2.7.1.4 付録

臨床開発に用いた Leniolisib 製剤のロット番号及び製造者の情報を付録 1 に示す。生体試料中薬物濃度分析法のライフサイクル情報を付録 2、生体試料中薬物濃度分析法のバリデーションの性能の概要を付録 3 に示す。臨床生物薬剤学試験におけるノンコンパートメント解析で得られた Leniolisib の PK パラメーターの要約を付録 4 に示す。

付録 1 臨床試験に用いた Leniolisib のロット

Study Number	Dosage Form	Dosage Strength[a]	Drug Product Batch Number	Manufacturer
CCDZ173X2101	Capsule	10 mg	X081 0312	[redacted]
		70 mg	1010005249	
		100 mg	X085 0312 and X120 0612	
CCDZ173X2102	Capsule	10 mg	1010004547	[redacted]
CCDZ173X2104	Capsule	70 mg	2014053	[redacted]
LE1101	Capsule	70 mg	1010029635 / E224717-0001L002	[redacted]
	Tablet	70 mg	PFV2100040 / E224717-0001L001	[redacted]
LE2101	Powder for oral solution	70 mg/ 40 µCi	RLM220	[redacted]
CCDZ173X2203	Capsule	70 mg	1010007017	[redacted]
CCDZ173X2201	Capsule	10 mg	1010004547	[redacted]
		70 mg	1010005249, 1010007017, 1010029635, 1010022946, 1010015388, and 1010010033	
CCDZ173X2201E1	Capsule	70 mg	Available upon request	[redacted]
	Tablet	70 mg	Available upon request	
LE5101	Tablet	70 mg	PFV2100040 / E240138-0001L001	[redacted]

付録 1 臨床試験に用いた Leniolisib のロット（続き）

Study Number	Dosage Form	Dosage Strength[a]	Drug Product Batch Number	Manufacturer
LE1102	Tablet	10 mg	PFV2100078 / E244897-0001L002	[redacted]
		30 mg	PFV2100058 / E244897-0001L003	
		40 mg	PFV2200147 / E244897-0001L004	
		50 mg	PFV2200148 / E244897-0001L005	
		70 mg	PFV2100080 / E244897-0001L001	
	Granules	15 mg	W072839 / E244897-0002L001	[redacted]
LE3301	Tablet	10 mg	PFV2100078 / E224740-0003L001	[redacted]
		30 mg	PFV2100058 / E224740-0003L002	
LE4301	Tablet	10 mg	PFV2100078 / E232571-0001L003	[redacted]
		30 mg	PFV2100079 / E232571-0001L002	
		70 mg	PFV2100080 / E232571-0001L001	

Sources: 5.3.3.1 CSR Study 2101; 5.3.1.2 CSR Study LE1101; 5.3.2.2 CSR Study LE5101; 5.3.3.1 CSR Study LE2101; 5.3.3.4 CSR Study 2102 and CSR Study 2104; 5.3.5.4 CSR Study 2203; 5.3.5.1 CSR Study 2201 Part 1 and CSR Study 2201 Part 2; and 5.3.5.2 IA-2 CSR Study 2201E1; 5.3.1.2 CSR Study LE1102; 5.3.5.2 CSR Study LE3301; 5.3.5.2 CSR Study LE4301.

[a] Clinical service form 1 (CSF1) included the Novartis HGC formulation at 10 and 100 mg dosage strengths. Clinical service form 2 (CSF2) included the Novartis HGC formulation at 70 mg dosage strength.

