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APPLICATION NUMBER:

214439Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Clinical Pharmacology Review
Addendum

NDA Number	214439
Submission Date	6/22/2020
Submission Type	505(b)(2)
Brand Name	NORLIQVA
Generic Name	Amlodipine oral solution, 1 mg/mL
Drug Class	Calcium channel blocker
Strength and Dosage form	1 mg/mL oral solution
Proposed Indications	Hypertension - Treatment of hypertension in adults and children 6-17 years, to lower blood pressure; Coronary artery disease - Chronic stable angina - Vasospastic angina (Prinzmetal's or Variant angina) - Angiographically documented coronary artery disease in patients without heart failure or an ejection fraction < 40%
Applicant	CMP Development LLC
OCP Division	Division of Cardiometabolic and Endocrine Pharmacology (DCEP)
Purpose	Addendum to clinical pharmacology review (DARRTS 03/19/2021) for NDA 214439
Reviewer	Snehal Samant MS, PhD
Date	04/22/2021

This memo is an addendum to the original clinical pharmacology review submitted to DARRTS on 03/19/2021.

Office of Clinical Pharmacology (OCP) requested an inspection (DARRTS 8/18/2020) of the clinical and bioanalytical sites of (b) (4) for the pivotal relative BA study 19-029 supporting NDA 214439 for amlodipine oral solution, 1 mg/mL. The findings of the clinical and bioanalytical inspection were pending at the time of the original clinical pharmacology review (DARRTS 3/19/2021). This addendum documents the findings from the Office of Study Integrity and Surveillance (OSIS) memo of the clinical site inspection (DARRTS 03/31/2021) and OSIS consult response regarding the Remote Record Review (RRR) (DARRTS 04/20/2021) of bioanalytical site inspection for study 19-029. The result of the OSIS RRR for the bioanalytical site inspection is currently pending. OCP recommends approval of amlodipine oral solution 1 mg/mL, pending the result of the OSIS RRR of the bioanalytical site.

Clinical site:
OSIS determined that an inspection of the clinical site of Synapse Labs Private Ltd, Pune, India is not warranted at this time because the clinical site was inspected in February 2020, which falls within the surveillance interval. The final classification for the clinical site inspection was 'No Action Indicated' (NAI) (Reference: OSIS memo DARRTS 03/31/2021).

Bioanalytical site:
OSIS conducted a RRR of the bioanalytical site (b) (4). During the RRR, OSIS observed an objectionable finding (b) (4) (b) (4) (b) (4) during Method Validation 109-01 and study 19-029 (Reference: OSIS consult response DARRTS 04/20/2021). The site did not address (b) (4) (b) (4). The site intends to provide written responses to OSIS by 4/30/2021. OSIS will assess the impact of the observation after the firm's written response is received. Review of the firm's response, once received, will be incorporated into the OSIS RRR memo for the bioanalytical site that is currently pending. OSIS consult response notes that currently there is no evidence indicating that the finding affects the data reliability of study 19-029. Office of Clinical Pharmacology (OCP) recommends approval of amlodipine oral solution 1 mg/mL, pending the result of the OSIS RRR for the bioanalytical site inspection.

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/s/

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Clinical Pharmacology Review

NDA Number	214439
Link to EDR	\\CDSESUB1\evsprod\nda214439\0000
Submission Date	6/22/2020
Submission Type	505(b)(2)
Brand Name	NORLIQVA
Generic Name	Amlodipine (b) (4) oral solution, 1 mg/mL
Drug Class	Calcium channel blocker
Route of Administration	Oral
Dosage form	Solution
Strength	1 mg/mL solution
Proposed Indications	Hypertension - Treatment of hypertension in adults and children 6-17 years, to lower blood pressure; Coronary artery disease - Chronic stable angina - Vasospastic angina (Prinzmetal's or Variant angina) - Angiographically documented coronary artery disease in patients without heart failure or an ejection fraction < 40%
Applicant	CMP Development LLC
OCP Division	Division of Cardiometabolic and Endocrine Pharmacology (DCEP)
OND Division	Division of Cardiology and Nephrology (DCN)
Primary reviewer	Kunal Jhunjhunwala MS, PhD
Secondary reviewer	Snehal Samant MS, PhD

