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APPLICATION NUMBER:

213260Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	213260
Links to EDR	\\cdsesub1\evsprod\NDA213260\0016\ \\cdsesub1\evsprod\NDA213260\0019\ \\cdsesub1\evsprod\NDA213260\0020\ \\cdsesub1\evsprod\NDA213260\0021\ \\CDSESUB1\evsprod\NDA213260\0022
Submission Dates	07/31/2022, 9/22/2022, 10/12/2022, 11/9/2022, and 11/22/2022
Submission Type	Response to Complete Response Letter
Brand Name	ATORVALIQ
Generic Name	Atorvastatin calcium
Dosage Form and Strength	Suspension; 4 mg/mL
Route of Administration	Oral
Proposed Indications	ATORVALIQ is an HMG-CoA reductase inhibitor indicated as an adjunct therapy to diet to: • Reduce the risk of myocardial infarction (MI), stroke, revascularization procedures, and angina in adult patients without coronary heart disease (CHD), but with multiple risk factors. • Reduce the risk of MI and stroke in adult patients with type 2 diabetes without CHD, but with multiple risk factors. • Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure (CHF), and angina in adult patients with CHD. • Reduce elevated total cholesterol (total-C), low-density lipoprotein-C (LDL-C), apo B, and triglyceride (TG) levels and increase high-density lipoprotein-C (HDL-C) in adult patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia. • Reduce elevated TG in adult patients with hypertriglyceridemia and primary dysbetalipoproteinemia. • Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH). • Reduce elevated total-C, LDL-C, and apo B levels in pediatric patients, 10 years to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) after failing an adequate trial of diet therapy.
Applicant	CMP Development LLC
Associated IND	137915
OCP Review Team	S. W. Johnny Lau, Yoo Jin (Elly) Moon
OCP Final Signatory	Jayabharathi Vaidyanathan

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1. EXECUTIVE SUMMARY

The applicant is developing a 4 mg/mL atorvastatin calcium oral suspension as an adjunct therapy for patients to reduce elevated lipid concentrations via the regulatory 505(b)(2) pathway. The reference listed drug (RLD) atorvastatin calcium tablets (LIPITOR) has the strengths of 10, 20, 40, and 80 mg atorvastatin per tablet and is indicated to treat hyperlipidemia (NDA 020702 approved on December 17, 1996). The applicant received the complete response letter for the original NDA 213260, which was submitted on January 13, 2020. This submission is the applicant's complete response to the complete response letter for NDA 213260 issued on October 16, 2020.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) has reviewed NDA 213260's clinical pharmacology data submitted on July 31, 2022, September 22, 2022, October 12, 2022, November 9, 2022, and November 22, 2022. OCP/DCEP finds that the submitted data are acceptable to support approval. Due to the significant effect of food on the exposure of atorvastatin calcium suspension, the product label needs to carry the following statement:

ATORVALIQ can be administered as a single dose at any time of the day, only on an empty stomach (1 hour before or 2 hours after a meal).

The following are the key review issues with specific recommendations and comments:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness and safety	A relative bioavailability study (1024) provides the scientific bridge to reference the effectiveness and safety of ATORVALIQ oral suspension to the Food and Drug Administration's findings of the innovators' effectiveness and safety.
General dosing instructions	ATORVALIQ can be administered as a single dose at any time of the day, only on an empty stomach (1 hour before or 2 hours after a meal). See section 2.2.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The proposed dosing is acceptable. See section 2.2.
Labeling	See section 2.4 for labeling recommendations.
Bridge between the "to-be-marketed" and clinical trial formulations	The applicant assessed the to-be-marketed formulation of the oral suspension in the pivotal relative bioavailability study (1024).

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Findings of 3 Relative Bioavailability Studies

Study C1B1021 is a pilot relative bioavailability study of partial replicate design between 40 mg atorvastatin calcium oral suspension and 40 mg LIPIROR tablet in healthy men. The atorvastatin Cmax was assessed via reference scaled bioequivalence approach, whereas the atorvastatin AUCt and AUCi were assessed via the 2-way average bioequivalence approach. The 95% upper confidence interval (critical bound) for the atorvastatin Cmax is -0.0084 (< 0). The 90% confidence interval of the ratio for atorvastatin AUC between atorvastatin suspension and LIPITOR tablet is 94.54% – 113.82% (within the 80% – 125%). Thus, the 40 mg/10 mL atorvastatin calcium oral suspension is bioequivalent to the 40 mg LIPITOR tablet.

Study C1B1023 is a pilot relative bioavailability study of full replicate design between 80 mg atorvastatin calcium oral suspension and 80 mg LIPIROR tablet in healthy men. The atorvastatin Cmax was assessed via reference scaled bioequivalence approach, whereas the atorvastatin AUCt and AUCi were assessed via the 2-way average bioequivalence approach. The 95% upper confidence interval (critical bound) for the atorvastatin Cmax is 0.0239 (not < 0). The 90% confidence interval of the ratio for atorvastatin AUC between atorvastatin suspension and LIPITOR tablet is 95.44% – 113.97% (within the 80% – 125%). Thus, the 80 mg/20 mL atorvastatin calcium oral suspension is not bioequivalent to the 80 mg LIPITOR tablet.

Study C1B1024 is a pivotal relative bioavailability study of full replicate design between 80 mg atorvastatin calcium oral suspension and 80 mg LIPIROR tablet in healthy men. The atorvastatin Cmax was assessed via reference scaled bioequivalence approach, whereas the atorvastatin AUCt and AUCi were assessed via the 2-way average bioequivalence approach. The 95% upper confidence interval (critical bound) for the atorvastatin Cmax is -0.03395 (< 0). The 90% confidence interval of the ratio for atorvastatin AUC between atorvastatin suspension and LIPITOR tablet is 107.71% – 121.12% (within the 80% – 125%). Thus, the 80 mg/20 mL atorvastatin calcium oral suspension is bioequivalent to the 80 mg LIPITOR tablet.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The RLD, LIPITOR is indicated as an adjunct therapy to diet to:

- Reduce the risk of MI, stroke, revascularization procedures, and angina in adult patients without CHD, but with multiple risk factors
- Reduce the risk of MI and stroke in adult patients with type 2 diabetes without CHD, but with multiple risk factors
- Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF, and angina in adult patients with CHD

- Reduce elevated total-C, LDL-C, apo B, and TG levels and increase HDL-C in adult patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia
- Reduce elevated TG in adult patients with hypertriglyceridemia and primary dysbetalipoproteinemia
- Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH)
- Reduce elevated total-C, LDL-C, and apo B levels in pediatric patients, 10 years to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) after failing an adequate trial of diet therapy

ATORVALIQ has the same proposed dosing regimen for general dosing as the RLD.

2.2.2 Therapeutic individualization

ATORVALIQ has the same proposed dosing paradigm for general dosing as the RLD.

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

Summary of labeling recommendation for different sections are listed below:

- Section 7: The proposed labeling for Drug Interactions is acceptable.
- Section 8: The proposed labeling for Use in Specific Populations is acceptable.

Section 2.1 Hyperlipidemia and Mixed Dyslipidemia:

ATORVALIQ can be administered as a single dose at any time of the day, only on an empty stomach (1 hour before or 2 hours after a meal). ~~with or without food~~.

Section 12.3 Pharmacokinetics:

Replace the following statement under Section 12.3 Pharmacokinetics of ATORVALIQ's proposed label because of the results of Study 0236. See Question 3.3.4 below.

~~Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether ATORVALIQ is given with or without food.~~

with the following statement under Section 12.3 Pharmacokinetics of ATORVALIQ's proposed label:

Administration of ATORVALIQ with high fat meal resulted in a 30% and 63% decrease in atorvastatin AUC and Cmax, respectively, compared with what was observed in the fasted state.

The decrease in exposure can be clinically significant, and therefore ATORVALIQ should be taken only on an empty stomach (1 hour before or 2 hours after a meal).

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

The Division of Diabetes, Lipid Disorders, and Obesity of the Office of Cardiology, Hematology, Endocrinology, and Nephrology issued a complete response letter for the atorvastatin calcium oral suspension on October 16, 2020 (DARRTS Reference ID: 4687276). The following shows the Clinical Pharmacology related issues:

Since the application does not contain clinical efficacy and safety data for the proposed atorvastatin calcium oral suspension (proposed product), relative bioavailability results are the fundamental bridge to the efficacy and safety data of the listed drug product. Relative bioavailability between the proposed product and the listed drug did not meet the conventional 80 – 125% criteria based on results from Study 18-VIN-0235. The 90% confidence interval for the geometric mean ratios (GMRs) between the proposed product and the listed drug for all primary PK parameters (AUC0-t, AUC0-∞ and Cmax) were outside the conventional 80 – 125% limits for all moieties measured (atorvastatin, 2-hydroxy atorvastatin and 4-hydroxy atorvastatin) under fasting conditions. The exposures of atorvastatin, 2-hydroxy atorvastatin, and 4-hydroxy atorvastatin were (b) (4) , respectively following administration of the proposed product as compared to those following administration of the listed drug. In addition, results from Study 18-VIN-0236 indicate that the proposed product had a greater magnitude of food effect (30% reduction in AUC and 63% reduction in Cmax) compared to the reported values of 9% reduction in AUC and 25% reduction in Cmax for the listed drug when administered with food. The deficiency cannot be addressed with labeling, because there is no condition of use that would ensure safety and effectiveness of the product. When the proposed product is administered under fed conditions, the magnitude of the decrease in atorvastatin and its metabolites exposure is much greater for the proposed product compared to the listed drug, which could lead to loss of efficacy. On the other hand, if the product is administered under fasting conditions, the large increase in atorvastatin and its metabolites exposure compared to the listed drug is a safety issue. Additionally, there is a wide fluctuation in atorvastatin and metabolite levels following administration of the proposed product compared to the listed drug under both fasting and fed conditions. Thus, the clinical pharmacology and other relevant findings of the listed drug cannot be relied upon for the proposed atorvastatin product and the data do not support its approval.

Reformulate the proposed product and conduct additional relative bioavailability studies to demonstrate the bioequivalence to the listed drug or conduct a clinical study to support the effective and safe use of the proposed atorvastatin oral suspension product.

For earlier Regulatory Background, see Clinical Pharmacology review by Dr. Sury Sista in DARRTS dated September 8, 2020, Reference ID: 4667680.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Atorvastatin calcium is a cholesterol lowering agent.

Mechanism of Action of Atorvastatin Calcium

Atorvastatin competitively inhibits HMG-CoA reductase, which is a rate-limiting enzyme in cholesterol biosynthesis in the liver.

Summary of General Clinical Pharmacology and Pharmacokinetics (according to the RLD, LIPITOR, label)

Pharmacodynamics	Atorvastatin, and some of its metabolites, are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance.
Effect of Intrinsic Factors on Pharmacokinetics	Except for body weight, population PK analysis did not identify any other covariate to have any clinically relevant impact on the PK of LIPITOR.
Renal or Hepatic Impairment	Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary. In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease severity. Cmax and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease severity.
Pediatric	Apparent oral clearance of atorvastatin in pediatric subjects appeared similar to that of adults when scaled allometrically by body weight as the body weight was the only significant covariate in atorvastatin population PK model with data including pediatric Heterozygous Familial Hypercholesterolemia (HeFH) patients (ages 10 years to 17 years of age, n=29) in an open-label, 8-week study.
Drug-Drug Interaction	Atorvastatin is a substrate of the hepatic transporters, OATP1B1 and OATP1B3 transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporter BCRP, which may limit the intestinal absorption and biliary clearance of atorvastatin. (https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020702s074lbl.pdf).
Absorption (Bioavailability)	The absolute bioavailability of atorvastatin (parent drug) is approximately 14%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.
Distribution	The mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥ 98% bound to plasma proteins. A blood/plasma ratio of about 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk.