付録 2 生体試料中薬物濃度分析法のライフサイクル情報

付録 2a. 生体試料中薬物濃度分析法のライフサイクル情報（Leniolisib）

	Method Validation 1100679b	Method Validation 15BASM071V1	Method Validation 1100679b and 15BASM071V1	Method Validation PKH/MOA/1031
Analyte	Leniolisib			
Validation type	Full	Full	Cross-validation	Full
eCTD reference number	Not available			
Method ID	1100679b	15BASM071V1	1100679b and 15BASM071V1	PKH/MOA/1031
Duration of time method is in use	24 Aug 2012 to 08 Feb 2016	25 Jun 2015 to 21 Aug 2017		05 Jun 2018 to 02 Sep 2021
Bioanalytical site	[redacted]	[redacted]	[redacted]	[redacted]
Matrix	Plasma	Plasma	Plasma	Plasma
Platform	LC-MS/MS			
Format	NA			
Stock reference, lot number, expiration date	Leniolisib phosphate, Batches 1110001 and 1251002.REF Retest dates Feb 2013 and Feb 2016	Leniolisib phosphate, Batches 1251002.REF, 1251002, and 1010006837 Retest dates Aug 2015, May 2016, and Sep 2017		Leniolisib phosphate, Batches 1010013786 and 1010013796 Retest dates Jan 2019, Jul 2019, Jul 2020, and Jan 2022
Calibration range from LLOQ to ULOQ	3.00 to 1000 ng/mL	3.00 to 1000 ng/mL		3.00 to 1000 ng/mL
Matrix study population	Healthy participants	Healthy participants		Healthy participants
Link to reports and applicable amendments	DMPK R[redacted]	DMPK R[redacted] and DMPK R[redacted]-01		DMPK R[redacted] and DMPK R[redacted]-01
Synopsis of amendment history	NA	Addition of long-term stability data in plasma		Added long-term stability and cross-validation data

付録 2a. 生体試料中薬物濃度分析法のライフサイクル情報（Leniolisib）（続き）

	Method Validation 15BASM071V1 and PKH/MOA/1031	Method Validation PKH/MOA/1464	Method Validation PKH/MOA/1411	Method Validation 1100679g
Analyte	Leniolisib		*(R)*- and *(S)*-enantiomers of leniolisib	Leniolisib
Validation type	Cross-validation	Partial	Full	Full
eCTD reference number	Not available			
Method ID	15BASM071V1 and PKH/MOA/1031	PKH/MOA/1464	PKH/MOA/1411	1100679g
Duration of time method is in use	05 Jun 2018 to 02 Sep 2021	27 Oct 2021 to ongoing	13 Aug 2021 to 13 Jan 2022	27 May 2014 to 28 Jun 2016
Bioanalytical site	[redacted]	[redacted]		[redacted]
Matrix	Plasma	Plasma	Plasma	Urine
Platform	LC-MS/MS			
Format	NA			
Stock reference, lot number, expiration date	Leniolisib phosphate, Batches 1010013786 and 1010013796 Retest dates Jan 2019, Jul 2019, Jul 2020, and Jan 2022	Leniolisib phosphate, Batch 1010013796 Retest date Jan 2022	*(R)*-enantiomer of leniolisib, Batch SB075-13 Retest date Jan 2022 *(S)*-enantiomer of leniolisib, Batch 1010013796 Retest date Jan 2022	Leniolisib phosphate, Batches 1251002.REF and 1010006837 Retest dates Feb 2016 and Sep 2016
Calibration range from LLOQ to ULOQ	3.00 to 1000 ng/mL	5.00 to 5000 ng/mL	3.00 to 1000 ng/mL	10.0 to 10000 ng/mL
Matrix study population	Healthy participants	Healthy participants	Healthy participants	Healthy participants
Link to reports and applicable amendments	DMPK R[redacted]-01	21-0315A	DOC-2946	DMPK R1100679g
Synopsis of amendment history	Added long-term stability and cross-validation data	partial validation for use of new internal standard	NA	NA