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1. EXECUTIVE SUMMARY

CMP Development LLC. has submitted a 505(b)(2) NDA for amlodipine (b) (4) oral solution 1 mg/mL (NORLIQVA). The application relies on Agency's findings of safety and efficacy for the listed drug NORVASC® (amlodipine besylate) tablets (NDA 019787). The applicant is seeking approval for the following indications at the same doses as approved for NORVASC®:

- Treatment of hypertension in adults and children 6 years of age and older, to lower blood pressure.
- Treatment of coronary artery disease: chronic stable angina, vasospastic angina (Prinzmetal's or variant angina), and angiographically-documented coronary artery disease in patients without heart failure or an ejection fraction of < 40%.

No additional clinical efficacy data is presented in this application and no new claims are being sought with this application.

The applicant has submitted two clinical pharmacology studies: 1) Open-label, randomized, single-dose, 2-way crossover study in healthy adults (19-029) to evaluate the relative bioavailability (BA) of amlodipine (b) (4) 1 mg/mL oral solution (10 mL equivalent to the dose of 10 mg amlodipine) compared to the listed drug NORVASC® tablet, 10 mg following fasted state administration 2) Open-label, randomized, single-dose, 2-way crossover food effect study (19-086) for amlodipine (b) (4) 1 mg/mL oral solution (10 mL equivalent to the dose of 10 mg amlodipine) in healthy adults. The applicant is relying on the relative BA study for bridging to the efficacy and safety of the listed drug.

1.1 Recommendations

The Office of Clinical Pharmacology/ Division of Cardiometabolic and Endocrine Pharmacology (OCP/ DCEP) has reviewed the NDA submission. The results of the relative BA study and food effect study support approval of NORLIQVA for the proposed indications at the doses as approved for the listed drug NORVASC® tablet. The food effect study results support administration of NORLIQVA with or without food. The clinical pharmacology section of the proposed label was updated to reflect the current 'Guidance on Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products'.

OCP requested an inspection (DARRTS 8/18/2020) of the clinical and bioanalytical sites of study 19-029 via Office of Study Integrity and Surveillance (OSIS). The results of the inspection are pending at the time of this review.

1.2 Post-Marketing Requirements and Commitments

None

1.3 Summary of important clinical pharmacology findings

The results of the relative BA assessment demonstrate that NORLIQVA is bioequivalent to the listed drug NORVASC® 10 mg tablet under fasted conditions. The results of the relative BA study are summarized in Table 4.

The results of food effect assessment show that fed state administration of NORLIQVA does not have a significant effect on the oral absorption of amlodipine. The results of the food effect study are summarized in Table 5.

The bioanalytical method used to measure amlodipine is validated and the performance of the method in the clinical study is acceptable as per the specifications outlined in the Bioanalytical Method Validation Guidance (See Table 3).

2. QUESTION BASED REVIEW

This is an abridged version of the question-based review. For detailed review of clinical pharmacology attributes of NORVASC®, refer to the original NDA 19787.

2.1 General attributes of the drug product

NORLIQVA is a clear pale straw-colored solution of amlodipine besylate formulated in the dosage strength of 1 mg/mL. Each 1 mL of NORLIQVA contains amlodipine besylate equivalent to 1 mg of amlodipine. The formulation also contains the following excipients: glycerin, maltitol (b) (4) butylated hydroxyanisole, ethanol, (b) (4) (alcohol) and (b) (4) peppermint flavor (b) (4).

2.1.1 What is the proposed mechanism of action of amlodipine?

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle.

2.1.2 What are the proposed therapeutic indication(s)?

The proposed therapeutic indications for NORLIQVA are:

• Hypertension - to lower blood pressure in adults and children 6 to 17 years of age. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.