Metabolism	Atorvastatin is extensively metabolized to ortho- and para-hydroxylated derivatives and various beta-oxidation products. In vitro inhibition of HMG-CoA reductase by ortho- and para-hydroxylated metabolites is equivalent to that of atorvastatin.
Excretion	Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is about 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The applicant did not reformulate the atorvastatin calcium oral suspension. To address the complete response letter, the applicant conducted 3 relative bioavailability studies. Studies C1B01021 and C1B01023 are pilot studies, whereas Study C1B01024 serves as the pivotal bridging study to reference the efficacy and safety of the RLD, LIPITOR. For the review of prior pivotal study (18-VIN-0235) that supported the original submission of NDA 213260, see Dr. Sury Sista's Clinical Pharmacology reviewed dated DARRTS dated September 8, 2020, Reference ID: 4667680. Of note, the sponsor used AUCt and AUCi to denote $AUC_{(0\text{-}t)}$ and $AUC_{(0\text{-}inf)}$, respectively.

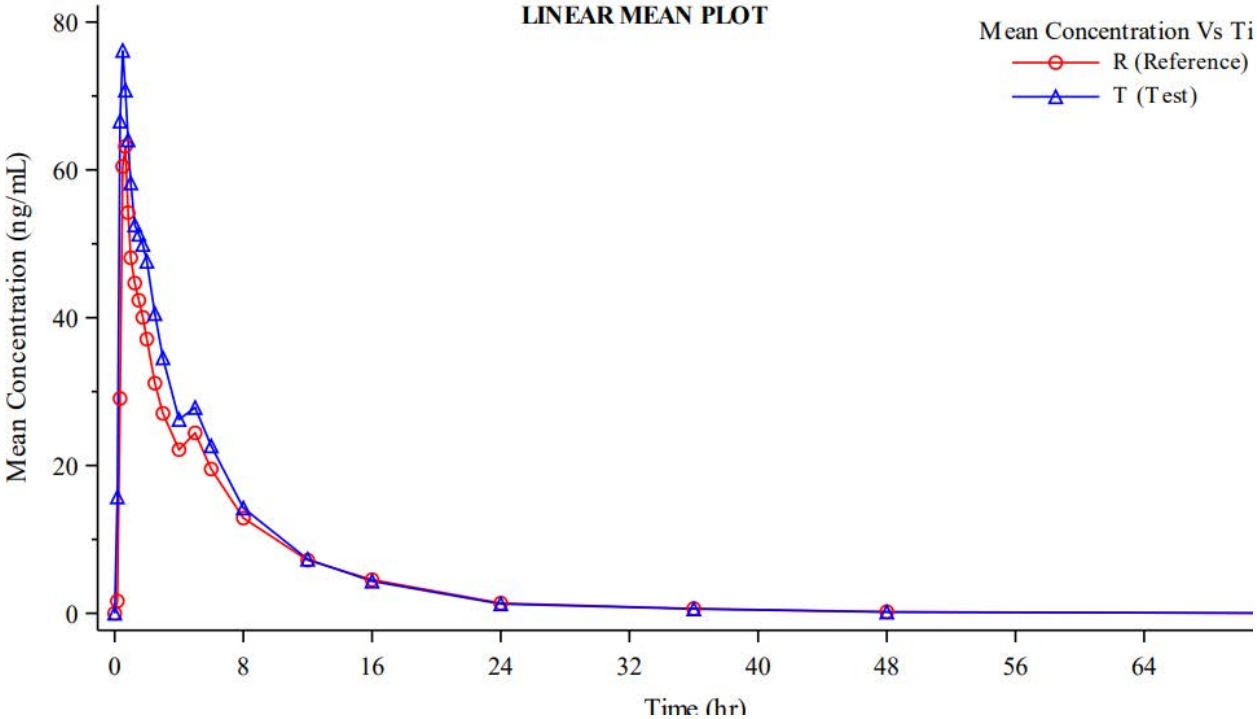
Study C1B1021 is a pilot relative bioavailability study of partial replicate design between 40 mg atorvastatin calcium oral suspension and 40 mg LIPIROR tablet in 15 healthy men under fasting. Atorvastatin Cmax was assessed via reference scaled bioequivalence approach, whereas the atorvastatin AUCt and AUCi were assessed via the 2-way average bioequivalence approach. The 95% upper confidence interval (critical bound) for the atorvastatin Cmax is -0.0084 (< 0). The 90% confidence interval of the ratio for atorvastatin AUCt between atorvastatin suspension and LIPITOR tablet is 94.54% – 113.82% (within the 80% – 125%). Thus, the 40 mg/10 mL atorvastatin calcium oral suspension is bioequivalent to the 40 mg LIPITOR tablet.

Study C1B1023 is a pilot relative bioavailability study of full replicate design between 80 mg atorvastatin calcium oral suspension and 80 mg LIPIROR tablet in 16 healthy men under fasting. The atorvastatin Cmax was assessed via reference scaled bioequivalence approach, whereas the atorvastatin AUCt and AUCi were assessed via the 2-way average bioequivalence approach. The 95% upper confidence interval (critical bound) for the atorvastatin Cmax is 0.0239 (not < 0). The 90% confidence interval of the ratio for atorvastatin AUCt between atorvastatin suspension and LIPITOR tablet is 95.44% – 113.97% (within the 80% – 125%). Thus, the 80 mg/20 mL atorvastatin calcium oral suspension is not bioequivalent to the 80 mg LIPITOR tablet.

Study C1B01024 is a study of the to-be-marketed 80 mg/20 mL of ATORVALIQ (biobatch size is the same as the proposed commercial batch size) versus administration of 80 mg LIPITOR tablet (US approved and marketed product). The design was an open label, randomized, 2-treatment, 4-period, 2-sequence, fully replicated, crossover, single dose study. A 7-day washout

separated the 2 oral administrations. Fifty-two healthy men received treatments and 51 men completed the treatments of single dose of the test atorvastatin calcium oral suspension and single dose of the LIPITOR tablet under fasting. Serial plasma samples were collected predose and 72 hours postdose to determine the atorvastatin, 2-hydroxyatorvastatin, and 4-hydroxyatorvastatin via a validated hybrid (protein precipitation + solid phase) extraction with liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) assay. This review focuses on the results of atorvastatin for the bioequivalence assessment.

Figure 1. Mean plasma atorvastatin concentration-time profiles upon dosing of the ATORVALIQ 80 mg/20 mL suspension (T) versus administration of individual 80 mg LIPITOR tablets (R) under fasting.



Source: Figure-11.4.1.1 in Study C1B01024's report Page 73 of 100

Table 1. Within subject standard deviation of the reference (S_{WR}) and Reference Intra-Subject CV (%) based on ln-transformed data for atorvastatin for Study C1B1024

Pharmacokinetic parameter	S_{WR}	Reference Intra-Subject CV (%)
Cmax (ng/mL)	0.366	37.833
AUCt (ng/mL)*(hr)	0.205	20.737
AUCi (ng/mL)*(hr)	0.203	20.461

Source: Table 11.4.7.4 in Study C1B01024's report Page 85 of 100

Because the within subject standard deviation of the atorvastatin Cmax is > 0.294, the assessment of atorvastatin Cmax will be through the reference scaled bioequivalence approach. Because the within subject standard deviation of the atorvastatin AUCt and AUCi are < 0.294, the assessment of atorvastatin AUCt and AUCi will be through the 2-way average bioequivalence approach. See Table 1.

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Table 2. The 95% Upper confidence interval of test versus reference, ratio, acceptance range and outcome of BE result based on Ln-transformed data for atorvastatin for Study C1B1024

Pharmacokinetic parameter	95% Upper Confidence Interval	Ratio (Point estimates)	Acceptance Range for 95% Upper Confidence Interval	Acceptance Range for Ratio	Outcome of BE result
Cmax (ng/mL)	-0.03395	1.1496	≤ 0.0000	0.8000-1.2500	Equivalent

Source: Table 11.4.7.5 in Study C1B01024's report Page 85 of 100

The 95% upper confidence interval (critical bound) for the atorvastatin Cmax is less than 0. Thus, the atorvastatin Cmax is deemed equivalent between atorvastatin calcium suspension and LIPITOR tablet. See Table 2.

Table 3. Test and reference geometric mean, ratio, 90% confidence intervals, acceptance criteria and outcome of be result based on ln-transformed data for atorvastatin for Study C1B1024

Pharmacokinetic parameter	Geometric mean				Ratio (%)
	N	Test	N	Reference	
Cmax (ng/ mL)	99	77.916	97	68.725	113.37
AUCt (ng/mL)*(hr)	99	329.208	97	288.226	114.22
AUCi (ng/mL)*(hr)	99	333.501	97	293.140	113.77
Pharmacokinetic parameter	**90% Confidence Intervals**		**Acceptance Criteria for BE**		**Outcome of BE result**
Cmax (ng/ mL)	(101.68%;126.42%)		Not Applicable		Not Applicable
AUCt (ng/mL)*(hr)	(107.71%;121.12%)		80.00% - 125.00%		Equivalent
AUCi (ng/mL)*(hr)	(107.35%;120.57%)		80.00% - 125.00%		

Source: Table 11.4.7.6 in Study C1B01024's report Page 86 of 100

The 90% confidence interval of the ratio for atorvastatin AUCt between atorvastatin suspension and LIPITOR tablet and the 90% confidence interval of the ratio for atorvastatin AUCi between atorvastatin suspension and LIPITOR tablet are within the 80% – 125%. Thus, the atorvastatin AUCt of atorvastatin suspension is equivalent to that of and LIPITOR. The atorvastatin AUCi of atorvastatin suspension is equivalent to that of and LIPITOR. Overall (atorvastatin Cmax, AUCt, and AUCi), the 80 mg/20 mL atorvastatin calcium oral suspension is bioequivalent to the 80 mg LIPITOR tablet.

The applicant's results of statistical analysis for Study C1B01024 is consistent with Dr. Yoo Jin Moon's results of statistical analysis for Study C1B01024. Dr. Yuzhuo Pan performed analysis with the Office of Generic Drugs' DABERS analysis tool (for checking data consistency, duplication, and outliers), which did not show data integrity issue for Study C1B01024.

For reference, Tables 4 and 5 show the analyses of 2-hydroxyatorvastatin and 4-hydroxyatorvastatin metabolites, respectively, for Study C1B01024.

Reference ID: 5113162

Table 4. Summary of statistical analysis of 2-hydroxyatorvastatin data

PARAMETER	Unit	REFERENCE LEAST SQUARES MEAN Ln DATA	TEST LEAST SQUARES MEAN Ln DATA	REFERENCE GEOMETRIC MEAN	TEST GEOMETRIC MEAN	RATIO OF GEOMETRIC MEANS	90% CONFIDENCE INTERVAL	Point Estimate	theta
Cmax	(ng/mL)	3.734	3.741	41.848	42.128	100.67%	(91.29%;111.01%)	1.0307	0.7967
AUCt	(ng/mL)*(hr)	5.739	5.835	310.628	342.082	110.13%	(104.16%;116.43%)	1.1198	0.7967
AUCi	(ng/mL)*(hr)	5.759	5.853	316.920	348.113	109.84%	(104.08%;115.92%)	1.1161	0.7967

PARAMETER	Unit	S_{WR}	S^2_{WR}	Reference Intra CV%	S_{WT}	S^2_{WT}	Test Intra CV%	95% Upper Confidence Bound	Bio-equivalence Approach	Acceptance Criteria	Acceptance Criteria Met (Yes/No/Not Applicable)
Cmax	(ng/mL)	0.322	0.1034	33.002	0.355	0.1261	36.666	-0.05513	Reference-Scaled Average	Not Applicable	Not Applicable
AUCt	(ng/mL)*(hr)	0.179	0.0320	18.044	0.158	0.0249	15.871	0.005225	Unscaled Average	Not Applicable	Not Applicable
AUCi	(ng/mL)*(hr)	0.175	0.0306	17.640	0.156	0.0242	15.644	0.004538	Unscaled Average	Not Applicable	Not Applicable

Source: Table 11.4.1.5 in Study C1B01024's report Page 80 of 100

According to Table 4, the 95% upper confidence interval (critical bound) for the 2-hydroxyatorvastatin Cmax is less than 0. Thus, the 2-hydroxyatorvastatin Cmax is deemed equivalent between atorvastatin calcium suspension and LIPITOR tablet.

