CLINICAL PHARMACOLOGY REVIEW

NDA	214439
Submission type	PMR Clinical Study Report
Submission date	February 7, 2024
Brand name	NORLIQVA
Generic name	Amlodipine
Applicant	CMP Development LLC
Primary reviewer	Leslie Kenna, PhD
Secondary reviewer	Brianna Cote, PharmD, PhD

BACKGROUND

Norliqva (amlodipine) 1 mg/mL oral solution was approved on February 24, 2022, for the treatment of hypertension in adults and children 6 years and older and for the 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 <40%].

This Prior Approval Supplement was submitted to address Post-Marketing Requirement (PREA Commitment) 4239-2 as described in the February 24, 2022, approval letter:

> Conduct an open-label, randomized, single oral dose, two-treatment, two period, two-sequence crossover bioequivalence and bioavailability study of amlodipine (ethanol-containing) oral solution versus amlodipine (ethanol-free) oral solution in healthy adults under fasting conditions.

The Applicant eliminated ethanol in their formulation and conducted Study C1B02037 ("An open label, randomized, two-period, two treatment, two-sequence, truncated crossover, balanced, single dose oral bioequivalence study*"*) in 28 adults to demonstrate bioequivalence between the formulations. The Applicant submitted a BE study report, BE study data, labeling, and analytical methods for review.

The protocol for Study C1B02037 was submitted on September 2, 2022, under IND 141056 (SDN 0009) and reviewed by the Office of Clinical Pharmacology in a review dated November 1, 2022. The proposed dose (10 mL; the highest labeled dose), PK endpoints (Cmax, AUC72 and Tmax), washout period (21 days), and PK sampling plan (1.0, 2.0, 3.0, 4.0, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 11.0, 12.0, 13.0, 14.0, 18.0, 24.0, 36.0, 48.0 and 72.0 hours post dose) in the protocol were deemed acceptable. The review states: "Considering the elimination half-life of amlodipine (52 hours), the study design appears acceptable." And "Considering the Tmax of amlodipine (6.5 hours), the proposed sampling plan appears acceptable."

Note that according to approved labeling*,* administration of Norliqva with a high-fat, high-calorie meal did not have a significant effect on its C_{max} or AUC.

RECOMMENDATION

The Office of Clinical Pharmacology has reviewed the results from Study C1B02037 and has determined that Post-Marketing Requirement 4239-2 has been fulfilled.

LABELING CHANGES

No labeling changes to clinical pharmacology information were proposed in this submission.

REVIEW – STUDY C1B02037

TITLE

Single dose oral bioequivalence study of Amlodipine Oral Solution, 1 mg /mL and Norliqva® (Amlodipine) Oral Solution, 1 mg/mL in healthy adult human subjects under fasting conditions

PRIMARY OBJECTIVE

To compare and evaluate the oral bioavailability of Amlodipine Oral Solution, 1 mg/mL with that of Norliqva® (Amlodipine) Oral Solution, 1 mg/mL in healthy, adult, human subjects under fasting conditions.

DESIGN

This is a randomized, two-period, two-treatment, two-sequence, truncated, crossover, single dose oral bioequivalence study in healthy adult human subjects under fasting condition to compare and evaluate the oral bioavailability of test formulation with that of reference formulation in 28 subjects. After an overnight fast of at least 10 hours, a single dose of 10 mL (1 mg/mL) oral solution of investigational product consistent with the maximum daily dose was administered.

Inclusion criteria relevant to Clinical Pharmacology considerations

- 18 to 45 years old, both inclusive.
- Male and/or non-pregnant, non-lactating female.
- 18.5 to 30.0 kg/m^2, both inclusive
- Judged by the principal or sub-investigator or physician as normal and healthy

Exclusion criteria relevant to Clinical Pharmacology considerations

- Had significant diseases or clinically significant abnormal findings during screening [medical history, physical examination (clinical examination), laboratory evaluations, ECG recording, gynecological history and examination (including pelvic examination and routine breast examination) (for female volunteers)].
- Any disease or condition like diabetes, psychosis or others, which might compromise the haemopoietic, gastrointestinal, renal, hepatic, cardiovascular, respiratory, central nervous system or any other body system.