• Coronary artery disease - Symptomatic treatment of chronic stable angina, treatment of confirmed or suspected vasospastic angina (Prinzmetal's or Variant angina) and in patients with recently documented coronary artery disease by angiography and without heart failure or an ejection fraction <40% NORLIQVA is indicated to reduce the risk of hospitalization for angina and to reduce the risk of a coronary revascularization procedure.

2.1.3 What are the proposed dose(s)?

The proposed doses of NORLIQVA are listed in Table 1. The proposed doses are the same as those for the listed drug NORVASC®.

Table 1 Proposed doses for NORLIQVA

Indication	Proposed dosing regimen for NORLIQVA
Adult hypertension	The usual initial antihypertensive oral dose of NORLIQVA is 5 mg once daily, and the maximum dose is 10 mg once daily. Small, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding NORLIQVA to other antihypertensive therapy.
Pediatric hypertension	2.5 mg to 5 mg once daily in pediatric patients aged 6-17 years
Angina	The recommended dose for chronic stable or vasospastic angina is 5 to10 mg, with the lower dose suggested in the elderly and in patients with hepatic insufficiency.
Coronary Artery Disease	The recommended dose range for patients with coronary artery disease is 5 to10 mg once daily.

2.2 Specific review questions

2.2.1 What are the design features of clinical pharmacology studies used to support dosing or label claims?

The applicant submitted two clinical pharmacology studies to support proposed doses and labelling (Table 2). The relative bioavailability study (19-029) compared the bioavailability of amlodipine (b) (4) from NORLIQVA (10 mL equivalent to the dose of 10 mg amlodipine) and the listed drug NORVASC® tablet, 10 mg following single oral dose administration in fasted state. The food effect study (19-086) evaluated the effect of high-fat, high-calorie meal on the bioavailability of amlodipine (b) (4) from NORLIQVA.

Table 2 Summary of clinical pharmacology studies

Study No. Study type	Design	Study participants
19-029 Relative bioavailability study	Randomized, single-dose, two-treatment, two-sequence, two-period, crossover, oral bioequivalence study of amlodipine (b) (4) 1 mg/mL oral solution (10 mL) (NORLIQVA) (Test) with NORVASC® 10 mg tablets (Reference) in healthy, adult, human subjects under fasting conditions.	Study population: Healthy adults, Completed: 32 (32 males and 0 females) Age range: 18 to 45 years (inclusive)
19-086 Food effect study	Randomized, single-dose, two-treatment (fed vs. fasting), two-sequence, two-period, crossover, food effect study of amlodipine (b) (4) 1 mg/mL oral solution (10 mL) in healthy, adult, human subjects under fed versus fasting conditions.	Study population: Healthy adults Completed: 32 (32 males and 0 females) Age range: 18 to 45 years (inclusive)

2.2.2 Is the active moiety in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

The active moiety analyzed is amlodipine. All blood samples were collected in K_2EDTA (Di-potassium salt of ethylene di-amine tetra acetic acid) vacutainers. Plasma concentrations of amlodipine were measured by a validated high-performance liquid chromatography-tandem mass spectrometry assay (LC-MS/MS). Amlodipine D4 was used as an internal standard (ISTD). Amlodipine and ISTD amlodipine D4 were extracted from human K_2EDTA plasma by liquid - liquid extraction method.

The bioanalytical validation summary for study 19-029 and 19-086 is provided in Table 3. Quality control samples at four different concentrations were analyzed along with the study samples. Accuracy and precision of QC samples for the LC-MS/MS bioanalytical assay were within acceptable limits (≤15% and ≤20% at LLOQ). Greater than two-thirds of the incurred samples concentration results were within 20% of the original concentration of the respective samples and meets the acceptance criteria for incurred samples reanalysis. The bioanalytical assay methods for amlodipine in plasma are acceptable, based on the limits specified in 'Guidance for Industry: Bioanalytical Method Validation.'

