077**
Inorg. Phosphate (mg/dL)	7.2	-	-	-	-	-	1.181**	-
Total protein (g/dL)	-	5.0	-	-	-	1.060*	-	1.140***
Albumin (g/dL)	3.4	3.6	-	-	-	1.083***	1.059*	1.111**
Cholesterol (mg/dL)	-	82	-	-	-	1.293*	-	1.415*
Triglycerides (mg/dL)	-	158	-	-	-	0.620*	-	0.386***
Urea nitrogen (mg/dL)	-	24.1	-	-	-	-	-	1.249**
Alk.phosphatase (U/L)	60	85	-	-	-	-	2.250***	2.976**
Alanine aminotransferase (U/L)	88	63	-	-	-	-	1.966	2.540***

a At the end of dosing period. For vehicle, group means are shown. For treated groups, multiples of control/baseline are shown. Statistical significance is based on actual data (not on the multiples of control/baseline); - = No noteworthy findings; * - p<0.05, ** - p<0.01, *** - p<0.001

Test Article: RPV

Report Title: 3-Month Repeated Dose Oral Toxicity Study in the Mouse (continued)	**Study no.:** TMC278-NC119

Noteworthy Findings:

Dose (mg base eq./kg/day)	**0 (vehicle)**		**20**		**80**		**320**	
No. of animals	**M:10**	**F:10**	**M:10**	**F:10**	**M:10**	**F:10**	**M:10**	**F:10**
Organ Weights[a,b]								
Liver (g)	1.81	1.37	-	-	1.204*	1.372**	2.066**	2.664**
Spleen (g)	-	0.103	-	-	-	-	-	1.666
Gross Pathology								
Kidneys	10	10	10	10	10	10	10	10
- Irregular surface	-	0	-	-	-	-	-	3
Liver	10	10	10	10	10	10	10	10
- Dark	0	0	-	-	-	4	10	10
- Swollen	0	0	-	-	-	-	10	10
Spleen	10	10	10	10	10	10	10	10
- Swollen	-	0	-	-	-	-	-	3
Histopathology								
Adrenal glands (n° examined)	10	10	10	10	10	10	10	10
Swollen/dense inner cortical cells	0	-	0	-	1	-	3	-
grade 1	0		0		1		3	
Prominent X-zone	-	5	-	4	-	1	-	0
grade 1		5		3		0		0
grade 2		0		1		1		0
Degeneration brown	-	4	-	5	-	5	-	6
grade 1		3		5		4		1
grade 2		1		0		1		5

a At the end of dosing period. For vehicle, group means are shown. For treated groups, multiples of control/baseline are shown. Statistical significance is based on actual data (not on the multiples of control/baseline); [b] = Both absolute and relative weights differed from controls in the direction indicated. Number indicates multiple of control for the absolute organ weights; - = No noteworthy findings; * - $p<0.05$, ** - $p<0.01$, *** - $p<0.001$

Test Article: RPV

Report Title: 3-Month Repeated Dose Oral Toxicity Study in the Mouse (continued)	**Study no.:** TMC278-NC119

Noteworthy Findings:

Dose (mg base eq./kg/day)	**0 (vehicle)**		**20**		**80**		**320**	
No. of animals	**M:10**	**F:10**	**M:10**	**F:10**	**M:10**	**F:10**	**M:10**	**F:10**
Histopathology (cont'd)								
Bone marrow, femur(n° examined)	10	10	10	10	10	10	10	10
Increased M/E ratio	0	0	0	0	0	0	1	4
grade 1	0	0	0	0	0	0	1	2
grade 2	0	0	0	0	0	0	0	1
grade 3	0	0	0	0	0	0	0	1
Cellularity	-	10	-	10	-	10	-	10
grade 2		1		1		0		0
grade 3		8		9		10		6
grade 4		1		0		0		3
grade 5		0		0		0		1
Bone marrow, sternum (n° examined)	10	10	10	10	10	10	10	10
Cellularity	-	10	-	10	-	10	-	10
grade 3		9		9		9		8
grade 4		1		1		1		1
grade 5								1
Increased M/E ratio	0	0	0	0	0	0	5	4
grade 1	0	0	0	0	0	0	5	2
grade 2	0	0	0	0	0	0	0	1
grade 4	0	0	0	0	0	0	0	1

- = No noteworthy findings.