- History or presence of bronchial asthma.
- Use of any hormone replacement therapy within 3 months prior to the first dose of study medication.
- A depot injection or implant of any drug within 3 months prior to the first dose of study medication.
- Use of CYP enzyme inhibitors or inducers within 30 days prior to the first dose of study medication.
- History or evidence of drug dependence or of alcoholism or of moderate alcohol use.
- Smokers who smoked 10 or more cigarettes per day or 20 or more biddies per day or those who could not refrained from smoking during the study period.
- Volunteers who had received a known investigational drug within seven elimination half-lives of the administered drug prior to the first dose of study medication.
- Use of any prescribed medications within 14 days prior to the first dose of study medication.
- Use of any OTC products, vitamin and herbal products, etc., within 7 days prior to the first dose of study medication.
- Use of grapefruit and grapefruit containing products within 7 days prior to the first dose of study medication.
- Ingestion of any caffeine or xanthine products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.), cigarettes and tobacco containing products, recreational drugs, alcohol or other alcohol containing products within 48 hours prior to the first dose of study medication.

Treatment

After an overnight fast of at least 10 hours, a single dose 10 mL (1 mg/mL) of oral solution of either test product (Amlodipine Oral Solution, 1 mg/mL) or reference product (Norliqva® Oral Solution, 1 mg/mL) consistent with the maximum daily dose as per the package insert, was administered. After a washout period of at least 21 days, participants received the other product.

Pharmacokinetic assessment

Blood samples were collected pre-dose and at 1.0, 2.0, 3.0, 4.0, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 11.0, 12.0, 13.0, 14.0, 18.0, 24.0, 36.0, 48.0 and 72.0 hours post dose.

Power/Sample size calculation

Assuming: Test/Reference ratio = 89.00% – 112.36%, Intra-subject CV (%) ~ 12, significance level = 5%, and Power = 90%, a sample size of 23 subjects was determined to be sufficient to establish bioequivalence with adequate power. Allowing for dropouts and withdrawals, there was a recruitment target of 30 subjects.

Pharmacokinetics and statistical analysis

The statistical method for testing bioequivalence was based on the determination of the 90% confidence interval around the ratio of the Ln-transformed population means (Test/Reference)

for the primary PK parameters Cmax and area under the plasma concentration to 72 hours (AUC72). AUC72 was calculated using the linear trapezoidal rule from the zero time point to 72 hours post-dose.

An analysis of variance model (ANOVA) was used to compare natural log transformed C_{max}, AUC_{72} with treatment, period, sequence, and subject as a fixed effect.

Bioanalytical

- Analysis was completed with high performance liquid chromatography followed by tandem mass spectrometric detection (LC-MS/MS) (Amlodipine in human plasma & AP LC/MS/MS, Analytical Procedure #: 577.MV.001)
- The analyte was quantified using a liquid-liquid extraction method with API 4000 LC/MS/MS system detection.

Table 1 provides a summary of the analytical method.

Table 1. Summary of Analytical Method to Measure Amlodipine in Human Plasma.

<table>
<tr><td>Analyte</td><td>Amlodipine</td></tr>
<tr><td>Matrix</td><td>Human plasma</td></tr>
<tr><td>Reference standard</td><td>Amlodipine d4</td></tr>
<tr><td>Limit of detection</td><td>0.05 ng/mL</td></tr>
<tr><td>QC (ng/mL)</td><td>0.1500 (LQC), 1.300 (MQC-2), 6.000 (MQC-1) and 11.25 (HQC)</td></tr>
<tr><td>Precision and Accuracy</td><td>
<table>
<tr><th></th><th>Precision (%CV):</th><th>Accuracy (%Bias):</th></tr>
<tr><td>LLOQ Intra-run</td><td>2.2% to 13.5%</td><td>-2.7% to 1.9%</td></tr>
<tr><td>LLOQ Inter-run</td><td>7.5%</td><td>-0.5%</td></tr>
<tr><td>ULOQ Intra-run</td><td>0.5% to 1.7%</td><td>-1.6% to 1.9%</td></tr>
<tr><td>ULOQ Inter-run</td><td>1.7%</td><td>0.3%</td></tr>
</table>
</td></tr>
<tr><td>Hook Effect / Dilution integrity</td><td>Samples can be diluted up to 10 times for amlodipine.
<table>
<tr><th colspan="4">Dilution Integrity</th></tr>
<tr><th colspan="2"></th><th>Precision (%CV):</th><th>Accuracy (%Bias):</th></tr>
<tr><td rowspan="2">Up to 120.0 ng/mL, Diluted 10 times</td><td>DIQC</td><td>1.8%</td><td>0.4%</td></tr>
<tr><td>DHQC</td><td>1.0%</td><td>8.9%</td></tr>
<tr><td rowspan="2">Up to 22.50 ng/mL, Diluted 02 times</td><td>DIQC</td><td>2.0%</td><td>4.5%</td></tr>
<tr><td>DHQC</td><td>1.9%</td><td>6.0%</td></tr>
</table>
</td></tr>
<tr><td>Linearity</td><td>0.05000 ng/mL to 15.00 ng/mL calibration range.</td></tr>
<tr><td>Recovery</td><td>The %CV for Amlodipine (at each level as well as across all levels) and for Amlodipine d4 (Internal Standard) (across all levels) was found within in-house SOP acceptance criteria. Overall mean recovery: 88.5% (CV: 3.2%).</td></tr>
<tr><td>Cross-Reactivity</td><td>No significant interference was observed between Amlodipine and the internal standard. No significant interference of Amlodipine Metabolite, Dehydro Amlodipine and Valsartan was observed at the retention time of Amlodipine and internal standard.</td></tr>
</table>