Table 3 Bioanalytical method validation summary for amlodipine plasma concentration analysis

Study	19-029	19-086
Method	LC-MS/MS	LC-MS/MS
LLOQ (ng/mL)	0.11	0.05
ULOQ (ng/mL)	15.20	20.04
Calibration curve standard (CS) concentration (ng/mL)	0.11, 0.21, 0.76, 3.04, 6.08, 9.12, 12.16, 15.2	0.05, 0.10, 0.40, 1.60, 8.00, 12.00, 16.00, 20.00
CS Accuracy (bias) (%)	93.22 – 102.49	95.76 – 102.33
CS Precision (%)	0.19 – 9.41	0.29 – 3.6
QC (mg/mL)	0.11, 0.28, 1.94, 6.56, 11.71	0.13, 0.49, 7.67, 15.97
QC Accuracy (bias) (%) Intra-batch accuracy Inter-batch accuracy	 88.77 – 107.88% 95.48 – 103.01%	 91.83 – 100.43% 93.54 – 100.04%
QC Precision (%) Intra-batch precision Inter-batch precision	 1.26 – 9.87% 4.57 – 8.62%	 0.38 – 4.08% 0.71 – 3.56%

2.2.3 What is the relative bioavailability of NORLIQVA compared to NORVASC® tablets? Does it support the proposed dosing and label claims?

The geometric mean ratios of C_{max}, AUC_{0-72h} and $AUC_{0-\infty}$ for NORLIQVA (10 mL equivalent to the dose of 10 mg amlodipine) compared to NORVASC® 10 mg tablet (study 19-029) are summarized in Table 4.

Table 4 Relative bioavailability assessment results (Study 19-029)

Parameter (units)	Geometric least squares mean		Geometric mean ratio T/R (%)	90% Confidence interval
	NORLIQVA (T) (n=32)	NORVASC® (R) (n=32)		
C_{max} (ng/mL)	8.6	8.2	104.3	99.2 – 109.7
AUC_{0-72h} (ng.h/mL)	336.0	319.9	105.0	100.9 – 109.2
$AUC_{0-\infty}$ (ng.h/mL)	552.3	517.7	106.7	100.3 – 113.4

Source: Reviewer's analysis
T: NORLIQVA (10 mL equivalent to the dose of 10 mg amlodipine); R: NORVASC® 10 mg tablet

The median time to reach peak amlodipine plasma concentration (T_{max}) was similar (6 h) for NORLIQVA and the listed drug NORVASC®. The mean terminal elimination half-life of amlodipine was similar for NORLIQVA (52.3 ± 14.6 h) and NORVASC® (50.4 ± 10.6 h). Based on the results of the relative BA study, NORLIQVA (10 mL equivalent to the dose of 10 mg amlodipine) is bioequivalent to NORVASC® 10 mg tablet. The results support labelling of NORLIQVA 1 mg/mL for the proposed doses as listed in Table 1.

2.2.4 What is the effect of food on the bioavailability of the drug from the drug product?

The geometric mean ratios of C_{max}, AUC_{0-72h} and $AUC_{0-\infty}$ for administration of NORLIQVA (10 mL equivalent to the dose of 10 mg amlodipine) with a high-fat, high-calorie meal compared to fasted state administration are summarized in the Table 5.

Table 5 Food effect assessment results (Study 19-086)

Parameter	Geometric Least Squares Mean (%CV)		Fed/Fasted Ratio (%)	90% C. I
	Fed state (N=31)	Fasted state (N=31)		
C_{max} (ng/mL)	8.3	8.6	97.1	93.1 – 101.3
AUC_{0-72h} (ng.hr/mL)	343.2	339.7	101.0	97 – 105.1
$AUC_{0-\infty}$ (ng.hr/mL)	563.2	539.7	104.3	98.3 – 110.7