Test Article: RPV

Report Title: 3-Month Repeated Dose Oral Toxicity Study in the Mouse (continued)	**Study no.:** TMC278-NC119

Noteworthy Findings:

Dose (mg base eq./kg/day)	**0 (vehicle)**		**20**		**80**		**320**	
No. of animals	**M:10**	**F:10**	**M:10**	**F:10**	**M:10**	**F:10**	**M:10**	**F:10**
Histopathology (cont'd)								
Kidneys (n° examined)	10	10	-	10	-	10	10	10
Nephropathy	-	0	-	0	-	0	-	5
grade 1								2
grade 2								2
grade 3								1
Glomerulopathy	-	0	-	1	-	0	-	5
grade 1		0		1		0		3
grade 2		0		0		0		2
Inflammation capsule/adjacent tissue	-	0	-	1	-	0	-	3
grade 1		0		1		0		2
grade 2		0		0		0		1
Inflammation exudative	-	0	-	0	-	0	-	1
grade 3		0		0		0		1
Inflammation granulocytic	-	0	-	0	-	0	-	2
grade 1		0		0		0		2
Fibrosis	-	0	-	0	-	0	-	4
grade 1		0		0		0		3
grade 2		0		0		0		1
Single cell death	-	0	-	0	-	0	-	2
grade 1		0		0		0		2
Dilatation tubule	-	0	-	0	-	0	-	3
grade 1		0		0		0		3
Infiltration mononuclear cell	-	3	-	4	-	4	-	7
grade 1		3		3		4		3
grade 2		0		1		0		3
grade 3		0		0		0		1
Basophilia tubule(s)	-	4	-	7	-	3	-	9
grade 1		4		6		3		4
grade 2		0		1		0		1
grade 3		0		0		0		3
grade 4		0		0		0		1

- = No noteworthy findings.

Test Article: RPV

Report Title: 3-Month Repeated Dose Oral Toxicity Study in the Mouse (continued)	**Study no.:** TMC278-NC119

Noteworthy Findings:

Dose (mg base eq./kg/day)	**0 (vehicle)**		**20**		**80**		**320**	
No. of animals	**M:10**	**F:10**	**M:10**	**F:10**	**M:10**	**F:10**	**M:10**	**F:10**
Histopathology (cont'd)								
Liver (n° examined)	10	10	10	10	10	10	10	10
Vacuolization hepatocellular	0	0	0	0	0	0	2	5
grade 1	0	0	0	0	0	0	2	3
grade 2	0	0	0	0	0	0	0	2
Pigmentation Kupffer cells	0	0	0	0	0	1	3	7
grade 1	0	0	0	0	0	1	3	4
grade 2	0	0	0	0	0	0	0	3
Extramedullary hematopoiesis	-	0	-	0	-	0	-	2
grade 1		0		0		0		1
grade 2		0		0		0		1
Necrosis, single cell	3	0	3	2	2	1	9	7
grade 1	3	0	3	2	2	1	8	7
grade 2	0	0	0	0	0	0	1	0
Hypertrophy hepatocellular	4	0	2	1	8	7	10	10
grade 1	4	0	2	1	8	7	0	1
grade 2	0	0	0	0	0	0	6	6
grade 3	0	0	0	0	0	0	4	3
Kupffer cell proliferation	-	0	-	0	-	0	-	3
grade 1		0		0		0		3
Ovaries (n° examined)		10		10		10		10
CL generations		10		10		10		9
grade 1		0		0		0		2
grade 2		3		4		3		2
grade 3		7		6		7		5
CL eosinophilic		10		10		10		7
grade 1		3		2		1		0
grade 2		2		2		1		3
grade 3		0		2		1		1
grade 4		1		1		2		1
grade 5		4		3		5		2

- = No noteworthy findings.