Stability

Amlodipine	
Stock Solution Stability at Room Temperature	50 hours
Stock Solution Stability at Refrigerator Temperature	33 days
Working Solution Stability at Room Temperature	51 hours
Working Solution Stability at Refrigerator Temperature	33 days
Amlodipine d4 (Internal Standard)	
Stock Solution Stability at Room Temperature	48 hours
Stock Solution Stability at Refrigerator Temperature	33 days
Working Solution Stability at Room Temperature	52 hours
Working Solution Stability at Refrigerator Temperature	16 days
Stability	
Blood Stability of Amlodipine in wet ice bath	02 Hours
Blood Stability of Amlodipine fortified with Amlodipine Metabolite/ Dehydro Amlodipine/Valsartan (0.01500/0.01500/12.00 µg/mL) in wet ice bath	02 Hours
Freeze-Thaw Stability of Amlodipine	06 cycles
Freeze-Thaw Stability of Amlodipine fortified with Amlodipine Metabolite/Dehydro Amlodipine/Valsartan (0.01500/0.01500/ 12.00 µg/mL)	06 cycles
Bench Top Stability of Amlodipine	24 hours
Bench Top Stability of Amlodipine fortified with Amlodipine Metabolite/Dehydro Amlodipine/Valsartan (0.01500/0.01500/ 12.00 µg/mL)	24 hours
Processed Stability of Extracted Samples of Amlodipine at Room Temperature	105 hours
Processed Stability of Extracted Samples of Amlodipine fortified with Amlodipine Metabolite/Dehydro Amlodipine/Valsartan (0.01500/0.01500/12.00 µg/mL) at Room Temperature	105 hours
Processed Stability of Extracted Samples of Amlodipine at Refrigerator Temperature	105 hours
Processed Stability of Extracted Samples of Amlodipine fortified with Amlodipine Metabolite/Dehydro Amlodipine/Valsartan (0.01500/0.01500/12.00 µg/mL) at Refrigerator Temperature	105 hours

Source: Reviewer formatted information provided in NDA 214439 In DARRTS: SDN 0056 February 7, 2024, Section 5.3.1.4 Method Validation Report

- Regression type: linear regression analysis with $1/x^2$ weighting
- Analytical run acceptance criteria:

1. The coefficient of variation (%CV) for QC samples at each concentration level must be less than or equal to 15%.
2. The % bias of calculated means for QC samples at each concentration level must be within ±15% of the nominal value.

3. Two-thirds of the QC samples at each level must have % bias within ±15% of the nominal value.
4. Not more than two QC samples (not at same concentration) can be excluded for all concentration levels with valid reason from the calculation of precision and %bias.

- Incurred sample reanalysis
    - The %difference between two measurements (original as the reference) should be within 20.0% for ≥ 2/3 of the duplicate pairs

RESULTS

Patient disposition

A total of 30 subjects were enrolled, and 28 subjects (93.3%) completed the treatments and the study. One (1) subject discontinued due to injury and one (1) subject discontinued due to ocular hyperemia. Both events were assessed as mild in severity and were not suspected of being related to any study drug.