Source: Reviewer's analysis

The median time to attain peak plasma concentration of amlodipine (T_{max}) following fed and fasted state administration was 6 h and 7.5 h, respectively. Taking NORLIQVA with a high-fat, high-calorie meal does not have a significant effect on the peak plasma concentration of amlodipine as compared to fasted state administration. Systemic exposure (AUC_{0-72h}, $AUC_{0-\infty}$) was similar after administration of NORLIQVA (10 mL equivalent to the dose of 10 mg amlodipine) under fed and fasted conditions indicating a lack of food effect for NORLIQVA, which is consistent with results reported for NORVASC® tablets. The study results support administration of NORLIQVA without regards to meal.

3. APPENDICES

3.1 Relative bioavailability study

Study No: 19-029	EDR: \\CDSESUB1\evsprod\nda214439\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\19-029\study-report-body.pdf
Clinical Study Start Date 25th July 2019 **Clinical Study Completion Date** 20th August 2019	
Title of Study: An open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover, oral bioequivalence study of Amlodipine (b) (4) 1 mg/mL oral solution (Dose: 10 mL equivalent to the dose of 10 mg of amlodipine) of CMP Development LLC, USA with NORVASC® (amlodipine besylate) 10 mg tablets, Marketing Authorization holder: Pfizer Labs (Division of Pfizer Inc., NY), NY 10017 in healthy adults under fasting conditions.	
Investigational Product: Amlodipine (b) (4) 1 mg/mL oral solution, Manufactured by: (b) (4) Manufactured for: CMP Development LLC, USA	

Study:

- **Design:** Randomized, single-dose, two-treatment, two-sequence, two-period, crossover study
- **Washout:** A washout period of 22 days was kept between each dose administration
- **Study participants:** 32 healthy adults, 18-45 years of age.
- **Treatments Administered**

Fasted state administration:

After an overnight fast of at least 10.00 hours, study drug amlodipine (b) (4) 1 mg/mL oral solution or NORVASC®10 mg tablets were administered to subjects orally with approximately 240 mL water at ambient temperature

- **Sampling times (h):** pre-dose, 0.25, 0.5, 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 12, 16, 24, 36, 48- and 72-hours post-dose in each period.
- **Pharmacokinetic parameters calculated**: C_{max} and AUC_{0-72h}, T_{max}, $t_{1/2}$ and K_{el}
- **Analytical Method:**
  - A validated LC-MS method for the estimation of amlodipine in human K_2EDTA plasma using amlodipine D4 as internal standard was used.
  - The analytical range for amlodipine in plasma was 0.11 - 15.19 ng/mL

Reviewer's comment: The performance of the analytical method is acceptable per the specifications in Bioanalytical Method Validation Guidance.

Statistical Methods:

- Statistical analysis of the PK parameters was carried out using the PROC GLM procedure of SAS® (SAS Institute Inc., USA) version 9.4.

- Descriptive statistics were computed and reported for the amlodipine pharmacokinetic parameters.
- The Ln-transformed PK parameters C_{max} and AUC_{0-72h} were subjected to Analysis of Variance (ANOVA) for bioequivalence assessment. The model included sequence, subject (sequence), period and formulation effects as fixed effects factors.
- A studentized residual test for outlier of T/R (Test/Reference) was computed for C_{max} and AUC_{0-72h}

Result:
32 subjects completed the study.

Pharmacokinetics:
The median T_{max} for NORLIQVA and NORVASC® tablets was 6 hours. For statistical summary of the relative BA assessment refer to Table 4 in section 2.2.3. The PK parameters of amlodipine are summarized in Table A1. The PK parameters of amlodipine following administration of NORLIQVA and NORVASC® tablets are summarized in Table A1.