Test Article: RPV

Report Title: 3-Month Repeated Dose Oral Toxicity Study in the Mouse (continued)	**Study no.:** TMC278-NC119

Noteworthy Findings:

Dose (mg base eq./kg/day)	**0 (vehicle)**		**20**		**80**		**320**	
No. of animals	**M:10**	**F:10**	**M:10**	**F:10**	**M:10**	**F:10**	**M:10**	**F:10**
Histopathology (cont'd)								
CL basophilic		10		10		8		6
grade 1		9		10		7		6
grade 2		1		0		1		0
Spleen (n° examined)	10	10	10	10	10	10	10	10
Extramedullary hematopoiesis	1	4	2	3	3	6	7	9
grade 1	1	3	2	3	3	4	5	3
grade 2	0	1	0	0	0	2	2	5
grade 3	0	0	0	0	0	0	0	1
Thymus (n° examined)		10		10		10		10
Involution	-	1	-	2	-	0	-	3
grade 1		1		2		0		2
grade 2		0		0		0		0
grade 3		0		0		0		1
Uterus (n° examined)		10		10		10		10
Infiltration granulocytic		9		10		9		6
grade 1		6		8		8		3
grade 2		3		2		1		3
Electronmicroscopy								
Liver (n° examined)	2	1					3	2
Increase of number of single membrane-bound organelles indicative of peroxisomes	0	0					2	2

- = No noteworthy findings.

7.2.2. One-Month Repeated Dose Oral Toxicity Study in the Rat

Test Article: RPV

Species/strain: Rat / Sprague Dawley	**Administration route/method:** Oral/gavage	
Age at first dose: approximately 6 weeks	**Doses:** 0 (water), 0 (vehicle), 10, 40 and 160 mg/kg/day TMC278 base.	**Study no.:** TMC278-EXP5692 **GLP compliance:** Yes
Duration of dosing: 4 weeks	**Test article batch:** [redacted]	**Date of first dose:** [redacted]
Duration of postdose: 0 days	**Vehicle/formulation:** PEG400 + CA	

No Observed Adverse Effect Level: 10 mg/kg/day

Toxicokinetics:

Dose (mg/kg/day)	**0 (water)**		**0 (vehicle)**		**10**		**40**		**160**	
No. of animals	**M:0**	**F:0**	**M:0**	**F:0**	**M:4**	**F:4**	**M:4**	**F:4**	**M:4**	**F:4**
Day 1										
C_{max} (µg/mL)	-	-	-	-	0.94	2.0	2.0	3.2	6.5	9.6
$AUC_{0-\infty}$ (µg·h/mL)	-	-	-	-	7.5	14	23	30	52	77
Day 29										
C_{max} (µg/mL)	-	-	-	-	0.88	1.6	2.6	5.8	6.7	8.8
AUC_{0-24h} (µg·h/mL)	-	-	-	-	7.2	14	27	42	51	89

Noteworthy Findings

Dose (mg/kg/day)	**0 (water)**		**0 (vehicle)**		**10**		**40**		**160**	
No. of animals	**M:10**	**F:10**	**M:10**	**F:10**	**M:10**	**F:10**	**M:10**	**F:10**	**M:10**	**F:10**
Died or Sacrified Moribund	0	0	0	0	0	0	0	0	0	0
Body Weight	-	-	-	-	-	-	-	-	-	-
Body Weight Gain	-	-	-	-	-	-	-	-	-	-
Food Consumption	-	-	-	-	-	-	-	-	-	-
Clinical Observations	-	-	-	-	-	-	-	-	-	-
Ophthalmoscopy	-	-	-	-	-	-	-	-	-	-

- = No noteworthy findings; PEG400: polyethylene glycol; CA: citric acid.