According to Table 4, the 90% confidence interval of the ratio for 2-hydroxyatorvastatin AUCt and AUCi between atorvastatin suspension and LIPITOR are within the 80% – 125%. Thus, the 2-hydroxyatorvastatin AUCt and AUCi of atorvastatin suspension is deemed equivalent to that of LIPITOR.

Table 5. Summary of statistical analysis of 4-hydroxyatorvastatin data

PARAMETER	Unit	REFERENCE LEAST SQUARES MEAN Ln DATA	TEST LEAST SQUARES MEAN Ln DATA	REFERENCE GEOMETRIC MEAN	TEST GEOMETRIC MEAN	RATIO OF GEOMETRIC MEANS	90% CONFIDENCE INTERVAL	Point Estimate	theta
Cmax	(ng/mL)	1.204	1.408	3.332	4.087	122.64%	(112.74%;133.42%)	1.2350	0.7967
AUCt	(ng/mL)*(hr)	4.312	4.447	74.569	85.375	114.49%	(108.93%;120.33%)	1.1621	0.7967
AUCi	(ng/mL)*(hr)	4.388	4.515	80.481	91.422	113.59%	(108.21%;119.25%)	1.1569	0.7967

PARAMETER	Unit	S_{WR}	S^2_{WR}	Reference Intra CV%	S_{WT}	S^2_{WT}	Test Intra CV%	95% Upper Confidence Bound	Bio-equivalence Approach	Acceptance Criteria	Acceptance Criteria Met (Yes/No/Not Applicable)
Cmax	(ng/mL)	0.343	0.1173	35.280	0.226	0.0511	22.901	0.003055	Reference-Scaled Average	Not Applicable	Not Applicable
AUCt	(ng/mL)*(hr)	0.214	0.0460	21.689	0.172	0.0296	17.322	0.006488	Unscaled Average	Not Applicable	Not Applicable
AUCi	(ng/mL)*(hr)	0.215	0.0462	21.743	0.171	0.0291	17.196	0.004603	Unscaled Average	Not Applicable	Not Applicable

Source: Table 11.4.1.5 in Study C1B01024's report Page 81 of 100

According to Table 5, the 95% upper confidence interval (critical bound) for the 4-hydroxyatorvastatin Cmax is not less than 0 (0.003055). Thus, the 4-hydroxyatorvastatin Cmax is deemed not equivalent between atorvastatin calcium suspension and LIPITOR tablet.

According to Table 5, the 90% confidence interval of the ratio for 4-hydroxyatorvastatin AUCt and AUCi between atorvastatin suspension and LIPITOR tablet are within the 80% – 125%. Thus, the 4-hydroxyatorvastatin AUCt and AUCi of atorvastatin suspension is deemed equivalent to that of and LIPITOR.

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Overall, Study C1B01024 provides adequate PK bridging of the atorvastatin suspension to the reference product, LIPITOR.

For Study C1B01024, OSIS declined to inspect the clinical site and bioanalytical site (Memorandum in DARRTS Reference ID: 5070446 dated November 1, 2022). The Office of Regulatory Affairs inspected the clinical site in November 2021, which falls within the surveillance interval. OSIS conducted a Remote Regulatory Assessment for the analytical site in (b) (4) which falls within the surveillance interval. No issues were identified in these inspections.

The OCP reviewers probed into the reason(s) for the prior pivotal Study 18-VIN-0235 that failed bioequivalence assessment. The applicant claimed that Study 18-VIN-0235 had the inappropriate study design. Table 6 shows the comparison of the 2 pivotal studies. The 2 studies were conducted at different site by different research companies. Study 18-VIN-0235 had a low within subject standard deviation for the reference (SW_R) of 23.83% so that the applicant could not use reference scaled bioequivalence approach to assess the equivalency of atorvastatin Cmax.

Table 6. Comparison of 2 pivotal studies for atorvastatin oral suspension 4 mg/mL for Study C1B1024

Study	Study 1: US Pivotal	Study 2: US Pivotal	Comments
Protocol	18-VIN-0235	C1B01024	
Title	An open-label, balanced, randomized, single-dose, two-treatment, three-sequence, three-period, partial replicate, crossover, oral bioequivalence study of Atorvastatin oral suspension 20mg/5ml at a dose of 80 mg (20mL) of LM Manufacturing Limited, UK and LIPITOR® (Atorvastatin calcium) 80 mg film-coated tablets of Parke-Davis, Division of Pfizer Inc. NY, NY 10017, in healthy, adult, human subjects under fasting condition.	An open-label, randomized, four-period, two-treatment, full replicate, crossover, balanced, single-dose oral bioavailability study of Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL) and 'LIPITOR®' (Atorvastatin calcium) tablets 80 mg in healthy adult human subjects under fasting conditions.	18-VIN-0235 was a partial replicate study design. C1B01024 was a full replicate study design.
Site	Veeda Clinical Research, Ahmedabad India.	Chiantha Research, Ahmedabad India	Study site is different
Dose	80 mg	80 mg	-
Design	Partial replicate	Full replicate	Study design is different
Submission	USFDA	USFDA	-
Year	2019	2020	-
Fast/Fed	Fasting	Fasting	-
Test Product Batch	VAL/18/0073/B	ATV21001	Different Test product batch was used.
Test Product Expiry	Mar 2020	Apr 2023	-
Reference Product Batch	W98358	EL0204	Different Reference product batch was used.
Reference Product Expiry	28 Feb 2021	Jul 2023	-
Number of Subjects	60	52	The number of subjects were lower in C1B01024 study since this was a full replicate study design.
Sampling Timepoints	27 Sampling timepoints, Predose (0.00), 0.17, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25 2.50, 2.75, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours	23 Sampling timepoints Predose (0.00), 0.167, 0.333, 0.5, 0.667, 0.833, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours	Based on earlier conducted pilot study, sampling time points in study C1B01024, were fewer than earlier 18-VIN-0235.
CV	(b) (4) % for C_{max}	37.83% for C_{max}	High Intrasubject variability as observed in a full replicate study (C1B01024) in line with reported literature.

Source: Applicant's cover letter of submission on November 9, 2022

Table 7. Results of the US Pivotal Study (18-VIN-0235):

Parameters	Geometric Least Squares Mean			% ISCV (R)	90% CI	BE
	(T)	(R)	T/R (%)			

Cmax (ng/mL)	(b) (4)	No
AUC0-t (ng hr/mL)		No
AUC0-inf (ng hr/mL)		No

Source: Applicant's cover letter of submission on November 9, 2022

Table 8. Results of the Pilot Study on 40 mg Strength (C1B01021)

Parameter	Geometric Least Squares Mean			SWR	% ISCVR	Point Estimate	95% Upper CI	BE Approach	90% CI	BE
	(T)	(R)	T/R (%)							
Cmax (ng/mL)	26.84	24.76	108.41	0.34	35.47	1.06	-0.0084	RSABE	NA	Yes
AUC0-t (ng hr/mL)	147.79	142.43	103.76	0.10	10.16	1.03	0.0045	ABE	94.67 - 13.73	Yes
AUC0-t (ng hr/mL)	153.34	149.01	102.91	0.09	9.94	1.02	0.0033	ABE	93.80 - 112.89	Yes

Source: Applicant's cover letter of submission on November 9, 2022

Study 18-VIN-0235 showed (b) (4) whereas in the pilot study, Study C1B1021 the 40 mg dose of LIPITOR yielded atorvastatin AUC0-t of 142 ng·hr/mL. The literature shows that the value of atorvastatin AUC0-t for an 80 mg oral dose is about 300 ng·hr/mL.

The value of atorvastatin AUC of the test product under fasting conditions in the food-effect study (18-VIN-0236; 308 ng·hr/mL) was comparable to the value of the test product of atorvastatin AUC in the 2nd pivotal study (C1B01024; 329 ng·hr/mL) and higher than the value of the test product (227 ng·hr/mL) in the 1st failed pivotal study (Study 18-VIN-0235).

All of these mentioned studies were conducted in India with heathy men. LIPITOR label does not suggest large sex or gender effect on the atorvastatin PK.

The Office of Product Quality confirmed both batches for pivotal studies were within specification. This information also supports the low value for test compared with other studies was not due to product quality but due to an error with the study conduct.

From the totality of data, the initial pivotal study (18-VIN-0235) has issues and should not be used to support bioequivalence assessment. Briefly, the issues are (b) (4) The reviewers thank Dr. Ethan Stier for consultation.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen is consistent with the dosing regimen of the reference product, LIPITOR.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

The effect of intrinsic factors on ATORVALIQ has not been studied. However, relevant information from the LIPITOR product label was incorporated into the ATORVALIQ product label as the following:

- ATORVALIQ is contraindicated in patients with active liver disease, (b) (4)

Patients with Hepatic Impairment

The LIPITOR product label has the following information on PK studies in patients with hepatic impairment:

- In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease. Cmax and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease *[see Contraindications (4)]*..

Patients with Renal Impairment

The LIPITOR product label has the following information on PK studies in patients with renal impairment:

- Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary *[see Dosage and Administration (2.5)* and *Warnings and Precautions (5.1)]*.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Food-drug Interaction

For the review of food-effect study (18-VIN-0236) that supported the original submission of NDA 213260, see Dr. Sury Sita's Clinical Pharmacology review in DARRTS dated September 8, 2020, Reference ID: 4667680.

Table 9. Summary of pharmacokinetic parameters and statistical analysis of relative bioavailability of (b) (4) under fed and fasting conditions for Study 18-VIN-0236

Treatment	PK Parameter	N	Geometric Means (C.I.)	Fed/Fasting Ratio (90% C.I.)
Atorvastatin				
(b) (4) (Fed)	$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	14	217.11 (182.41, 258.43)	70.48 (63.44, 78.30)
(Fasting)		14	308.06 (258.81, 366.67)	
(Fed)	$AUC_{(0\text{-}t)}$ (ng.hr/mL)	14	213.01 (178.62, 254.02)	70.00 (62.93, 77.85)
(Fasting)		14	304.31 (255.18, 362.89)	
(Fed)	C_{max} (ng/mL)	14	26.47 (20.85, 33.59)	37.19 (28.69, 48.21)
(Fasting)		14	71.16 (56.06, 90.33)	
(Fed)	T_{max}[a] (h)	14	4.50 (0.50, 8.00)	
(Fasting)		14	1.50 (0.33, 3.00)	

(b) (4) is the former proposed trade name of ATORVALIQ.
Source: Dr. Sury Sita's review in DARRTS dated September 8, 2020, Reference ID: 4667680

The applicant did not conduct any food-effect study to respond to the complete response letter. Instead, the applicant used the redacted review of LIPITOR and claimed that the food effect was estimated via natural log transformed least square mean values of atorvastatin Cmax and AUC(0-24). See Table 10 below (appeared as Table 7 from the image of the redacted review).

TABLE 7. Least squares mean atorvastatin-equivalent pharmacokinetic parameter values following administration of 10 mg atorvastatin QD (crystalline) for 15 days in the evening with meals and after meals (N=15)

Parameter	With Meals	After Meals	Difference (%)	95% Confidence Interval
Cmax[a], ng eq/mL	5.31	7.10	-25.2	-34.5 to -14.5
tmax, hr	4.4	3.4	29.8	-50.6 to 110.1
AUC(0-24)[a], ng eq hr/mL	83.9	91.8	-8.6	-23.1 to 8.6

[a] Based on analysis of natural log transformed parameter estimates

Source: Redacted review of NDA 20-702 for LIPITOR Page 267 of 373

Likewise, the applicant natural log transformed the least square means of atorvastatin Cmax and AUC values for Study 18-VIN-0236. See Table 11 below.