付録 2a. 生体試料中薬物濃度分析法のライフサイクル情報（Leniolisib）（続き）

	Clinical Study CCDZ173X2101	Clinical Study CCDZ173X2102	Clinical Study CCDZ173X2104	Clinical Study CCDZ173X2203
Analyte	Leniolisib			
Validation type	NA	NA	NA	NA
eCTD reference number	Not available			
Method ID	1100679b and 1100679g	15BASM071V1	15BASM071V1	15BASM071V1
Duration of time method is in use	12 Oct 2012 to 10 May 2016	16 Sep 2015 to 10 Oct 2015	25 May 2016 to 02 Jul 2016	28 May 2017 to 21 Aug 2017
Bioanalytical site	[redacted]		[redacted]	
Matrix	Plasma and urine	Plasma	Plasma	Plasma
Platform	LC-MS/MS			
Format	NA			
Stock reference, lot number, expiration date	Leniolisib phosphate, Batches 1110001, 1251002, and 1251002.REF Retest dates Feb 2013, Feb 2014, Oct 2014, and May 2016	Leniolisib phosphate, Batches 1251002.REF and 1251002 Retest dates Aug 2015 and May 2016	Leniolisib phosphate, Batch 1251002 Retest date May 2016	Leniolisib phosphate, Batch 1010006837 Retest date Sep 2017
Calibration range from LLOQ to ULOQ	Plasma: 3.00 to 1000 ng/mL Urine: 10.0 to 10000 ng/mL	3.00 to 1000 ng/mL	3.00 to 1000 ng/mL	3.00 to 1000 ng/mL
Matrix study population	Healthy participants	Healthy participants	Healthy participants	Patients with Sjögren's Syndrome
Link to reports and applicable amendments	DMPK RCCDZ173X2101	DMPK RCCDZ173X2102	DMPK RCCDZ173X2104	DMPK RCCDZ173X2203
Synopsis of amendment history	NA	NA	NA	NA

付録 2a. 生体試料中薬物濃度分析法のライフサイクル情報（Leniolisib）（続き）

	Clinical Study LE2101	Clinical Study LE1101	Clinical Study CCDZ173X2201 Part 1	Clinical Study CCDZ173X2201 Part 2
Analyte	Leniolisib			
Validation type	NA	NA	NA	NA
eCTD reference number	Not available			
Method ID	PKH/MOA/1464	PKH/MOA/1464	1100679b	PKH/MOA/1031
Duration of time method is in use	23 Nov 2021 to 15 Dec 2021	23 Nov 2021 to 14 Jan 2022	05 Oct 2015 to 21 Oct 2016	17 Sep 2018 to 20 Sep 2021
Bioanalytical site	[redacted]			
Matrix	Plasma	Plasma	Plasma	Plasma
Platform	LC-MS/MS			
Format	NA			
Stock reference, lot number, expiration date	Leniolisib phosphate, Batch 1010013796 Retest date Jan 2022	Leniolisib phosphate, Batch 1010013796 Retest date Jan 2022	Leniolisib phosphate, Batches 1251002 and 1010006837 Retest dates May 2016 and Sep 2016	Leniolisib phosphate, Batches 1010013786 and 1010013796 Retest dates Jan 2019, Jul 2019, and Jan 2022
Calibration range from LLOQ to ULOQ	5.00 to 5000 ng/mL	5.00 to 5000 ng/mL	3.00 to 1000 ng/mL	3.00 to 1000 ng/mL
Matrix study population	Healthy participants	Healthy participants	Patients with APDS	Patients with APDS
Link to reports and applicable amendments	LE 2101 BAR LE	LE 1101 BAR LE	DMPK RCCDZ173X2201	DMPK RCCDZ173X2201a
Synopsis of amendment history	NA	NA	NA	NA