Test Article: RPV

Report Title: TMC278-TOX5692: One-Month Repeated Dose Oral Toxicity Study in the Rat (continued)

Noteworthy Findings

Dose (mg/kg/day)	**0 (water)**		**0 (vehicle)**		**10**		**40**		**160**	
No. of animals	**M:10**	**F:10**	**M:10**	**F:10**	**M:10**	**F:10**	**M:10**	**F:10**	**M:10**	**F:10**
Hematology	-	-	-	-	-	-	-	-	-	-
Serum analysis[a]										
Glucose (g/dL)	-	0.96	-	0.88	-	-	-	-	-	0.898***
Urinalysis	-	-	-	-	-	-	-	-	-	-
Organ weights (absolute)[a]										
Liver (g)	12.08	7.16	10.87	7.30	-	-	1.149	1.105*	1.233	1.119*
Thyroid (g)	0.021	0.020	0.017	0.016	-	-	1.249	1.236	1.235	1.224
Pituitary gland (g)	0.011	0.014	0.010	0.013	-	-	1.074	-	1.162	1.136
Histopathology[a]										
Thyroid										
Follicular hypertrophy	0	0	0	0	0	0	2	0	6	4
No. of animals	**M:8**	**F:8**	**M:8**	**F:8**	**M:8**	**F:8**	**M:8**	**F:8**	**M:8**	**F:8**
PFC assay	-	-	-	-	-	-	-	-	-	-

a For vehicle, group means are shown. For treated groups, multiples of vehicles are shown. Statistical significance is based on actual data (not on the multiples of control/baseline). - = No noteworthy findings; * - $p<0.05$, *** - $p<0.001$; PFC: plaque forming cell.

7.2.3. Six-Month Repeated Dose Oral Toxicity Study with 1-Month Recovery in the Rat

Test Article: RPV

Species/strain: Rat / Sprague Dawley	**Administration route/method:** Oral/gavage	
Age at first dose: 42 days	**Doses:** 0 (vehicle), 40, 120 and 400 mg/kg TMC278 base	**Study no.:** TMC278-NC101
Duration of dosing: 186 days	**Test article batch:** [redacted]	**GLP compliance:** Yes
Duration of postdose: 158 days	**Vehicle/formulation:** PEG400 + CA	**Date of first dose**: [redacted]

No Observed Adverse Effect Level: /

Toxicokinetics:

Dose (mg/kg/day)	**0 (vehicle)**		**40**		**120**		**400**	
No. of animals	**M:3**	**F:3**	**M:6**	**F:6**	**M:6**	**F:6**	**M:6**	**F:6**
Day 1								
C_{max} (µg/mL)	-	-	2.9	6.5	6.4	8.5	9.1	17
$AUC_{0-\infty}$ (µg·h/mL)	-	-	19	32	53	83	92	160
Day 83								
C_{max} (µg/mL)	-	-	3.4	8.2	3.4	11	3.9	15
AUC_{0-24h} (µg·h/mL)	-	-	19	41	41	100	57	184
Day 175								
C_{max} (µg/mL)	-	-	1.7	6.6	3.0	8.8	6.2	16
AUC_{0-24h} (µg·h/mL)	-	-	12	50	35	116	73	244

Noteworthy Findings:

Dose (mg/kg/day)	**0 (vehicle)**		**40**		**120**		**400**	
No. of animals	**M:30**	**F:30**	**M:20**	**F:20**	**M:20**	**F:20**	**M:30**	**F:30**
Mortality	0	0	0	0	0	0	0	0
Clinical observations								
Salivation	15	5	15	14***	14	13***	25*	17**
Wet urogenital region	7	2	-	-	-	-	13	11*

/ = not determined; - = No noteworthy findings; PEG400: polyethylene glycol; CA: citric acid; * - $p<0.05$, ** - $p<0.01$, *** - $p<0.001$; M: male; F: female.