Table 11. Percent reduction calculated using natural transformed least square means of Study 18-VIN-0236

PK Parameters (Unit)	LSM Test Product (TFe)	LSM Test Product (TFa)	Ratio (A)	% Reduction from fasting to fed (100-A)
Cmax (ng/mL)	3.2759	4.2650	76.81	-23.19
AUC0-t (hr*ng/mL)	5.3953	5.7342	94.06	-5.94
AUC0-inf (hr*ng/mL)	5.4139	5.7463	94.18	-5.82

Source: Applicant's submission sequence 016 "ator-be-response-final.pdf"

The applicant compared the % reduction observed after food administration in Study 18-VIN-0236 calculated via natural log-transformed least square mean values with the innovator's reported % reduction after food administration (natural log-transformed parameters). (b) (4)

(b) (4)

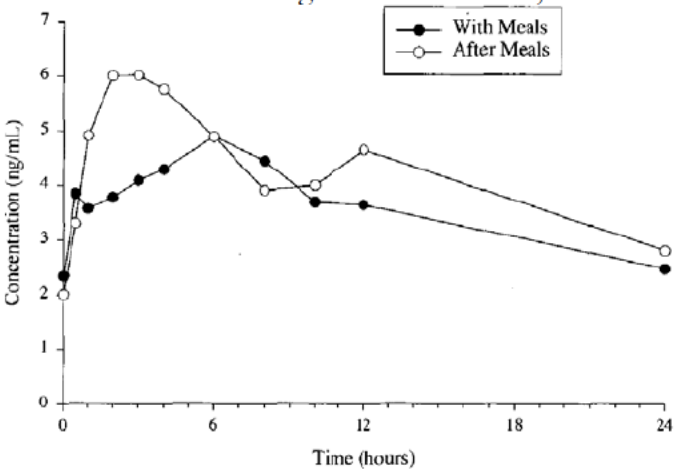
Table 12. Comparison of least-square means of LIPTOR and Study 18-VIN-0236

Parameter	LSM-Innovator Study 981-098-0			LSM-Applicant's Study 18-VIN-0236		
	With Meals	After Meals	Difference (%)	Test Fed	Test Fasting	Difference (%)
Cmax (ng. /mL)	5.31	7.10	-25.2	3.2759	4.2650	-23.19
AUC0-t (hr*ng. /mL)	83.9	91.8	-8.6	5.4027	5.7438	-5.94

Source: Applicant's submission sequence 016 "ator-be-response-final.pdf"

The innovator of LIPITOR published the food effect study of atorvastatin as "L.R. Whitfield et al. Effect of food on the pharmacodynamics and pharmacokinetics of atorvastatin, an inhibitor of HMG-CoA reductase. *European Journal of Drug Metabolism and Pharmacokinetics* 2000;25:97-101." The Whitfield et al. article clearly shows that the food effect was not after natural log transformed least square mean values of atorvastatin Cmax and AUC(0-24). See Figure 2 below for the scale of atorvastatin Cmax and tmax that match the atorvastatin Cmax and tmax in Table 4. The food effect of Study 18-VIN-0236 should be assessed without the natural log transformed least square mean values of atorvastatin Cmax and AUC(0-24). Thus, the results of Study 18-VIN-0236 indicate that the atorvastatin calcium oral suspension had a greater magnitude of food effect (30% reduction in AUC and 63% reduction in Cmax) compared with the reported values of 9% reduction in AUC and 25% reduction in Cmax for LIPITOR when administered with food.

Figure 2. Mean atorvastatin equivalent plasma-concentration time curves obtained after administration of 10 mg atorvastatin with, and 3 h after evening meals.



Source: Whitfield et al. *European Journal of Drug Metabolism and Pharmacokinetics* 2000;25:97-101.

As a result, the label of ATORVALIQ should state: ATORVALIQ can be administered as a single dose at any time of the day, only on an empty stomach (1 hour before or 2 hours after a meal).

Drug-drug Interactions

The applicant did not conduct drug interaction study to support NDA 213260. However, relevant information from the LIPITOR product label was incorporated into the ATORVALIQ product label as the following:

(b) (4)

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Table 13. Bioanalytical method validation for atorvastatin.

Information Requested	Data
Bioanalytical Method Validation Report Location	Method Validation Report Module 5/ Section 5.3.1.4/ Attachment 1 (i)/ Method Validation Report/ Page 01 to 430 Addendum-I Module 5/ Section 5.3.1.4/ Attachment 1 (ii)/ Addendum-I to the Method Validation Report/ Page 01 to 100 Addendum-II Module 5/ Section 5.3.1.4/ Attachment 1 (iii)/ Addendum-II to the Method Validation Report/ Page 01 to 17 Addendum-III Module 5/ Section 5.3.1.4/ Attachment 1 (iv)/ Addendum-III to the Method Validation Report/ Page 01 to 17 Addendum-IV Module 5/ Section 5.3.1.4/ Attachment 1 (v)/ Addendum-IV to the Method Validation Report/ Page 01 to 132 Addendum-V Module 5/ Section 5.3.1.4/ Attachment 1 (vi)/ Addendum-V to the Method Validation Report/ Page 01 to 310 Addendum-VI Module 5/ Section 5.3.1.4/ Attachment 1 (vii)/ Addendum-VI to the Method Validation Report/ Page 01 to 241
Analyte	Atorvastatin

Information Requested	Data	
Internal Standard (IS)	Atorvastatin d5	
Method Description	Hybrid (Protein Precipitation + Solid Phase) extraction method with LC/MS/MS method	
Limit of Quantitation	0.2500 ng/mL	
Average Recovery of Drug (%)	91.2%	
Average Recovery of IS (%)	86.8%	
Standard Curve Concentrations (ng/mL)	0.2500, 0.5000, 1.500, 4.500, 9.000, 18.00, 54.00, 100.0, 160.0 and 200.0	
QC Concentrations (ng/mL)	$ 0.2500 (LLOQ), 0.7500 (LQC), 11.00 (MQC-2), 80.00 (MQC-1), 150.0 (HQC) and 200.0 (ULOQ)	
	* 0.2500 (LLOQ), 0.7500 (LQC), 110.0 (MQC), 150.0 (HQC) and 200.0 (ULOQ)	
	Intra-run	
QC Intraday Precision Range (%)	$ 0.7% to 5.4%	* 1.6% to 9.9%
QC Intraday Accuracy Range (%)	$ 87.1% to 107%	* 90.4% to 102%
	Inter-run	
QC Interday Precision Range (%)	$ 2.0% to 9.7%	* 3.8% to 7.7%
QC Interday Accuracy Range (%)	$ 97.4% to 103%	* 93.9% to 97.5%
Bench-Top Stability (hrs)	24 hours at room temperature in wet ice bath [For Atorvastatin] 20 hours at room temperature in wet ice bath [For Atorvastatin ffortified with Atorvastatin Lactone/O-Hydroxy Atorvastatin Lactone/P-Hydroxy Atorvastatin Lactone (100.0/100.0/10.00 ng/mL)]	
Stock Stability (days)	25 days for drug and internal standard-1 at refrigerator temperature	
Processed Stability (hrs)	98 hours at room temperature and 97 hours at refrigerator temperature	
Freeze-Thaw Stability (cycles)	06 freeze thaw cycles (at -70ºC temperature and wet ice bath) [For Atorvastatin] 05 freeze thaw cycles (at -70ºC temperature and wet ice bath) (b) (4)	
Long-Term Storage Stability (days)	100 days at -70ºC temperature [For Atorvastatin] 103 days at -70ºC temperature (b) (4)	
Dilution Integrity	1000 ng/mL, Diluted to 10 times 300.0 ng/mL, Diluted to 02 times	

Information Requested	Data
Selectivity	No significant interfering peak noted in blank plasma lots

$ = Data reported from the three batch validation performed during core validation.
* = Data reported from the four batch validation performed during partial validation (Addendum-V) due to method modification.

5. REFERNCES

Lennernäs H. Clinical pharmacokinetics of atorvastatin. *Clin Pharmacokinet* 2003;42:1141-60.

6. APPENDIX

2.0 SYNOPSIS

Name of Sponsor: LiQmeds Limited	Individual Study Table Referring to Part of The Dossier	For National Authority Use Only
Name of Finished Product: Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL)	Volume: Page:	
Name of Active Ingredient: Atorvastatin and its metabolites, 2-Hydroxyatorvastatin and 4-Hydroxyatorvastatin		
Title of the study: Single dose oral comparative bioavailability study of Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL) and 'LIPITOR®' (Atorvastatin calcium) tablets 80 mg in healthy adult human subjects under fasting conditions.		
Investigators: Principal Investigator: Dr. Minesh Patel, MBBS Sub-Investigator(s): Dr. Mayur Soni, MBBS Dr. Bhavik Poshiya, MBBS Dr. Udit Pandit, MBBS Dr. Dhruv Patel, MBBS Dr. Kanuji Thakor, MBBS Dr. Pallav Bharpoda, MBBS Dr. Vikash kumar Singh, MBBS Dr. Milap Shah, MBBS		
Study Centers (Clinical, Screening, Clinical Laboratory and Radiology, PK and Statistical, Bioanalytical and CDISC Deliverables):		
Clinical:	Cliantha Research Limited Cliantha Corporate, TP 86, FP 28/1, Off S.P. Ring Road, Sarkhej, Ahmedabad-382210, Gujarat, India Tel# +91-2717-698500	

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Reference ID: 5113162

Name of Sponsor: LiQmeds Limited	Individual Study Table Referring to Part of The Dossier	For National Authority Use Only
Name of Finished Product: Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL)	Volume: Page:	
Name of Active Ingredient: Atorvastatin and its metabolites, 2-Hydroxyatorvastatin and 4-Hydroxyatorvastatin		
CDISC Deliverables:	[redacted] (b) (4)	

Studied Period of Clinical Phase:

Period	Check-In	Dosing	Check-Out	Last Ambulatory
1	31 Jan 22	01 Feb 22	02 Feb 22	04 Feb 22
2	07 Feb 22	08 Feb 22	09 Feb 22	11 Feb 22
3	14 Feb 22	15 Feb 22	16 Feb 22	18Feb 22
4	21 Feb 22	22 Feb 22	23 Feb 22	25 Feb 22

Development Phase of the Study:	Bioequivalence and Bioavailability Study

Study Objectives:

Primary objective:

- To compare and evaluate the oral comparative bioavailability of Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL) with that of 'LIPITOR®' (Atorvastatin calcium) tablets 80 mg in healthy, adult, human subjects under fasting conditions.

Secondary objective:

- To prove the bioequivalence between Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL) and 'LIPITOR®' (Atorvastatin calcium) tablets 80 mg in healthy, adult, human subjects under fasting conditions.
- To monitor the safety and tolerability of the subjects.

Reference ID: 5113162

Name of Sponsor: LiQmeds Limited	Individual Study Table Referring to Part of The Dossier	For National Authority Use Only
Name of Finished Product: Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL)	Volume: Page:	
Name of Active Ingredient: Atorvastatin and its metabolites, 2-Hydroxyatorvastatin and 4-Hydroxyatorvastatin		

Methodology:

This open label, randomized, four-period, two-treatment, two-sequence, fully replicated, crossover, balanced, single dose oral comparative bioavailability study in healthy, adult, human subjects under fasting conditions was conducted to compare and evaluate the oral comparative bioavailability of test formulation with that of reference formulation and prove the bioequivalence between test formulation and reference formulation. The study was conducted with 52 (51 completed the study) subjects in accordance with protocol. After an overnight fasting of at least 10 hours, a single oral dose of investigational product [either Test Product: Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL) or Reference Product: 'LIPITOR®' (Atorvastatin calcium) tablets 80 mg] was administered to the subjects in a sitting posture with about 240 mL of water at ambient temperature under the supervision of trained study personnel in each study period. The subjects received the test product (twice) and reference product (twice) in the study as per the randomization schedule.

Blood samples were collected at pre-dose (0.0 hour) and at 0.167, 0.333, 0.5, 0.667, 0.833, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours after administration of each dose. The plasma samples were transferred to the Bioanalytical facility for analysis.

Statistical analysis was performed on the pharmacokinetic data to compare and evaluate the oral bioavailability and bioequivalence of test formulation to the reference formulation. Bioequivalence and bioavailability was determined by a statistical comparison of Cmax, AUCt and AUCi for the test and reference products for Atorvastatin. The data for 2-Hydroxyatorvastatin and 4-Hydroxyatorvastatin were submitted as supporting evidence.