付録 2a. 生体試料中薬物濃度分析法のライフサイクル情報（Leniolisib）（続き）

	Clinical Study CCDZ173X2201E1		Clinical Study LE1102	Clinical Study LE4301	Clinical Study LE5101
Analyte	Leniolisib	*(R)*- and *(S)*-enantiomers of leniolisib		Leniolisib	
Validation type	NA		NA	NA	NA
eCTD reference number	Not available				
Method ID	PKH/MOA/1031	PKH/MOA/1411	PKH/MOA/1464	PKH/MOA/1464	PKH/MOA/1464
Duration of time method is in use	17 Sep 2018 to 10 Nov 2021	24 Nov 2021 to 13 Jan 2022	27 May 2024 to 14 July 2024	14 May 2024 to 24 May 2024	26 March 2024 to 30 July 2024
Bioanalytical site	[redacted]				
Matrix	Plasma		Plasma	Plasma	Plasma
Platform	LC-MS/MS			LC-MS/MS	
Format	NA			NA	
Stock reference, lot number, expiration date	Leniolisib phosphate, Batches 1010013786 and 1010013796 Retest dates Jan 2019, Jul 2019, Jul 2020, and Jan 2022	*(R)*-enantiomer of leniolisib, Batch SB075-13 Retest date Jan 2022 *(S)*-enantiomer of leniolisib, Batch 1010013796 Retest date Jan 2022	Leniolisib phosphate, Batch CC210008B Retest date May 2024	Leniolisib phosphate, Batch CC210008B Retest date May 2024	Leniolisib phosphate, Batch CC210008B Retest date May 2024
Calibration range from LLOQ to ULOQ	3.00 to 1000 ng/mL	3.00 to 1000 ng/mL	5.00 to 5000 ng/mL	5.00 to 5000 ng/mL	5.00 to 5000 ng/mL
Matrix study population	Patients with APDS	Patients with APDS	Healthy participants	Patients with APDS	Healthy participants
Link to reports and applicable amendments	DMPK RCCDZ173X2201E1	DOC-2946	LE 1102 BAR LE	LE 4301 BAR LE	LE 5101 BAR LE

付録 2a. 生体試料中薬物濃度分析法のライフサイクル情報（Leniolisib）（続き）

		Clinical Study CCDZ173X2201E1	Clinical Study LE1102	Clinical Study LE4301	Clinical Study LE5101
Synopsis of amendment history	NA	NA	NA	NA	NA

APDS=activated PI3Kδ syndrome; LC-MS/MS=liquid chromatography with tandem mass spectroscopy; LLOQ=lower limit of quantitation; NA=not applicable; PI3Kδ=phosphoinositide 3-kinase δ; ULOQ=upper limit of quantitation.

付録 2b. 生体試料中薬物濃度分析法のライフサイクル情報（イトラコナゾール）

	Method Validation 15BAS0302	Clinical Study CCDZ173X2102
Analyte	Itraconazole	
Validation type	Full	NA
eCTD reference number	Not available	
Method ID	15BAS0302	15BAS0302
Duration of time method is in use	Available upon request	16 Sep 2015 to 10 Oct 2015
Bioanalytical site	[redacted]	
Matrix	Plasma	Plasma
Platform	LC-MS/MS	
Format	NA	
Stock reference, lot number, expiration date	Available upon request	Itraconazole, Batch IRNNI Retest date Aug 2016
Calibration range from LLOQ to ULOQ	10.0 to 10000 ng/mL	10.0 to 10000 ng/mL
Matrix study population	Healthy participants	Healthy participants
Link to reports and applicable amendments	Available upon request	DMPK RCCDZ173X2102
Synopsis of amendment history	NA	NA

LC-MS/MS=liquid chromatography with tandem mass spectroscopy; LLOQ=lower limit of quantitation; NA=not applicable; ULOQ=upper limit of quantitation.

付録 2c. 生体試料中薬物濃度分析法のライフサイクル情報（エチニルエストラジオール及びレボノルゲストレル）

	Method Validation Draft10BASM032V2		Clinical Study CCDZ173X2104	
Analyte	Ethinylestradiol	Levonorgestrel	Ethinylestradiol	Levonorgestrel
Validation type	Full		NA	
eCTD reference number	Not available			
Method ID	Draft10BASM032V2		Draft10BASM032V2	
Duration of time method is in use	12 Apr 2010 to 16 Nov 2010		25 May 2016 to 02 Jul 2016	
Bioanalytical site	[redacted]			
Matrix	Plasma	Plasma	Plasma	Plasma
Platform	LC-MS/MS			
Format	NA			
Stock reference, lot number, expiration date	Ethinylestradiol, Lot 2-QL-193-1 Retest date Oct 2010	Levonorgestrel, Lot F0H323, Retest date Jun 2011	Ethinylestradiol, Lot 16-XJZ-61-1 Retest date Sep 2019	Levonorgestrel, Lot G0L474, Retest date Mar 2016
Calibration range from LLOQ to ULOQ	5.00 to 2500 pg/mL	50.0 to 25000 pg/mL	5.00 to 2500 pg/mL	50.0 to 25000 pg/mL
Matrix study population	Healthy participants		Healthy participants	
Link to reports and applicable amendments	09BAS0248 and Amendment 1		DMPK RCCDZ173X2104	
Synopsis of amendment history	Updated administrative information; included references; and appended signed statements of compliance and quality assurance		NA	

LC-MS/MS=liquid chromatography with tandem mass spectroscopy; LLOQ=lower limit of quantitation; NA=not applicable; ULOQ=upper limit of quantitation.