Test Article: RPV

Report Title: TMC278-NC101: Six-Month Repeated Dose Oral Toxicity Study with 1-Month Recovery in the Rat (continued)

Noteworthy Findings:

Dose (mg/kg/day)	**0 (vehicle)**		**40**		**120**		**400**	
No. of animals	**M:30**	**F:30**	**M:20**	**F:20**	**M:20**	**F:20**	**M:30**	**F:30**
Body weight	-	-	-	-	-	-	-	-
Food consumption	-	-	-	-	-	-	-	-
Ophthalmoscopy	-	-	-	-	-	-	-	-
Hematology[a]								
Interim analysis (3 months)								
Act. Part. Thromb. Time (sec)	25.62	-	1.116***	-	1.230***	-	1.190***	-
Prothrombine Time (sec)	20.52	-	1.125*	-	1.274***	-	1.133*	-
End of dosing (6 months)								
Act. Part. Thromb. Time (sec)	20.85	-	1.148**	-	1.249***	-	1.164***	-
Prothrombine Time (sec)	18.82	-	1.134**	-	1.272***	-	1.159**	-
Red blood cells (10^6/µL)	9.20	-	-	-	-	-	0.948**	-
Hemoglobin (g/dL)	16.4	-	-	-	-	-	0.951***	-
Hematocrit (%)	48.6	-	-	-	-	-	0.955**	-
Mean cell volume (fL)	-	55.1	-	-	-	0.976*	-	0.978*
Mean cell hemoglobin (pg)	-	18.7	-	-	-	0.973*	-	0.973*
Eosinophils (10^3/µL)	-	0.15	-	0.733**	-	0.733**	-	0.667***
End of recovery	**M:10**	**F:10**					**M:10**	**F:10**
Act. Part. Thromb. Time (sec)	21.61	-	-	-	-	-	1.140*	-
Prothrombine Time (sec)	20.46	-	-	-	-	-	1.123*	-

a For controls, group means are shown. For treated groups, multiples of control/baseline are shown. Statistical significance is based on actual data (not on the multiples of control/baseline); - = No noteworthy findings; * - p<0.05, ** - p<0.01, *** - p<0.001; M: male; F: female.

Test Article: RPV

Report Title: TMC278-NC101: Six-Month Repeated Dose Oral Toxicity Study with 1-Month Recovery in the Rat (continued)

Noteworthy Findings:

Dose (mg/kg/day)	**0 (vehicle)**		**40**		**120**		**400**	
No. of animals	**M:30**	**F:30**	**M:20**	**F:20**	**M:20**	**F:20**	**M:30**	**F:30**
Serum Chemistry[a]								
Interim analysis (3months)								
Inorg. Phosphorus (mg/dl)	7.6	6.4	-	1.063*	1.026*	1.063*	1.105***	1.078***
Total protein (g/dl)	-	7.0	-	-	-	-	-	1.043**
Albumin (g/dl)	4.5	4.9	-	-	1.089***	1.041**	1.089***	1.082***
Triglycerides (mg/dl)	76	53	0.724**	0.849*	0.855	0.811*	0.632***	0.755***
Total bilirubin (mg/dl)	0.12	0.13	0.833***	0.769***	0.750***	0.692***	0.667***	0.769***
Alkaline phosphatase (U/l)	79	-	-	-	1.291***	-	1.532***	-
End of dosing (6 months)								
Calcium (mg/dl)	11.7	-	-	-	-	-	0.957**	-
Total protein (g/dl)	7.4	7.7	-	-	-	-	-	1.039**
Albumin (g/dl)	4.5	5.2	-	-	1.067***	-	1.067***	1.077***
Glucose (mg/dl)		88		-		0.886**		0.886**
Triglycerides (mg/dl)	91	83	-	-	-	-	0.681**	0.590***
Urea nitrogen (mg/dl)	18.1	-	-	-	1.099*	-	1.099*	-
Creatinine (mg/dl)	0.26	-	1.115*	-	1.115**	-	1.115*	-
Total bilirubin (mg/dl)	0.13	0.15	0.769**	0.667***	0.692***	0.600***	0.615***	0.667***
Alkaline phosphatase (U/l)	69	-	-	-	1.319**	-	1.696***	-
Urinalysis[a]								
End of recovery	**M:10**	**F:10**					**M:10**	**F:10**
Specific gravity	1.032	-					1.005*	-
Ketones (grade)	0.67	-					2.493*	-

a For controls, group means are shown. For treated groups, multiples of control/baseline are shown. Statistical significance is based on actual data (not on the multiples of control/baseline); - = No noteworthy findings * - $p<0.05$, ** - $p<0.01$, *** - $p<0.001$