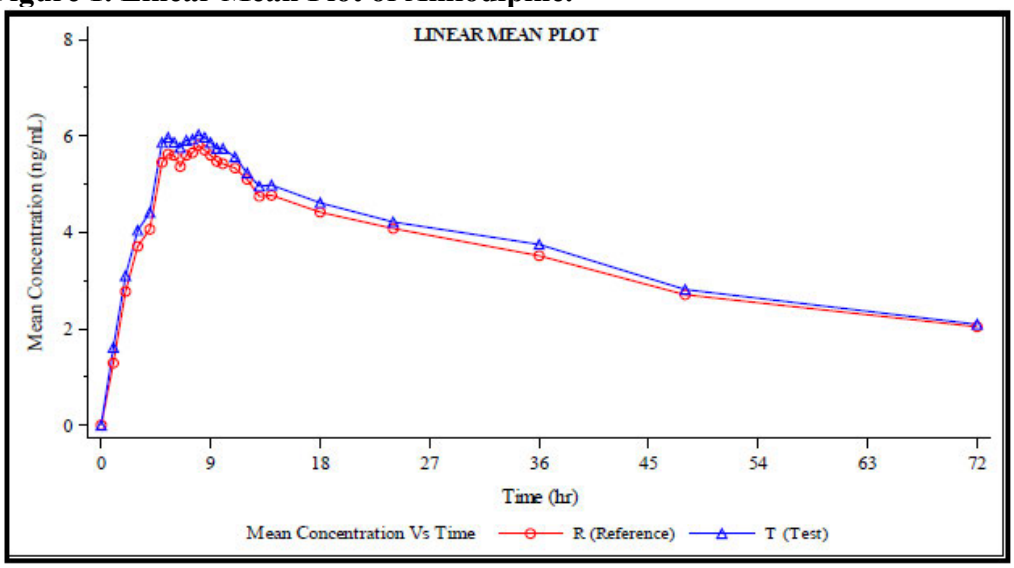
Pharmacokinetics

Blood samples were collected at pre-dose (0.0 hours) and at 1.0, 2.0, 3.0, 4.0, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 11.0, 12.0, 13.0, 14.0, 18.0, 24.0, 36.0, 48.0 and 72.0 hours post dose in each period after administration of each dose. Thirty subjects were dosed in period 1 and 28 subjects were dosed in period 2. Data from 28 subjects is included in the bioequivalence analysis.

Criteria for evaluation

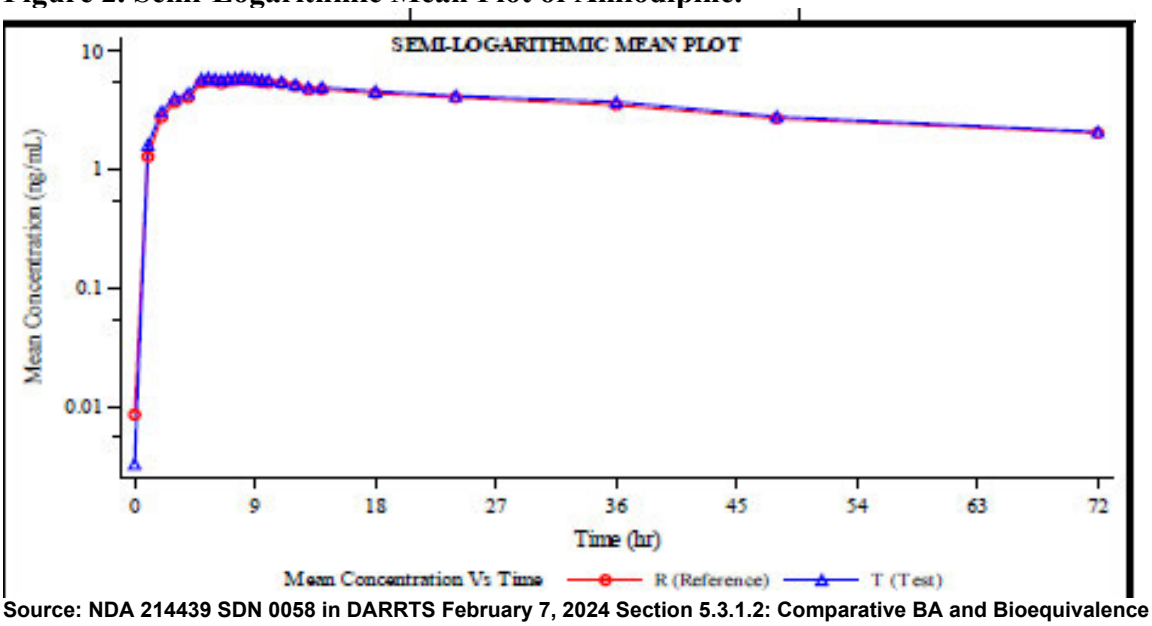
The 90% confidence intervals of the relative mean (Geometric least square mean) of the test to reference formulation for Ln-transformed Cmax and AUC72 were to be within 80.00% and 125.00% for amlodipine to establish bioequivalence. Figure 1 and Figure 2 show the results of the BE study.