付録 2d. 生体試料中薬物濃度分析法のライフサイクル情報（pAkt 陽性 B 細胞）

	Method Validation 0750979	Method Validation ICDFC 6	Method Validation ICDFC 6	Method Validation 0750979 and ICDFC 6
Analyte	pAkt-positive B cells			
Validation type	Full	Full	Partial	Cross-validation
eCTD reference number	Not available			
Method ID	0750979	ICDFC 6	ICDFC 6	0750979 and ICDFC 6
Duration of time method is in use	Available upon request	20 Jun 2012 to 08 Aug 2012	02 May 2016 to 22 Sep 2016	
Bioanalytical site	[redacted]	[redacted]	[redacted]	[redacted]
Matrix	Whole blood	Whole blood	Whole blood	
Platform	Flow cytometry			
Format	NA			
Stock reference, lot number, expiration date	NA	NA	NA	NA
Calibration range from LLOQ to ULOQ	NA	NA	NA	NA
Matrix study population	Healthy participants	Healthy participants	Healthy participants	
Link to reports and applicable amendments	Available upon request	BMD R1250114	BMD R1600304	
Synopsis of amendment history	NA	NA	NA	

付録 2d. 生体試料中薬物濃度分析法のライフサイクル情報（pAkt 陽性 B 細胞）（続き）

	Clinical Study CCDZ173X2101	Clinical Study CCDZ173X2203	Clinical Study CCDZ173X2201
Analyte		pAkt-positive B cells	
Validation type	NA	NA	NA
eCTD reference number		Not available	
Method ID	ICDFC 6	ICDFC 6	ICDFC 6
Duration of time method is in use	20 Sep 2012 to 07 Apr 2016	08 Jul 2016 to 26 Apr 2017	24 Sep 2015 to 28 Sep2016
Bioanalytical site	[redacted]	[redacted]	[redacted]
Matrix	Whole blood	Whole blood	Whole blood
Platform		Flow cytometry	
Format		NA	
Stock reference, lot number, expiration date	NA	NA	NA
Calibration range from LLOQ to ULOQ	NA	NA	NA
Matrix study population	Healthy participants	Patients with Sjögren's Syndrome	Patients with APDS
Link to reports and applicable amendments	BMD RCCDZ173X2101	BMD RCCDZ173X2203	BMD RCCDZ173X2201
Synopsis of amendment history	NA	NA	NA

APDS=activated PI3Kδ syndrome; LLOQ=lower limit of quantitation; NA=not applicable; pAkt=phosphorylated Akt; PI3Kδ=phosphoinositide 3-kinase δ; ULOQ=upper limit of quantitation.