Test Article: RPV

Report Title: TMC278-NC101: Six-Month Repeated Dose Oral Toxicity Study with 1-Month Recovery in the Rat (continued)

Noteworthy Findings

Dose (mg/kg/day)	**0 (vehicle)**		**40**		**120**		**400**	
No. of animals	**M:30**	**F:30**	**M:20**	**F:20**	**M:20**	**F:20**	**M:30**	**F:30**
Endocrinology[a]								
End of dosing								
TSH (ng/ml)	4.7	3.9	1.447**	1.769***	1.766*	2.410***	1.234*	2.487***
T4 (nmol/l)	44	32	0.636**	0.750*	0.432***	0.563***	0.545***	0.563***
T3 (nmol/l)	0.82	1.2	0.707*	-	-	-	1.341*	-
Corticosterone (nmol/l)	1065	1291	-	-	0.922	0.775*	0.823	0.914
Progesterone (nmol/l)	11	39	-	-	1.727	-	1.909	1.385**
ACTH (pg/mL)	-	-	-	-	-	-	-	-
End of recovery	**M:10**	**F:10**					**M:10**	**F:10**
T4 (nmol/l)	-	32					-	1.375**
Organ Weights[a,b]								
End of dosing								
Liver (mg)	13036	7883	-	-	1.207**	1.110**	1.246***	1.239***
Thyroids (mg)	24	19	1.208**	1.158*	1.375***	1.368***	1.500***	1.526***
End of recovery	**M:10**	**F:10**					**M:10**	**F:10**
Thyroids (mg)	-	18					-	1.389**
Gross Pathology								
End of dosing								
Liver (n° examined)	20	20	20	20	20	20	20	20
- dark	0	0	-	-	-	-	2	3
- yellow focus		0		-		-		3
- more pronounced lobulation	0	0	-	-	2	-	7*	5
- swollen	1	-	-	-	-	-	5	
Thyroid glands (n° examined)	20	20	20	20	20	20	20	20
- swollen	0	0	-	-	2	3	6*	9**

a For controls, group means are shown. For treated groups, multiples of control/baseline are shown. Statistical significance is based on actual data (not on the multiples of control/baseline); b = Both absolute and relative weights differed from controls in the direction indicated. Number indicates multiple of control for the absolute organ weights; - = No noteworthy findings; * - $p<0.05$, ** - $p<0.01$, *** - $p<0.001$

Test Article: RPV

Report Title: TMC278-NC101: Six-Month Repeated Dose Oral Toxicity Study with 1-Month Recovery in the Rat (continued)

Noteworthy Findings:

Dose (mg/kg/day)	**0 (vehicle)**		**40**		**120**		**400**	
No. of animals	**M:30**	**F:30**	**M:20**	**F:20**	**M:20**	**F:20**	**M:30**	**F:30**
Histopathology								
Liver (n° examined)	19	19	20	20	20	20	19	20
- hypertrophy		3	-	3	7**	8	16***	16***
Grade 1	-	2	-	3	7	8	6	10
Grade 2	-	1	-	0	0	0	10	6
Lymph nodes, mesenteric (n° examined)	19	19	19	19	19	19	19	19
- swollen-vacuolated small macrophage-aggregates	-	-	-	-	-	-	5*	4
Grade 1	-	-	-	-	-	-	4	4
Grade 3	-	-	-	-	-	-	1	0
Pituitary gland (n° examined)	18	-	18	-	19	-	19	-
- large vacuolated cells/swollen cells (pars distalis)	2	-	11**	-	12**	-	9*	-
Grade 1	2	-	10	-	10	-	9	-
Grade 2		-	1	-	2	-	-	-
Thyroid glands (n° examined)	17	19	16	18	19	19	18	19
- high follicular epithelium	2	-	4	12***	15***	19***	18***	19***
Grade 1	2	-	4	12	14	16	5	2
Grade 2		-	-	-	1	3	13	17
- small follicles	4	3	12**	17***	18***	18***	11*	17***
Grade 1	4	3	6	12	6	5	7	2
Grade 2	0	-	6	5	12	13	4	10
Grade 3	0	0	0	0	0	0	0	5