Number of Subjects:

No. of subjects planned:	52
No. of subjects dosed:	Period 1: 52 Period 2: 51 Period 3: 47 Period 4: 47

Reference ID: 5113162

Name of Sponsor: LiQmeds Limited	Individual Study Table Referring to Part of The Dossier	For National Authority Use Only
Name of Finished Product: Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL)	Volume: Page:	
Name of Active Ingredient: Atorvastatin and its metabolites, 2-Hydroxyatorvastatin and 4-Hydroxyatorvastatin		

No. of subjects discontinued from study:	01 (b) (6)
No. of subjects discontinued for particular period only:	(b) (6) was discontinued for Period 3 only. (b) (6) was discontinued for Period 4 only. Subjects (b) (6) were discontinued for Period 3 & 4 only. Earlier, (b) (6) was discontinued for Period 2 & 3 and then he was discontinued from the study.
No. of subjects completed the study:	51
No. of subjects analyzed:	52 (51 completed & 01 discontinued) (For Atorvastatin, 2-Hydroxyatorvastatin and 4-Hydroxyatorvastatin)
No. of subjects included in pharmacokinetic & statistical analysis:	51 ((For Atorvastatin, 2-Hydroxyatorvastatin and 4-Hydroxyatorvastatin)

As per protocol section 16.0, No. of subjects included in bioequivalence evaluation for Atorvastatin n= 51

Inclusion of subjects for bioequivalence evaluation

For BE Evaluation	Swr calculations	Evaluation of Scaled Average Bioequivalence		Evaluation of Unscaled Average Bioequivalence
		95% upper confidence bound	Point estimates (T/R ratio) using Scaled Average BE (if Swr ≥ 0.294)	
Subjects Included	46	46	46	51
List of Subjects included				(b) (6)

Reference ID: 5113162

Name of Sponsor: LiQmeds Limited	Individual Study Table Referring to Part of The Dossier	For National Authority Use Only
Name of Finished Product: Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL)	Volume: Page:	
Name of Active Ingredient: Atorvastatin and its metabolites, 2-Hydroxyatorvastatin and 4-Hydroxyatorvastatin		

Subjects not considered for BE evaluation due to incomplete of study periods	Subject[redacted] (b) (6) were not completed two periods of the study with reference product.	Subject# (b) (6) (b) (6) were not completed all the periods of the study.	-

Main Criteria for Inclusion:

Healthy adult, human volunteers, non-alcoholic, non-smokers and non-tobacco users (i.e. had no past history of alcoholism, smoking and tobacco consuming for at least one year prior to study), no past history of drug of abuse, 18 to 45 years old (both inclusive) with a Body Mass Index (BMI) 18.5 to 30.0 kg/m^2 both inclusive, who were judged as healthy on the basis of a pre-study physical examination (clinical examination) and clinical laboratory tests.

Test Product T:

Name:	Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL)
Manufactured By:	(b) (4)
Manufactured For:	LiQmeds Limited, UK
Batch No.:	ATV21001
Manufacturing Date:	May 2021
Expiry Date:	APR 2023
Dose:	20 mL (80 mg) Oral Suspension
Mode of Administration:	Oral

Reference ID: 5113162

Name of Sponsor: LiQmeds Limited	Individual Study Table Referring to Part of The Dossier	For National Authority Use Only
Name of Finished Product: Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL)	Volume: Page:	
Name of Active Ingredient: Atorvastatin and its metabolites, 2-Hydroxyatorvastatin and 4-Hydroxyatorvastatin		

Reference Product R:	
Name:	Lipitor® (Atorvastatin calcium) Tablets 80 mg
Distributed By:	Parke-Davis, Division of Pfizer Inc., NY, NY 10017
Lot No.:	EL0204
Expiry Date:	2023 Jul 31
Dose:	1 × 80 mg Table
Mode of Administration:	Oral

Duration of Treatment:

A single oral dose of investigational product [either Test Product: Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL) or Reference Product: 'LIPITOR®' (Atorvastatin calcium) tablets 80 mg] was administered to the subjects under fasting condition on below mentioned dosing dates. The interval between doses was 07 days.

Dosing Period 1: 01 Feb 22

Dosing Period 2: 08 Feb 22

Dosing Period 3: 15 Feb 22

Dosing Period 4: 22 Feb 22

Pharmacokinetic and Statistical analysis:

Pharmacokinetic parameters calculated using Phoenix® WinNonlin® professional software (version: 8.1.1) and Statistical analysis was performed on the pharmacokinetic parameters using SAS® statistical software (Version: 9.4, SAS Institute Inc., USA).

Reference ID: 5113162

Name of Sponsor: LiQmeds Limited	Individual Study Table Referring to Part of The Dossier	For National Authority Use Only
Name of Finished Product: Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL)	Volume: Page:	
Name of Active Ingredient: Atorvastatin and its metabolites, 2-Hydroxyatorvastatin and 4-Hydroxyatorvastatin		

For Atorvastatin

- Primary pharmacokinetic parameters: Cmax, AUCt and AUCi
- Secondary pharmacokinetic parameters: Tmax, Kel, AUC_%Extrap_obs and tHalf

For 2-Hydroxyatorvastatin and 4-Hydroxyatorvastatin

- Pharmacokinetic parameters: Cmax, AUCt, AUCi, Tmax, Kel, AUC_%Extrap_obs and tHalf

Criteria for evaluation:

Assessment of bioavailability: The statistical method for testing bioavailability was to be 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, AUCt and AUCi.

Assessment of bioequivalence: Based on the within subject standard deviation (S_{WR}) of Reference product, the bioequivalence between Test product and Reference product was to be determined using either average bioequivalence or scaled average bioequivalence criteria. Please refer Section 9.7.1 for more details.

The data for 2-Hydroxyatorvastatin and 4-Hydroxyatorvastatin were submitted as supporting evidence.

Reference ID: 5113162

Name of Sponsor: LiQmeds Limited	Individual Study Table Referring to Part of The Dossier	For National Authority Use Only
Name of Finished Product: Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL)	Volume: Page:	
Name of Active Ingredient: Atorvastatin and its metabolites, 2-Hydroxyatorvastatin and 4-Hydroxyatorvastatin		

SUMMARY OF RESULTS:

Table 2.1: Summary of Pharmacokinetic Data for Atorvastatin

Dose: 1 × 20 mL (80 mg) Oral Suspension (For Test Product)

1 × 80 mg Tablet (For Reference Product)

PARAMETER	Test Product (n=51)		Reference Product (n=51)	
	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))	N	Arithmetic mean ±Std Deviation (Coeff of Variation (%))
Cmax (ng/mL)	99	93.888 ±64.598 (68.803)	97	78.848 ±43.012 (54.551)
AUCt (ng/mL)*(hr)	99	369.204 ±213.748 (57.894)	97	318.290 ±149.580 (46.995)
AUCi (ng/mL)*(hr)	99	373.311 ±214.541 (57.470)	97	323.047 ±150.452 (46.573)
Kel (1/hr)	99	0.119 ±0.039 (32.452)	97	0.108 ±0.038 (35.295)
tHalf (hr)	99	6.691 ±2.990 (44.680)	97	7.396 ±3.079 (41.627)
AUC_Extrap_obs (%)	99	1.279 ±0.710 (55.489)	97	1.658 ±1.069 (64.458)
Tmax (hr)^	99	0.667 (0.333- 5.000)	97	0.667 (0.333- 5.000)

(^) Tmax is presented as Median (Range)

Table 2.2: S_{WR} and Reference Intra-Subject CV (%) based on Ln-transformed data for Atorvastatin

Pharmacokinetic parameter	S_{WR}	Reference Intra-Subject CV (%)
Cmax (ng/mL)	0.366	37.833
AUCt (ng/mL)*(hr)	0.205	20.737
AUCi (ng/mL)*(hr)	0.203	20.461

Name of Sponsor: LiQmeds Limited	Individual Study Table Referring to Part of The Dossier	For National Authority Use Only
Name of Finished Product: Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL)	Volume: Page:	
Name of Active Ingredient: Atorvastatin and its metabolites, 2-Hydroxyatorvastatin and 4-Hydroxyatorvastatin		

As the within subject standard deviation (S_{WR}) of Reference product for Cmax was greater than 0.294, hence Scaled Average Bioequivalence approach was used to assess bioequivalence for Cmax parameter and the within subject standard deviation (S_{WR}) of Reference product of AUCt and AUCi were less than 0.294, hence Average Bioequivalence approach was used to assess bioequivalence for AUCt and AUCi parameters.

Scaled Average Bioequivalence

Table 2.3: 95% Upper Confidence Bound of Test versus Reference, Point Estimate, Acceptance Range and Outcome of BE result based on Ln-transformed data for Atorvastatin

Pharmacokinetic parameter	95% Upper Confidence Interval	Ratio (Point estimates)	Acceptance Range for 95% Upper Confidence Interval	Acceptance Range for Ratio	Outcome of BE result
Cmax (ng/mL)	-0.03395	1.1496	≤ 0.0000	0.8000-1.2500	Bioequivalent

Unscaled Average Bioequivalence

Table 2.4: Test & Reference Geometric mean, Ratio, 90% Confidence Intervals, Acceptance Criteria and Outcome of BE result based on Ln-transformed data for Atorvastatin

Pharmacokinetic parameter	Geometric mean				Ratio (%)
	N	Test	N	Reference	
Cmax (ng/ mL)	99	77.916	97	68.725	113.37
AUCt (ng/mL)*(hr)	99	329.208	97	288.226	114.22
AUCi (ng/mL)*(hr)	99	333.501	97	293.140	113.77

Reference ID: 5113162

Name of Sponsor: LiQmeds Limited	Individual Study Table Referring to Part of The Dossier	For National Authority Use Only
Name of Finished Product: Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL)	Volume: Page:	
Name of Active Ingredient: Atorvastatin and its metabolites, 2-Hydroxyatorvastatin and 4-Hydroxyatorvastatin		

Pharmacokinetic parameter	90% Confidence Intervals	Acceptance Criteria for BE	Outcome of BE result
Cmax (ng/ mL)	(101.68%;126.42%)	Not Applicable	Not Applicable
AUCt (ng/mL)*(hr)	(107.71%;121.12%)	80.00% - 125.00%	Bioequivalent
AUCi (ng/mL)*(hr)	(107.35%;120.57%)	80.00% - 125.00%	

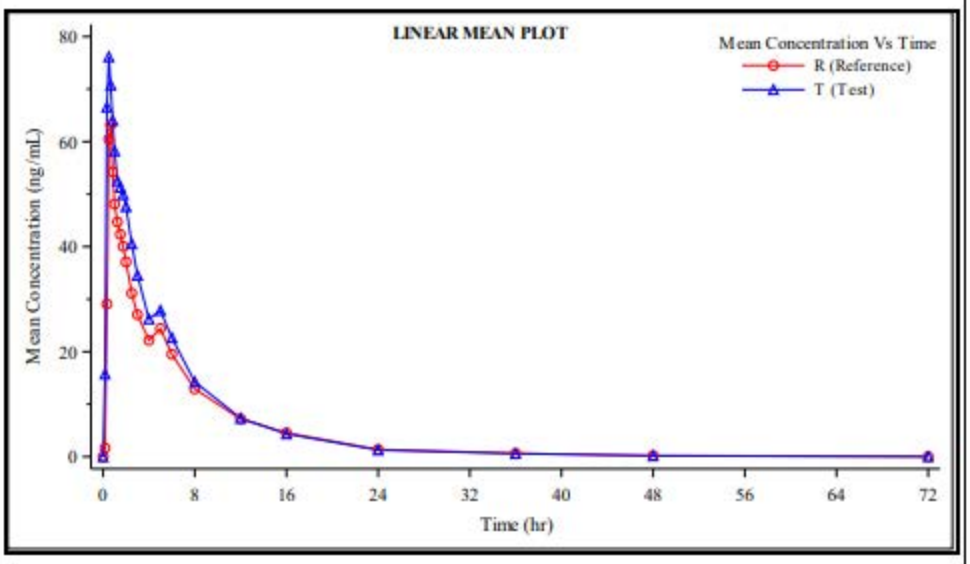
Table 2.5: Palatability Assessment

Parameter	Mean score immediately after dosing	Mean score after 10 min	Conclusion
Bitterness	3.570	2.920	Very slightly bitter immediate after dosing Acceptable/Tolerable after 10 min dosing
Sweetness	2.730	2.550	Acceptable/ Tolerable
Overall Mouth feel	3.660	-	Creamy
Flavor	3.390	-	Acceptable
Overall Acceptability	-	3.200	Acceptable