付録 2e. 生体試料中薬物濃度分析法のライフサイクル情報（カフェイン、パラキサンチン、ミダゾラム及び α-ヒドロキシミダゾラム）

	Method Validation 23302		Clinical Study LE5101	
Analyte	Caffeine, paraxanthine, midazolam and alpha-hydroxymidazolam		Caffeine	Midazolam
Validation type	Full		NA	
eCTD reference number	Not available			
Method ID	23302		23303	
Duration of time method is in use	17 Sep 2023 to 18 Apr 2024		10 to 18 Apr 2024	
Bioanalytical site	[redacted]			
Matrix	Plasma		Plasma	Plasma
Platform	LC-MS/MS			
Format	NA			
Stock reference, lot number, expiration date	Caffeine Lot 0000181333 Retest date May 2026 Midazolam Lot 111.1B0.6 Retest date Jul 2025	Paraxanthine Lot 2-AAH-100-1 Retest date Aug 2029 Alpha-hydroxymidazolam Lot 330.1B15.1L2 Retest date Apr 2031	Caffeine Lot 0000181333 Retest date May 2026 Midazolam Lot 111.1B0.6 Retest date Jul 2025	Paraxanthine Lot 2-AAH-100-1 Retest date Aug 2029 Alpha-hydroxymidazolam Lot 330.1B16.1L1 Retest date Nov 2032
Calibration range from LLOQ to ULOQ	5.00 to 2000 ng/mL (caffeine, paraxanthine), 0.100 to 100 ng/ml (midazolam, alpha-hydroxymidazolam)		5.00 to 2000 ng/mL (caffeine, paraxanthine), 0.100 to 100 ng/ml (midazolam, alpha-hydroxymidazolam)	
Matrix study population	Healthy participants		Healthy participants	
Link to reports and applicable amendments	23302		23303	
Synopsis of amendment history	NA		NA	

LC-MS/MS=liquid chromatography with tandem mass spectroscopy; LLOQ=lower limit of quantitation; NA=not applicable; ULOQ=upper limit of quantitation.

付録 2f. 生体試料中薬物濃度分析法のライフサイクル情報（フロセミド及びロスバスタチン）

	Method Validation 23452		Clinical Study LE5101	
Analyte	Furosemide	Rosuvastatin	Furosemide	Rosuvastatin
Validation type	Full		NA	
eCTD reference number	Not available			
Method ID	23452		23307	
Duration of time method is in use	15 Feb to 08 May 2024		26 Mar to 06 Jun 2024	
Bioanalytical site	[redacted]			
Matrix	Plasma	Plasma	Plasma	Plasma
Platform	LC-MS/MS			
Format	NA			
Stock reference, lot number, expiration date	Furosemide Lot 2023-CPO-070 Retest date Mar 2027	Rosuvastatin Lot 711865109-1-1 Retest date Jun 2027	Furosemide Lot 2023-CPO-070 Retest date Mar 2027	Rosuvastatin Lot 711865109-1-1 Retest date Jun 2027
Calibration range from LLOQ to ULOQ	0.200 to 200 ng/mL	0.100 to 100 ng/mL	0.200 to 200 ng/mL	0.100 to 100 ng/mL
Matrix study population	Healthy participants		Healthy participants	
Link to reports and applicable amendments	23452		23307	
Synopsis of amendment history	NA		NA	

LC-MS/MS=liquid chromatography with tandem mass spectroscopy; LLOQ=lower limit of quantitation; NA=not applicable; ULOQ=upper limit of quantitation.

付録 2g. 生体試料中薬物濃度分析法のライフサイクル情報（メトホルミン）

	Method Validation 23306		Clinical Study LE5101	
Analyte	Metformin		Metformin	
Validation type	Full		NA	
eCTD reference number	Not available			
Method ID	23306		23307	
Duration of time method is in use	22 Jan to 19 Apr 2024		26 Mar to 06 Jun 2024	
Bioanalytical site	[redacted]			
Matrix	Plasma	Plasma	Plasma	Plasma
Platform	LC-MS/MS			
Format	NA			
Stock reference, lot number, expiration date	Metformin Lot 1-MJS-112-1 Retest date Mar 2029		Metformin Lot 1-MJS-112-1 Retest date Mar 2029	
Calibration range from LLOQ to ULOQ	5.00 to 2000 ng/mL		5.00 to 2000 ng/mL	
Matrix study population	Healthy participants		Healthy participants	
Link to reports and applicable amendments	23306		23307	
Synopsis of amendment history	NA		NA	

LC-MS/MS=liquid chromatography with tandem mass spectroscopy; LLOQ=lower limit of quantitation; NA=not applicable; ULOQ=upper limit of quantitation.