Table A1 Summary of PK parameters

Pharmacokinetic Parameters (Units)	Mean ± SD (Un-transformed data)	
	NORLIQVA	NORVASC®
C_{max} (ng/mL)	8.76 ± 1.84	8.39 ± 1.79
AUC_{0-72h} (ng.hr/mL)	343.26 ± 71.36	325.67 ± 62.47
K_{el} (hr^{-1})	0.014 ± 0.003	0.014 ± 0.003
$t_{1/2}$ (hr)	52.31 ± 14.64	50.39 ± 10.56
T_{max} (hr)*	6.00	6.00

*: Median

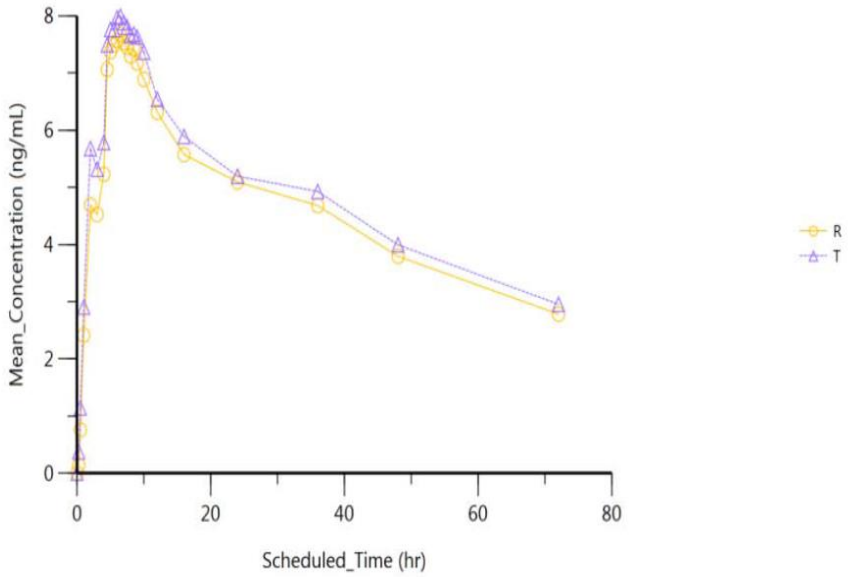

Figure A1. Linear scale plot of mean plasma amlodipine concentration vs time profiles (T: NORLIQVA (10 mL equivalent to the dose of 10 mg amlodipine); R: NORVASC® 10 mg tablet) (N = 32)
Source: Clinical Study Report Study No. 19-029

Conclusion:
The study results demonstrate bioequivalence between the NORLIQVA (10 mL equivalent to 10 mg amlodipine) and NORVASC® (amlodipine besylate) 10 mg tablet under fasted conditions.

3.2 Food effect study

Study No: 19-086	EDR: \\CDSESUB1\evsprod\nda214439\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\19-086\study-report-body.pdf

Clinical Study Start Date 30th December 2019
Clinical Study Completion Date 30th January 2020

Title of Study:
An open-label, balanced, randomized, single-dose, two-treatment (fed vs. fasting), two-sequence, two-period, crossover, food effect study of amlodipine (b) (4) 1 mg/mL oral solution (Dose: 10 mL equivalent to the dose of 10 mg of amlodipine) of CMP Development LLC, USA in healthy adults under fed versus fasting conditions.

Investigational Product:
NORLIQVA – Amlodipine (b) (4) 1 mg/ml oral solution (10 mL equivalent to 10 mg amlodipine)
Manufactured by: (b) (4)
Manufactured for: CMP Development LLC, Farmville, NC, USA 27828

Study:

- **Design:** randomized, single-dose, two-treatment (fed vs. fasting), two-sequence, two-period, crossover, food effect study
- **Washout:** A washout period of 27 days was kept between each dose administration.
- **Study participants:** 32 healthy adults, 18-45 years of age.
- **Treatments Administered**

  Fasted state administration:
  A single oral dose of test product was administered with 240 mL (milliliter) of drinking water, at an ambient temperature after an overnight fasting of at least 10 hours