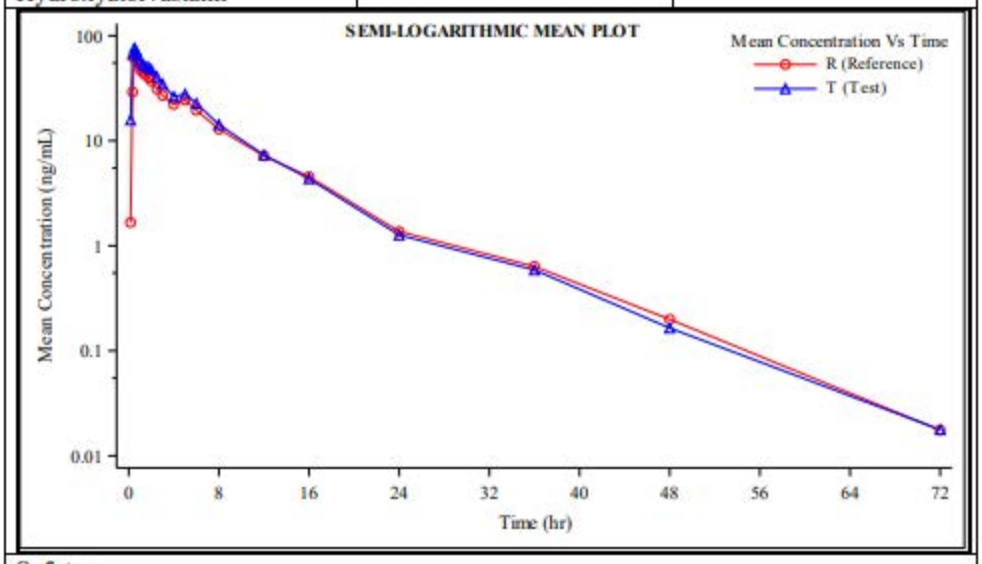
Reference ID: 5113162

Name of Sponsor: LiQmeds Limited	Individual Study Table Referring to Part of The Dossier	For National Authority Use Only
Name of Finished Product: Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL)	Volume: Page:	
Name of Active Ingredient: Atorvastatin and its metabolites, 2-Hydroxyatorvastatin and 4-Hydroxyatorvastatin		

Figure 2.1 Linear and Semi-Logarithmic Mean Plots of Atorvastatin



Name of Sponsor: LiQmeds Limited	Individual Study Table Referring to Part of The Dossier	For National Authority Use Only
Name of Finished Product: Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL)	Volume: Page:	
Name of Active Ingredient: Atorvastatin and its metabolites, 2-Hydroxyatorvastatin and 4-Hydroxyatorvastatin		



Safety:

During the course of study safety parameters assessed were medical history, medication history & family medical history, vital signs and well-being, physical examination (clinical examination), Chest X-ray (within past six months), ECG examination and safety related clinical laboratory assessment (hematology, biochemistry, urinalysis, immunological tests) at baseline.

Vital Signs Measurement:

- Sitting blood pressure, pulse rate and body temperature were measured at the time of check-in and prior to check-out in each period.
- Sitting blood pressure, pulse rate and body temperature were measured prior to dosing in each period and during the visit for the last study sample.

Reference ID: 5113162

Name of Sponsor: LiQmeds Limited	Individual Study Table Referring to Part of The Dossier	For National Authority Use Only
Name of Finished Product: Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL)	Volume: Page:	
Name of Active Ingredient: Atorvastatin and its metabolites, 2-Hydroxyatorvastatin and 4-Hydroxyatorvastatin		
Bioequivalence conclusion: Based on the results provided in Table#2.3 & 2.4, the Test Product Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL) is bioequivalent with the Reference product Lipitor® (Atorvastatin calcium) Tablets 80 mg, under fasting conditions. Refer to Section 11.4.7 for more detail. **Palatability Assessment conclusion:** Based on the mean score provided in Table#2.5, After administration of the oral solution, palatability assessment was performed and it can be concluded, that the test formulation was very slightly bitter, Acceptable/Tolerable in sweetness, Acceptable in flavor & Creamy in overall Mouth Feel immediately after dosing and Acceptable/Tolerable in bitterness, Acceptable/Tolerable in Sweetness and Acceptable in Overall Acceptability after 10 min of dosing. Refer to Section 11.4.7 for more detail. Overall, test and reference formulations were well tolerated as a single oral dosage administered under fasting condition.		
Date of Report: 04 May 22		

Reference ID: 5113162

Name of Sponsor: LiQmeds Limited	Individual Study Table Referring to Part of The Dossier	For National Authority Use Only
Name of Finished Product: Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL)	Volume: Page:	
Name of Active Ingredient: Atorvastatin and its metabolites, 2-Hydroxyatorvastatin and 4-Hydroxyatorvastatin		

- Sitting blood pressure and pulse rate were measured at 2.0 hours (± 40 minutes) post dose in each period.
- Sitting blood pressure, pulse rate and body temperature were measured at 6.0 and 10.0 hours (± 40 minutes) post dose in each period.

Physical examination (clinical examination) was conducted at the time of check-in, prior to check-out of each study period and during the visit for the last study sample.

Well-being assessment: Subjects were advised to report any AE during the study and were specifically asked for these by trained study personnel in a non-leading manner at the time of physical examination (clinical examinations), during vital signs recording, at about 16.0 and 24.0 hours post dose and during ambulatory visits in each period.

Laboratory parameters (hematology, biochemistry) were reassessed at the end of the study (except Subjects 12, 36 & 41 who did not report to the facility for end study procedures, so end study procedures were not performed).

Safety Results:

There was no serious adverse event reported in the study.

A total of three (03) adverse events were reported by three (03) subjects during the entire study. AEs were mild in severity.

A tabulation of these events is presented in Appendix 16.2.7.

Conclusion:

Bioavailability conclusion: S_{WR} is greater than 0.294 for Cmax parameter and 95% CI & point estimate fell within the acceptance range of scaled average BE approach and S_{WR} is less than 0.294 for AUCt and AUCi parameter hence using unscaled average BE approach, the 90% CI of AUCt and AUCi fell within the acceptance range 80.00% to 125.00%, hence it is concluded that, the bioavailability of Test product Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL) is comparable with respect to all three primary pharmacokinetic parameters, with Reference product Lipitor® (Atorvastatin calcium) Tablets 80 mg, under fasting conditions. Refer Section 11.4.7 for more table.

Reference ID: 5113162

Name of Sponsor: LiQmeds Limited	Individual Study Table Referring to Part of The Dossier	For National Authority Use Only
Name of Finished Product: Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL)	Volume: Page:	
Name of Active Ingredient: Atorvastatin and its metabolites, 2-Hydroxyatorvastatin and 4-Hydroxyatorvastatin		

Bioequivalence conclusion: Based on the results provided in Table#2.3 & 2.4, the Test Product Atorvastatin oral suspension 4mg/ml (80 mg/ 20 mL) is bioequivalent with the Reference product Lipitor® (Atorvastatin calcium) Tablets 80 mg, under fasting conditions. Refer to Section 11.4.7 for more detail.

Palatability Assessment conclusion: Based on the mean score provided in Table#2.5, After administration of the oral solution, palatability assessment was performed and it can be concluded, that the test formulation was very slightly bitter, Acceptable/Tolerable in sweetness, Acceptable in flavor & Creamy in overall Mouth Feel immediately after dosing and Acceptable/Tolerable in bitterness, Acceptable/Tolerable in Sweetness and Acceptable in Overall Acceptability after 10 min of dosing. Refer to Section 11.4.7 for more detail.

Overall, test and reference formulations were well tolerated as a single oral dosage administered under fasting condition.

Date of Report: 04 May 22

Reference ID: 5113162

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Office of Clinical Pharmacology Review

NDA Number	213260
Link to EDR	\\Cdsesub1\evsprod\NDA213260\213260.enx
Submission Date	13 JAN 2020
Submission Type	505(b)(2)
Brand Name	(b) (4) (Proposed)
Generic Name	Atorvastatin Calcium Oral Suspension
Dosage Form and Strength	Oral Suspension (4 mg/mL)
Route of Administration	Oral
Proposed Indication	(b) (4) is an HMG-CoA reductase inhibitor indicated as an adjunct therapy to diet to: • Reduce the risk of myocardial infarction (MI), stroke, revascularization procedures, and angina in adult patients without coronary heart disease (CHD), but with multiple risk factors • Reduce the risk of MI and stroke in adult patients with type 2 diabetes without CHD, but with multiple risk factors • Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure (CHF), and angina in adult patients with CHD • Reduce elevated total cholesterol (total-C), low-density lipoprotein-C (LDL-C), apo B, and triglyceride (TG) levels and increase high-density lipoprotein-C (HDL-C) in adult patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia • Reduce elevated TG in adult patients with hypertriglyceridemia and primary dysbetalipoproteinemia • Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH) • Reduce elevated total-C, LDL-C, and apo B levels in pediatric patients, 10 years to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) after failing an adequate trial of diet therapy
Applicant	CMP Development LLC
Associated IND	IND-137915
OCP Review Team	Suryanarayana Sista, PhD; Jayabharathi Vaidyanathan, PhD
OCP Final Signatory	Doanh Tran, PhD

Reference ID: 4667680

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1. EXECUTIVE SUMMARY

CMP Development LLC (Applicant) submitted the current application, NDA 213260 on 13 January 2020 for atorvastatin calcium oral suspension (4 mg/mL) via the 505(b)(2) pathway using LIPITOR (atorvastatin calcium) oral tablets 80 mg, as the reference listed drug (RLD). Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. The proposed tradename for atorvastatin calcium oral suspension is [redacted] (b) (4) In this review the names [redacted] (b) (4) and atorvastatin calcium oral suspension will be used interchangeably.

NDA 213260 is primarily supported by two in-vivo bioavailability studies. These studies are:

Study 18-VIN-0235 - "*An open label, balanced, randomized, single-dose, two-treatment, three-sequence, three period, partial replicate, crossover, oral bioequivalence study of Atorvastatin oral suspension 20 mg/5mL at a dose of 80 mg (20 mL) of* [redacted] (b) (4) *and LIPITOR® (Atorvastatin calcium) 80 mg film-coated tablets of Parke-Davis, Division of Pfizer Inc. NY, NY 10017, in healthy, adult, human subjects under fasting condition*" and

Study 18-VIN-0236 - "*An open label, balanced, randomized, single-dose, one-treatment, two-sequence, two period, crossover, oral bioavailability (pharmacokinetic comparison) study of Atorvastatin oral suspension 20 mg/5 mL at a dose of 80 mg (20 mL) of* [redacted] (b) (4) *in healthy, adult, human subjects under fasting and fed condition*."

In addition, the submission relies on 1) the Agency's previous findings of safety and effectiveness in accordance with section 505(b)(2) for the Federal Food, Drug and Cosmetic Act for the listed drug LIPITOR® (atorvastatin calcium) tablets (NDA 020702). LIPITOR tablets 10, 20, 40 mg strengths were initially approval on Dec 17, 1996, and the 80 mg strength was approved on Apr 7, 2000.

The to-be-marketed formulation of [redacted] (b) (4) was used in the relative bioavailability studies. Study 18-VIN-0235 was conducted to bridge the proposed product, [redacted] (b) (4) to the reference listed product, LIPITOR. Relative bioavailability between [redacted] (b) (4) and LIPITOR (RLD) did not meet the conventional 80 -125% criteria. The 90% confidence interval for the geometric mean ratios (GMRs) between [redacted] (b) (4) and RLD for all primary PK parameters (AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}) were outside the conventional 80-125% limits for all moieties measured (atorvastatin, 2-hydroxy atorvastatin and 4-hydroxy atorvastatin) under fasting conditions (Figure 1). The exposure of atorvastatin, 2-hydroxy atorvastatin, and 4-hydroxy atorvastatin was [redacted] (b) (4) higher, respectively following administration of [redacted] (b) (4) as compared to those following administration of LIPITOR.