付録 3 分析法の性能、変更及びクロスバリデーションの概要

付録 3a. ヒト血漿中 Leniolisib 濃度測定に用いた分析法の性能の概要（[redacted]）

Bioanalytical method validation report name, amendments, and hyperlinks	Quantitative determination of CDZ173 in human plasma by LC-MS/MS Method Validation Report DMPK R[redacted]		
Method description	Protein precipitation from human plasma (K_3EDTA) samples followed by pellet filtration using solid phase extraction and analysis of filtrate by LC-MS/MS in SRM mode using ESI in positive mode as the ionization technique		
Materials used for standard calibration curve and concentration	Leniolisib phosphate, [redacted] Batches 1110001 and 1251002.REF Calibration standards: 3.00, 30.0, 150.0, 375.0, 600, 800, and 1000 ng/mL Internal standard: $^{13}CD_3$-leniolisib, [redacted], Batches SSE 208-1 and SSE 261-1		
Validated assay range	3.00 to 1000 ng/mL		
Material used for QCs and concentration	Leniolisib phosphate, [redacted] Batches 1110001 and 1251002.REF QC levels: 3.00 (LLOQ), 9.00 (LQC), 500 (MQC), 750 (HQC), and 2000 (Dilution QC) ng/mL Internal standard: $^{13}CD_3$-leniolisib, [redacted], Batches SSE 208-1 and SSE 261-1		
Minimum required dilutions	NA		
Source and lot of reagents	Human plasma, K_3EDTA-treated (Sera Lab Int) Methanol, Lichrosolv® gradient grade (Merck) Acetonitrile, Chromasolv® grade (Sigma-Aldrich) Tetrahydrofuran, Chromasolv® grade (Sigma-Aldrich) Formic acid (Fluka) Purified deionized water using Integra UV Plus (SG)		
Regression model and weighting	Quadratic ($y=ax^2+bx+c$), weighted ($1/x^2$)		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	7	DMPK R[redacted] Table 6-12
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-1.30% to 2.10%	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤7.80%	

付録 3a. ヒト血漿中 Leniolisib 濃度測定に用いた分析法の性能の概要（[redacted]）（続き）

Performance of QCs during accuracy and precision runs	**Cumulative accuracy (%bias) in 4 QC levels**	1.90% to 6.20%	DMPK R[redacted] Table 6-14
	Interbatch %CV	≤7.90%	
	Total error	NR	
Selectivity and matrix effect	Selectivity for leniolisib was considered acceptable in 6 batches of plasma tested. Interference from blank matrix was 0% of response at LLOQ for leniolisib and 0% of response at working concentration for IS. Matrix effect from LQC to HQC: Mean matrix factor: 0.98 to 1.01, precision (%CV): ≤5.94% Mean IS-normalized matrix factor: 0.98 to 1.02, precision (%CV): ≤6.90%		DMPK R[redacted] Table 6-1, Table 6-2, Table 6-5, Table 6-6, and Table 6-7
Interference and specificity	Contribution of IS to the signal of leniolisib (4.00% interference) and of leniolisib to the signal of IS (0.30% interference) was not significant.		DMPK R[redacted] Table 6-3 and Table 6-4
Hemolysis effect	NA		NA
Lipemic effect	NA		NA
Dilution linearity and hook effect	100-fold dilution of 2000 ng/mL, accuracy (%bias): 1.50%, precision (%CV): 3.89% Hook effect: NA		DMPK R[redacted] Table 6-17
Bench-top/process stability	71 h in plasma at room temperature. 25.2 h for processed extract in autosampler at room temperature.		DMPK R[redacted] Table 6-18 and Table 6-20
Freeze-thaw stability	3 cycles at <-15°C.		DMPK R[redacted] Table 6-19
Long-term storage	182 days in spiked plasma at <-15°C. 461 days in incurred plasma samples at <-15°C.		DMPK R[redacted] Table 6-21 and Table 6-22
Parallelism	NR		NA
Carryover	Carryover was evaluated by injecting blank matrix samples after the ULOQ standard. There was no significant carryover evident for leniolisib (≤16.9% carryover) or IS (0% carryover).		DMPK R[redacted] Table 6-10
	Method Performance in CCDZ173X2101 **Bioanalytical Report: DMPK RCCDZ173X2101**		
Assay passing rate	54 of 67 runs (81%) in plasma met acceptance criteria		DMPK RCCDZ173X2101, Table 5-1
Standard curve performance	Cumulative accuracy (%bias): -0.5% to 0.3% Cumulative precision (%CV): ≤6.3%		DMPK RCCDZ173X2101, Table 5-7
QC performance	Cumulative accuracy (%bias): -0.6% to 9.2% Cumulative precision (%CV): ≤98.7%* Total error: NR * The high CV is due to 2 datapoints of 135 datapoints (121 and -0.513 ng/mL) at LQC (9.00 ng/mL). Excluding these 2 datapoints, the cumulative precision across the QC range is ≤8.7% CV.		DMPK RCCDZ173X2101, Table 5-9