- = No noteworthy findings; * - p<0.05, ** - p<0.01, *** - p<0.001

Test Article: RPV

Report Title: TMC278-NC101: Six-Month Repeated Dose Oral Toxicity Study with 1-Month Recovery in the Rat (continued)

Noteworthy Findings:

Dose (mg/kg/day)	**0 (vehicle)**		**40**		**120**		**400**	
No. of animals	**M:10**	**F:10**					**M:10**	**F:10**
End of recovery	-	-					-	-
Lymph nodes, mesenteric (n° examined)	9	9					6	10
- swollen-vacuolated small macrophage-aggregates	0	0					2	3
Grade 1							2	2
Grade 2							0	1
Thyroid glands (n° examined)	9	9					6	10
- high follicular epithelium	0	0					2	0
Grade 1	0						2	
- small follicles	4	1					6*	5
Grade 1	3	0					4	3
Grade 2	1	1					2	2

- = No noteworthy findings; * - $p<0.05$.

7.2.4. One-Month Repeated Dose Oral Toxicity Study in the Dog with 1-Month Recovery

Test Article: RPV

Species/strain: Dog/Beagle	**Administration route/method:** Oral/Gavage	
Age at first dose: approximately 6 to 8 months	**Doses:** 0 (water), 0 (vehicle), 5, 10, 40 mg/kg/day TMC278 base	**Study No.:** TMC278-Exp5650
Duration of dosing: 1-month	**Test article batch:** [redacted]	**GLP compliance:** Yes
Duration of postdose: 1-month	**Vehicle/formulation:** PEG400 + CA	**Date of first dose:** [redacted]

No Observed Adverse Effect Level:

Toxicokinetics

Doses (mg/kg/day)	**0 (control)**		**5**		**10**		**40**	
No. of Animals	**M:3**	**F:3**	**M:3**	**F:3**	**M:3**	**F:3**	**M:3**	**F:3**
Day 1								
C_{max} (µg/mL)	-	-	0.94	1.3	1.3	1.3	2.8	2.4
$AUC_{0\text{-}24h}$ (µg·h/mL)	-	-	13	15	22	14	51	40
Day 28								
C_{max} (µg/mL)	-	-	1.5	2.0	5.6	2.5	12	9.5
$AUC_{0\text{-}24h}$ (µg·h/mL)	-	-	27	37	103	47	204	160

Test Article: RPV

Noteworthy Findings										
Doses (mg/kg/day)	**0 (control)**		**0 (vehicle)**		**5**		**10**		**40**	
No. of Animals	**M:3**	**F:3**	**M:3**	**F:3**	**M:3**	**F:3**	**M:3**	**F:3**	**M:3**	**F:3**
Mortality	0	0	0	0	0	0	0	0	0	0
Clinical observations	-	-	-	-	-	-	-	-	-	-
ECG	-	-	-	-	-	-	-	-	-	-
Eye examination	-	-	-	-	-	-	-	-	-	-
Body Weight (g)	12.0	10.5	12.6	10.9	-	-	-	0.917	0.976	0.917
Food Consumption (kg)	1.96	0.32	2.31	0.35	-	0.743	0.848	0.771.	0.710	0.857
Hematology[b]										
Hematocrit (%)	50.6		47.4		-		-		0.973	
Hemoglobin (g/dL)	16.5		15.4		-		-		0.968	
Red blood cells ($10^{\wedge 3}$/µl)	7.02		6.49		-		-		0.980	
White blood cells ($10^{\wedge 3}$/µl)	8.77		9.18		-		-		1.121	
Doses (mg/kg/day)	**0 (control)**		**0 (vehicle)**		**5**		**10**		**40**	
No. of Animals	**M:3**	**F:3**	**M:3**	**F:3**	**M:3**	**F:3**	**M:3**	**F:3**	**M:3**	**F:3**
Serum analysis[b]										
Albumin (g/dL)	3.8		3.7		-		0.973		0.973	
Total protein (g/dL)	6.2		6.0		-		0.983		0.983	
Cholesterol (mg/dL)	135		128		-		-		1.320**	
Triglycerides (mg/dL)	32		28		-		0.857		0..786	
Total bilirubin (mg/dL)	0.13		0.11		-		-		2.363***	
Alkaline phosphatase (U/L)	111		138		-		-		2.210**	
Alanine aminotransferase (U/L)	47		44		-		-		2.932*	