In addition, Study 18-VIN-0236 was conducted to evaluate the effect of food on the PK of atorvastatin following administration of [redacted] (b) (4) under fasting and fed conditions. This study showed that [redacted] (b) (4) had a greater magnitude of food effect (30% reduction in AUC and 63% reduction in C_{max}) (Figure 1) compared to the reported values of 9% reduction in AUC and 25% reduction in C_{max} for the RLD when administered with food.

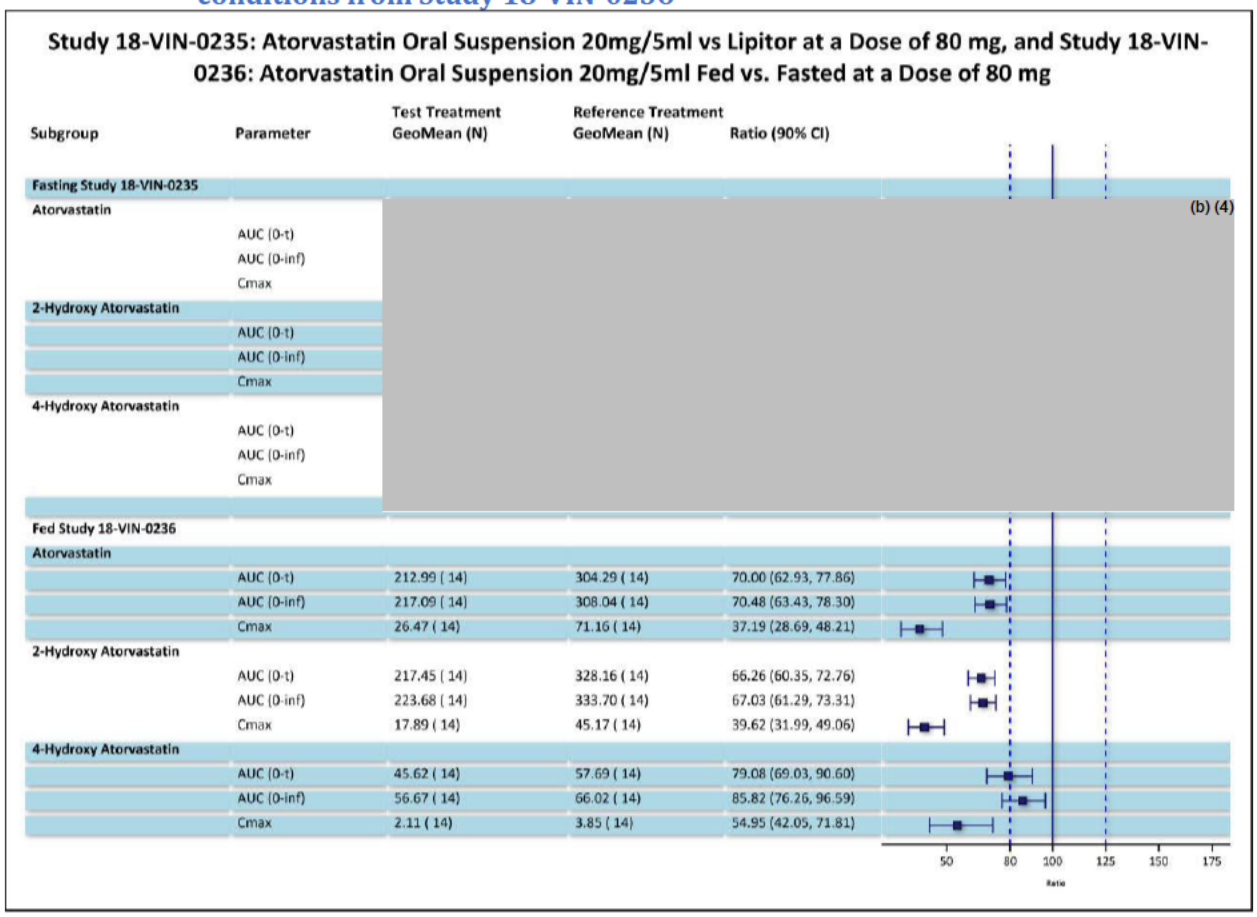
Since the application does not contain clinical efficacy and safety data for the proposed formulation ([redacted] (b) (4) relative bioavailability results are fundamental bridge to the efficacy and safety data of the innovator product, LIPTOR. The Sponsor claimed [redacted] (b) (4)

[redacted] (b) (4)

[redacted] However, these arguments are not adequate to overcome the failed bioequivalence study results. There is a wide fluctuation in atorvastatin and metabolite levels following administration of [redacted] compared to LIPITOR under fasting and fed conditions. This could lead to loss of efficacy when [redacted] is administered under fed condition since the magnitude of decreased atorvastatin and metabolites exposure is much larger for [redacted] compared to LIPITOR. On the other hand, if the product is administered under fasting conditions, the large increase in atorvastatin and metabolites exposure following [redacted] compared to LIPITOR could lead to a safety issue. Thus, the clinical pharmacology and other relevant findings of LIPITOR cannot be relied upon for the proposed [redacted] product.

Therefore, these data do not support approval of the proposed atorvastatin oral suspension (4 mg/mL). We recommend that the Applicant 1) reformulate the proposed product and conduct additional relative bioavailability studies to demonstrate bioequivalence to the reference listed drug, LIPITOR or 2) conduct a clinical efficacy study to support the effective and safe use of the proposed atorvastatin oral suspension.

Figure 1 **Forest Plot of Comparison of PK Parameters Between [redacted] (b) (4) and LIPITOR from Study 18-VIN-0235 and [redacted] (b) (4) under fed and fasting conditions from Study 18-VIN-0236**



1.1 Recommendations

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) has reviewed the clinical pharmacology data submitted in support of NDA 213260, and found the results ***unacceptable*** to support approval and recommends a Complete Response.

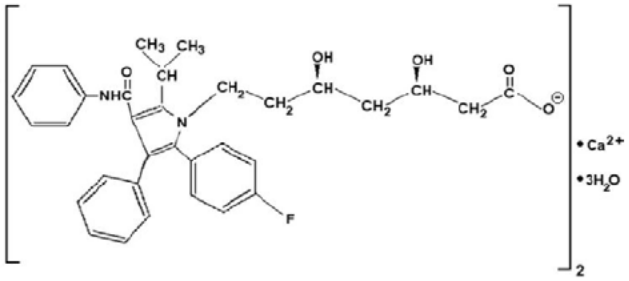
1.2 Post-Marketing Requirements and Commitments

N/A.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Atorvastatin, an HMG-CoA reductase inhibitor is approved for multiple indications[2]. The listed drug, LIPITOR, is available as oral tablets in10, 20, 40, and 80 mg strengths. The proposed drug product, (b) (4) will be available as a 20 mg/5mL (4 mg/mL) oral suspension. Atorvastatin calcium has the following primary structure:



A summary of the PK and PD characteristics of (b) (4) is presented below.

Absorption:	(b) (4)
Distribution:	
Elimination:	
Metabolism:	• Human metabolism studies were not conducted for (b) (4) The Applicant is referencing the information available in the approved label for the RLD.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The RLD, LIPITOR is indicated as an adjunct therapy to diet to:

- Reduce the risk of MI, stroke, revascularization procedures, and angina in adult patients without CHD, but with multiple risk factors
- Reduce the risk of MI and stroke in adult patients with type 2 diabetes without CHD, but with multiple risk factors
- Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF, and angina in adult patients with CHD
- Reduce elevated total-C, LDL-C, apo B, and TG levels and increase HDL-C in adult patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia
- Reduce elevated TG in adult patients with hypertriglyceridemia and primary dysbetalipoproteinemia
- Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH)

[2] Prescribing information for LIPITOR®, dated 11/2019, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020702s074lbl.pdf

- Reduce elevated total-C, LDL-C, and apo B levels in pediatric patients, 10 years to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) after failing an adequate trial of diet therapy

(b) (4) is proposing the same dosing paradigm for general dosing as the RLD.

2.2.2 Therapeutic individualization

(b) (4) is proposing the same dosing paradigm for patient subgroups as the RLD.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

As the clinical pharmacology recommendation is a Complete Response, labeling recommendations will not be provided at this time.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

(b) (4) was developed under IND 137915. Relevant regulatory history regarding these communications is summarized below:

Dates	Communication/Meeting Type	Key Communication Points
08 Mar 2018	Type B (Pre-IND) Meeting Written Response	• Agency agreed to Applicant's plan to conduct the following studies: ▪ Open-label, randomized, reference replicate, single oral dose, two treatment, three period, three-way crossover relative bioavailability study of 10mls of atorvastatin oral suspension, 40mg/5ml versus 80mg LIPITOR tablets in healthy adults under fasting conditions ▪ Open-label, randomized, single oral dose, one-treatment, two period, two-way crossover food effect study of 10mls of [atorvastatin] oral suspension, 40mg/5ml, administered under fed versus fasted conditions in healthy adults
15 Jul 2019	Pediatric Review Committee (PeRC) Recommendation	• The PeRC agreed with the Applicant's plan to request partial waiver for studies of HeFH in pediatrics birth to 10 years of age because studies are impossible or highly impracticable and assessment in pediatrics 10 to 17 years of age. • The PeRC agreed with the plan to request partial waiver for studies of HoFH in pediatrics birth to 6 years of age because studies are impossible or highly impracticable and assessment in pediatrics 6 to 17 years of age.
20 Sep 2019	PeRC Recommendation	• The PeRC agreed with the plan to request a full waiver for pediatric studies birth to less than 18 years of age with CVD, mixed dyslipidemia, familial hypertriglyceridemia and dysbetalipoproteninemia because studies are impossible or highly impracticable; partial waiver for pediatric studies for pediatrics 0 to less than 9 years of age with HeFH and pediatrics 0 to 5 years of age with HoFH because studies are impossible or highly impracticable; and assessment for pediatrics 10 to less than 17 years of age with HeFH and pediatrics 6 to less than 17 years of age with HoFH.

3.2 General Pharmacological and Pharmacokinetic Characteristics

(b) (4) is an oral suspension presentation of atorvastatin calcium and is available in a single strength of 20 mg/5 mL. The clinical pharmacology characteristics of (b) (4) was investigated in two studies in healthy subjects. A list of clinical pharmacology studies is outline in Table 1. General Pharmacological and Pharmacokinetic Characteristics of (b) (4) are listed in Table 2.

Table 1 Tabular Listing of Clinical Pharmacology Studies with Atorvastatin Calcium

Study ID	Objectives	Population	Study Design	Treatment
18-VIN-0235	Compare bioavailability of Atorvastatin oral suspension to LIPITOR® (Atorvastatin calcium) tablets under fasting conditions, safety and tolerability, palatability	Healthy Adult Male (n = 59)	Open Label, Balanced, Randomized, Single-Dose, Two-Treatment, Three-Period, Three-Sequence, Partial Replicate, Crossover, Fasting	**Test** Atorvastatin Oral Suspension 4 mg/mL, 20 mL Suspension; Single dose; Oral **Reference** LIPITOR® (atorvastatin calcium) 80 mg tablet; Single dose (one tablet); Oral
18-VIN-0236	Compare pharmacokinetics of Atorvastatin oral suspension under fasting and fed conditions, safety and tolerability, palatability	Healthy Adult Male (n = 14)	Open Label, Balanced, Randomized, Single-Dose, One-Treatment, Two-Period, Two-Sequence, Crossover, Fasting and Fed	Atorvastatin Oral Suspension 4 mg/mL, 20 mL suspension (80 mg); Single dose; Oral

Table 2 General Pharmacological and Pharmacokinetic Characteristics of (b) (4)

Pharmacology	
Mechanism of Action	Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. In animal models, atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell surface to enhance uptake and catabolism of LDL; Atorvastatin also reduces LDL production and the number of LDL particles.
Active Moieties	Atorvastatin, 2-hydroxy atorvastatin, 4-hydroxy atorvastatin
Pharmacodynamics	Atorvastatin, as well as some of its metabolites, are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance.
General Information	
Bioanalysis	Atorvastatin, 2-hydroxy atorvastatin and 4-hydroxy atorvastatin concentrations in plasma were determined using validated liquid chromatography with electrospray ionization and tandem mass spectrometry (LC-ESI-MS/MS). (b) (4)
Effect of Intrinsic Factors on Pharmacokinetics	Effect of Intrinsic factors on the PK of (b) (4) were not carried out.