  Fed state administration:
  A single oral dose of test product was administered with 240 mL (milliliter) of drinking water, at an ambient temperature, 30 minutes after the start of high-fat high-calorie, non-vegetarian breakfast.
- **Sampling times (h):** pre-dose, 0.25, 0.5, 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 12, 16, 24, 36, 48- and 72-hours post-dose in each period.
- **Pharmacokinetic parameters calculated:** C_{max}, and AUC_{0-72h}, T_{max}

Analytical Method:

- A validated LC-MS method for the estimation of amlodipine in human K_2EDTA plasma using amlodipine D4 as internal standard was used.
- The analytical range for amlodipine in plasma was 0.05- 20.01 ng/mL

Reviewer's comment: The performance of the analytical method is acceptable per the specifications in Bioanalytical Method Validation Guidance.

Statistical Methods:

- Statistical analysis of the pharmacokinetic parameters was carried out using the PROC GLM procedure of SAS® (SAS Institute Inc., USA) version 9.4.
- The Ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-72h} were subjected to ANOVA for food effect assessment. The model included sequence, subject (sequence), period and formulation effects as fixed effects factors.

Result:

32 subjects completed the study. Statistical analysis was performed using data from 31 subjects that completed the study according to the protocol.

Pharmacokinetics:

The median time to attain peak plasma concentration of amlodipine (T_{max}) following fed and fasted state administration was 6 h and 7.5 h, respectively. For statistical summary of the food effect assessment refer to Table 5 in section 2.2.4. The PK parameters of amlodipine following fed and fasted state administration are summarized in Table A2.

Table A2 Summary of PK parameters

Pharmacokinetic Parameters (Units)	Mean ± SD (Un-transformed data)	
	Fed state	Fasted state
C_{max} (ng/mL)	8.51 ± 1.58	8.71 ± 1.39
AUC_{0-72h} (ng.hr/mL)	348.91 ± 63.16	345.17 ± 63.17
T_{max} (hr)*	6.00	7.00

*: Median

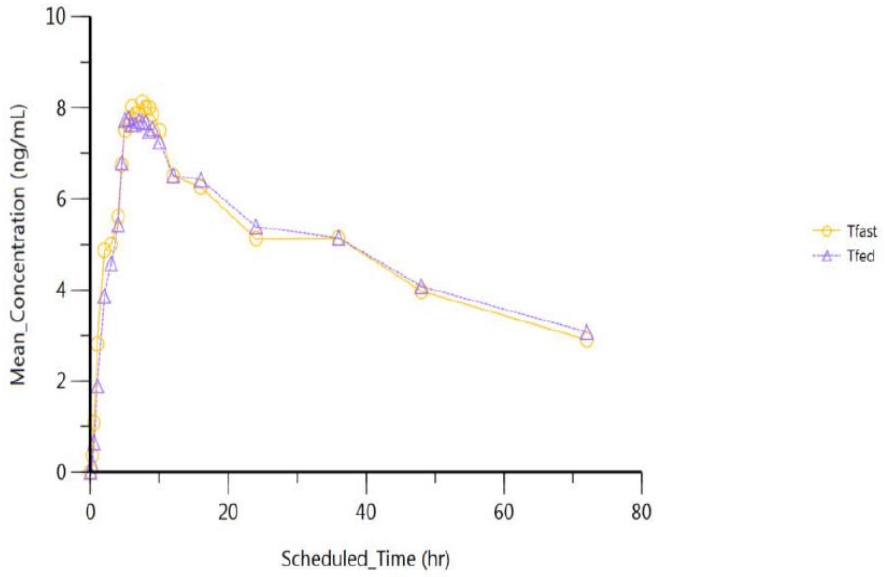

Figure A2. Linear scale plot of mean plasma concentrations vs. time for amlodipine (T_{fed}- fed state administration, T_{fast} – fasted state administration) (N = 31)
Source: Clinical Study Report Study No. 19-086

Conclusion:
Fed state administration of the NORLIQVA does not have a significant effect on the oral absorption of amlodipine. NORLIQVA may be administered without regards to food.

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