付録 3a. ヒト血漿中 Leniolisib 濃度測定に用いた分析法の性能の概要（[redacted]）（続き）

Method reproducibility	Incurred sample reanalysis was performed on 441 samples, and 368 (83%) of which were within ±20% difference from original results.	DMPK RCCDZ173X2101, Table 9-4
Study sample analysis stability	Samples were received frozen and stored at ≤-15°C. Samples were analyzed within the established stability limit of 182 days in spiked plasma at <-15°C and 461 days in incurred plasma samples at <-15°C.	DMPK RCCDZ173X2101, Section 1 and Section 6
Standard calibration curve performance during accuracy and precision	53 calibrator sets with 2 replicates at each of 7 concentration levels from 3.00 to 1000 ng/mL (total 742 datapoints) – 35 excluded from curve fitting due to no value, technical issue, or value deviating by ≥15%.	
	Method Performance in CCDZ173X2201 Part 1 Bioanalytical Report: DMPK RCCDZ173X2201	
Assay passing rate	LIMS Study CCDZ173X2201_A1: 2 of 2 runs (100%) met acceptance criteria. LIMS Study CCDZ173X2201_A2: 12 of 13 runs (92%) met acceptance criteria.	DMPK RCCDZ173X2201, Section 5.2
Standard curve performance	Cumulative accuracy (%bias) LIMS Study CCDZ173X2201_A1: -3.8% to 4.3% LIMS Study CCDZ173X2201_A2: -1.3% to 2.7% Cumulative precision (%CV) LIMS Study CCDZ173X2201_A1: NR LIMS Study CCDZ173X2201_A2: ≤7.2%	DMPK RCCDZ173X2201, Table 5-3 and Table 5-4
QC performance	Cumulative accuracy (%bias) LIMS Study CCDZ173X2201_A1: -2.2% to 2.8% LIMS Study CCDZ173X2201_A2: -3.0% to 5.0% Cumulative precision (%CV) LIMS Study CCDZ173X2201_A1: ≤11.7% LIMS Study CCDZ173X2201_A2: ≤7.9% Total error: NR	DMPK RCCDZ173X2201, Table 5-5 and Table 5-6
Method reproducibility	Not performed	DMPK RCCDZ173X2201, Section 7
Study sample analysis stability	Samples were received frozen and stored at ≤-15°C. Samples were analyzed within the established stability limit of 182 days in spiked plasma at <-15°C and 461 days in incurred plasma samples at <-15°C.	DMPK RCCDZ173X2201, Section 1 and Section 6
Standard calibration curve performance during accuracy and precision	LIMS Study CCDZ173X2201_A1: 2 calibrator sets with 2 replicates at each of 7 concentration levels from 3.00 to 1000 ng/mL (total 28 datapoints) – none excluded from curve fitting. LIMS Study CCDZ173X2201_A2: 12 calibrator sets with 2 replicates at each of 7 concentration levels from 3.00 to 1000 ng/mL (total 168 datapoints) – 4 datapoints rejected due to deviation of 15% or 20% from nominal.	

CV=coefficient of variation; ESI=electrospray ionization; HQC=high QC; IS=internal standard; LC-MS/MS=liquid chromatography coupled with tandem mass spectroscopy; LLOQ=lower limit of quantification; LQC=low QC; MQC=middle QC; NA=not applicable; NR=not reported; QC=quality control; SRM=selective reaction monitoring; ULOQ=upper limit of quantification.