Figure 1. Linear Mean Plot of Amlodipine.



Source: NDA 214439 SDN 0058 in DARRTS February 7, 2024 Section 5.3.1.2: Comparative BA and Bioequivalence (BE) Study Reports: Study C1B02037 Report page 11 of 72.

Figure 2. Semi-Logarithmic Mean Plot of Amlodipine.



Source: NDA 214439 SDN 0058 in DARRTS February 7, 2024 Section 5.3.1.2: Comparative BA and Bioequivalence (BE) Study Reports: Study C1B02037 Report page 11 of 72.

Table 2 summarizes the pharmacokinetic data.

Table 3 summarizes the results of bioequivalence testing.

Table 2. Summary of Pharmacokinetic Data for 10 mL Amlodipine Oral Solution (1 mg/mL)

	Test Product (T): (n=28)		Reference Product (R): (n=28)	
PARAMETER	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))
Cmax (ng/mL)	28	6.644 ±1.644 (24.748)	28	6.281 ±1.637 (26.058)
AUC72 (ng/mL)*(hr)	28	259.388 ±59.695 (23.014)	28	247.595 ±59.517 (24.038)
Tmax (hr)^	28	7.000 (5.000 - 11.000)	28	6.750 (5.000 - 12.000)
(^) Tmax is presented as Median (Range)				

Source: NDA 214439 SDN 0058 in DARRTS February 7, 2024 Section 5.3.1.2: Comparative BA and Bioequivalence (BE) Study Reports: Study C1B02037 Report page 10 of 72.

Table 3. Test & Reference Geometric mean, Ratio, 90% Confidence Intervals, Acceptance Criteria and Outcome of BE result based on Ln-transformed data for Amlodipine.

Pharmacokinetic parameter	Geometric mean				Ratio (%)
	N	Test	N	Reference	
Cmax (ng/mL)	28	6.451	28	6.077	106.14
AUC72 (ng/mL)*(hr)	28	252.108	28	240.612	104.78
Pharmacokinetic parameter	90% Confidence Intervals		Acceptance Criteria		Outcome of BE result
Cmax (ng/mL)	(101.18%;111.35%)		80.00% - 125.00%		Bioequivalent
AUC72 (ng/mL)*(hr)	(100.24%;109.52%)		80.00% - 125.00%		

Source: NDA 214439 SDN 0058 in DARRTS February 7, 2024 Section 5.3.1.2: Comparative BA and Bioequivalence (BE) Study Reports: Study C1B02037 Report page 11 of 72.

Safety

There was no serious adverse event (AE) reported in the study. There were three (3) total AEs reported by three (3) subjects during the entire study. All AEs were mild in severity. The events were grade 1 headache, ocular hyperemia, and injury to left hand.

Incurred Sample Reanalysis

Table 4 provides the results of incurred sample reanalysis.

Table 4. Incurred Sample Reanalysis Results.

Number of samples analyzed	1448
Number of ISR samples analyzed	126
Percentage (%) of ISR samples analyzed	8.70%
Total number of incurred samples reproducible	125
Total % of reproducible Sample	99.21%
	ISR 01
Number of samples analyzed	126
Number of samples found reproducible	125
Percentage of reproducible Samples	99.21%
Date Extracted	10 Aug 23
Date Injected	10 Aug 23
Table Reference	**Table 5**

Source: NDA 214439 SDN 0058 in DARRTS February 7, 2024 Section 5.3.1.4 Sample Analysis Report page 22 of 59

CONCLUSION

The Applicant concludes that test product Amlodipine Oral Solution, 1 mg/mL is bioequivalent with the Reference product Norliqva® (Amlodipine) Oral Solution, 1 mg/mL, under fasting conditions.

Reviewer's Comment
The Applicant conducted bioequivalence study C1B02037 in accordance with the protocol that was submitted on September 2, 2022, under IND 141056 (SDN 0009) and deemed acceptable in a review by the Office of Clinical Pharmacology dated November 1, 2022. The 90% confidence intervals of the relative mean (Geometric least square mean) of the test to reference formulation for Ln-transformed Cmax and AUC72 were within 80.00% and 125.00% for Amlodipine. The Applicant has established pharmacokinetic similarity between their new formulation and the reference. They have satisfied post-marketing requirement 4239-2 from a clinical pharmacology perspective.

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/s/

LESLIE A KENNA
07/24/2024 12:13:33 PM

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07/24/2024 12:54:03 PM