a For controls, group means are shown. For treated groups, multiples of control/baseline are shown. Statistical significance is based on actual data (not on the multiples of control/baseline); b = For hematology and serum analysis, males and female values are combined; - = No noteworthy findings; / = not determined; * - p<0.05, ** - p<0.01, *** - p<0.001; F = female, M = male; / = not determined; PEG400: polyethylene glycol; CA: citric acid

Test Article: RPV

Report Title: TMC278-Exp5650: One-Month Repeated Dose Oral Toxicity Study in the Dog with 1-Month Recovery (continued)

Noteworthy Findings

Doses (mg/kg/day)	**0 (control)**		**0 (vehicle)**		**5**		**10**		**40**	
No. of animals	**M:3**	**F:3**	**M:3**	**F:3**	**M:3**	**F:3**	**M:3**	**F:3**	**M:3**	**F:3**
Urinalysis	-		-		-	-	-	-	-	-
Endocrinology										
ACTH (pg/mL.h)	965	737	521	785	-	-	1.710	1.237	3.77	2.964
Cortisol (nmol/L.h)	1386	1521	674	1256	-	-	-	0.557	-	0.581
Progesterone (nmol/L)	0.81	0.86	0.76	0.84	-	-	7.500	17.86	28.95*	11.43*
Organ weights										
Ovaries		0.826		0.771		1.326		2.597		2.384*
Gross pathology										
Swollen cervix		0		1		0		2		2
Swollen ovaries		0		1		0		2		2
Swollen uterus		0		1		0		2		2
Swollen vagina		0		1		0		2		2
Swollen mammary gland	0	0	0	0	0	0	0	1	0	0
Histopathology										
Adrenal cortex										
Reduced vacuolation diffuse (z.f.)	-	-	-	-	-	-	P	P	P	P
Largely vacuolated cells, multifocal (z.f.)	-	-	-	-	-	-	P	-	P	-
Mixed leucocytic infiltrates (z.f.)	-	-	-	-	-	-	-	-	P	-
Swollen cells (z.f./z.r.)	-	-	-	-	-	-	-	P	P	P

Test Article: RPV

Report Title: TMC278-Exp5650: One-Month Repeated Dose Oral Toxicity Study in the Dog with 1-Month Recovery (continued)

Noteworthy Findings

Doses (mg/kg/day)	**0 (control)**		**0 (vehicle)**		**5**		**10**		**40**	
No. of animals	**M:3**	**F:3**	**M:3**	**F:3**	**M:3**	**F:3**	**M:3**	**F:3**	**M:3**	**F:3**
Female genital tract										
Prominent activation	-	-	-	-	-	-	-	P	-	P
Liver										
(sub)chronic centrilobular perivascular inflammation	-	-	-	-	-	-	P	P	P	P
Mammary gland										
Prominent activation	-	-	-	-	-	-	P	P	P	P
Recovery	-	-	-	-	-	-	-	-	liver	liver

F = female; M = male; - = No noteworthy findings; P = present; ACTH = Adreno CorticoTropic Hormone; z.f. = zona fasciculate; z.r. = zona reticularis;
* - $p<0.05$, ** - $p<0.01$, *** - $p<0.001$