	Information from the product label for LIPITOR indicates that except for body weight, PopPK analysis did not identify any other covariate to have any clinically relevant impact on the PK of LIPITOR.
Intra-Subject Variability	The intra-subject variability (CV%) for atorvastatin following oral administration of [redacted] were as follows: [redacted]
Renal or Hepatic Impairment	[redacted] was not studied in patients with renal or hepatic impairment. Information from the product label for LIPITOR indicates that renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary. In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. C_{max} and AUC are each 4-fold greater in patients with Childs-Pugh A disease severity. C_{max} and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease severity.
Pediatric	[redacted] has not been studies in pediatric patients. Information from the product label for LIPITOR indicates that apparent oral clearance of atorvastatin in pediatric subjects appeared similar to that of adults when scaled allometrically by body weight as the body weight was the only significant covariate in atorvastatin population PK model with data including pediatric Heterozygous Familial Hypercholesterolemia (HeFH) patients (ages 10 years to 17 years of age, n=29) in an open-label, 8-week study.
Drug-Drug Interaction	No drug-drug interaction study was carried out with [redacted] Atorvastatin is a substrate of the hepatic transporters, OATP1B1 and OATP1B3 transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporter BCRP, which may limit the intestinal absorption and biliary clearance of atorvastatin. The potential drug-drug interactions for [redacted] will be the same as listed for LIPITOR (https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020702s074lbl.pdf).
Absorption	
Bioavailability	The absolute bioavailability of atorvastatin from [redacted] has not been determined. Information from the product label for LIPITOR indicates that the absolute bioavailability of atorvastatin (parent drug) is approximately 14% The low systemic availability is attributed to pre-systemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.
T_{max}	Atorvastatin appeared in the circulation with a median T_{max} [redacted] after oral administration of a [redacted] 80 mg dose.
ADME	
Distribution	The apparent atorvastatin volume of distribution (V_z/F) following [redacted] is [redacted] liters. Information from the product label for LIPITOR indicates that mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk.
Elimination	Findings from Study 18-VIN-0235 indicated that the median (range) apparent clearance (CL/F) of atorvastatin following oral administration of an 80 mg dose of [redacted] was [redacted] L/h ([redacted] L/h) with a median (range) elimination half-life of [redacted] hours [redacted] hours).
Metabolism	The Sponsor did not conduct human metabolism studies with [redacted] Information from the product label for LIPITOR indicates that atorvastatin is extensively metabolized to ortho- and para-hydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and para-hydroxylated metabolites is equivalent to that of atorvastatin.

	Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following co-administration with erythromycin, a known inhibitor of this isozyme. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.
Excretion	LIPITOR (atorvastatin) and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of LIPITOR in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of LIPITOR is recovered in urine following oral administration.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness and safety?

The clinical pharmacology data presented in this NDA does not provide supportive evidence of effectiveness for [redacted] (b) (4) to treat hyperlipidemias and cardiovascular event risk reduction as indicated on the approved labeling of the reference drug, LIPITOR (atorvastatin calcium) tablets (NDA 020702).

[redacted] (b) (4) contains the same active ingredient, atorvastatin, as LIPITOR. To establish a scientific bridge with LIPITOR, the applicant conducted a reference-scaled, partial replicate-design comparative bioavailability study in healthy adult male subjects. Bioequivalence estimation criteria was pre-specified in the study protocol as follows:

> For any log-transformed parameter where the within-subject standard deviation (SD), for the reference product (SWR) ≥: 0.294, the Scaled Average Bioequivalence (SABE) method will be used. The upper 95% confidence bound on the linearized SABE statistic will be calculated.
>
> For those log-transformed parameters where the within-subject SD for the reference product (SWR) <0.294, the Average Bioequivalence (ABE) method will be used. The 90% confidence interval will be constructed for the Test-to-Reference ratio of geometric least squares means.

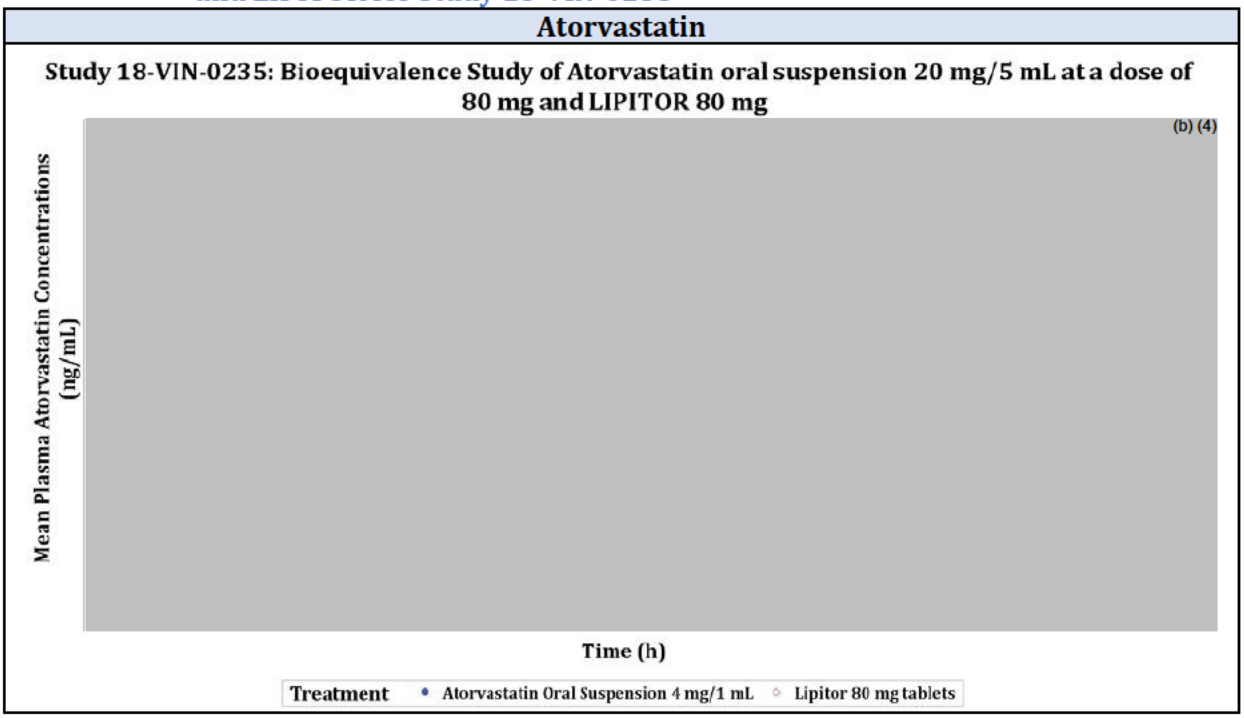
The within-subject standard deviation of reference formulation (SWR) for atorvastatin was less than [redacted] (b) (4) for primary pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf}. Bioequivalence determination between test and reference formulations were therefore evaluated using conventional average bioequivalence approach for ln-transformed primary pharmacokinetic parameters, C_{max}, AUC_{0-t} and AUC_{0-inf}. The 90% confidence interval of geometric mean ratio (GMR) for C_{max}, AUC_{0-t} and AUC_{0-inf} of plasma atorvastatin were outside the pre-specified acceptance criteria of 80 to 125% under fasting conditions, thus failing to establish a scientific bridge between [redacted] (b) (4) and LIPITOR (Figure 2, Table 3). Similarly, the 90% confidence interval of geometric mean ratio (GMR) for C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ of plasma 2-hydroxy atorvastatin and 4-hydroxy atorvastatin were outside the pre-specified acceptance criteria of 80 to 125% under fasting conditions, thus failing to establish a scientific bridge between [redacted] (b) (4) and LIPITOR (Figure 3, Figure 4 and Table 3). Hence, the clinical pharmacology and other relevant findings of LIPITOR cannot be relied upon for the proposed [redacted] (b) (4) product.

The Sponsor claimed [redacted] (b) (4)

(b) (4)

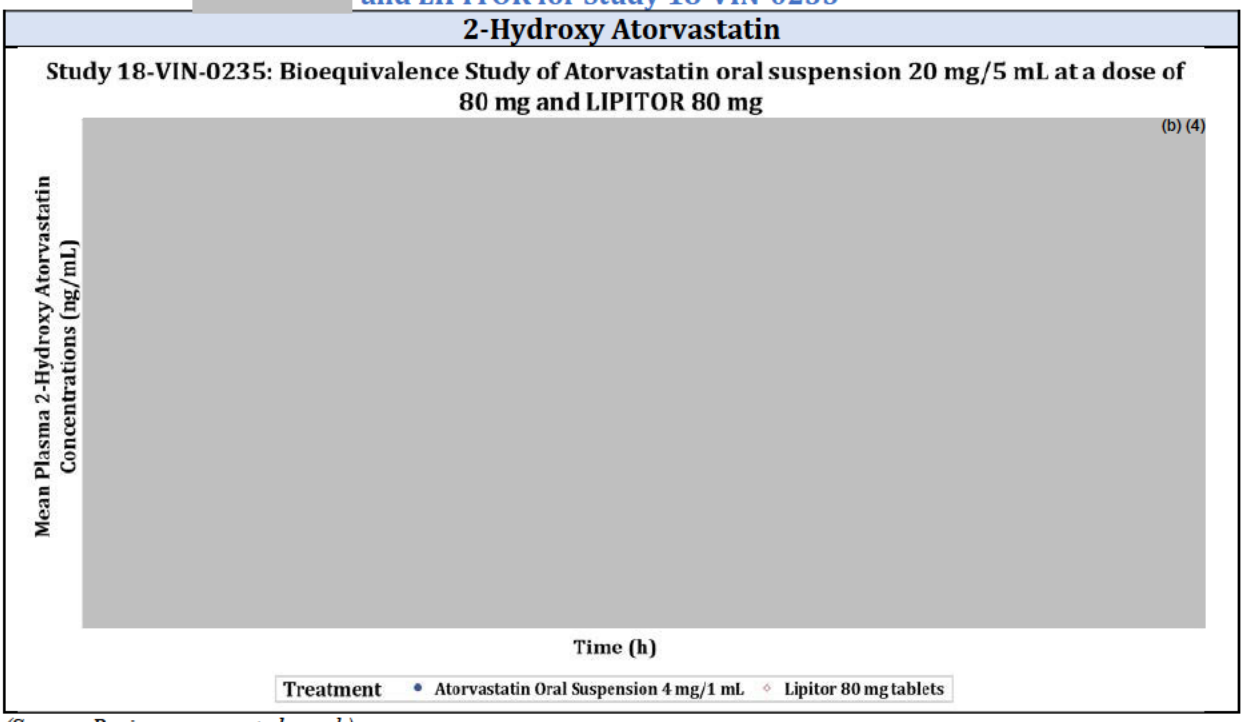
However, these arguments are not adequate to overcome the failed bioequivalence results. There is a wide fluctuation in atorvastatin and metabolite levels following administration of (b) (4) compared to LIPITOR under fasting and fed conditions. This could lead to loss of efficacy when (b) (4) is administered under fed condition since the magnitude of decreased atorvastatin and metabolites exposure is much larger for (b) (4) compared to LIPITOR. On the other hand, if the product is administered under fasting conditions, the large increase in atorvastatin and metabolites exposure following (b) (4) compared to LIPITOR could lead to a safety issue.

Figure 2 Mean Atorvastatin Concentration (±SD) Versus Time by Treatment (inset showing profiles for the first 8 hours) following 80 mg Doses of (b) (4) and LIPITOR for Study 18-VIN-0235



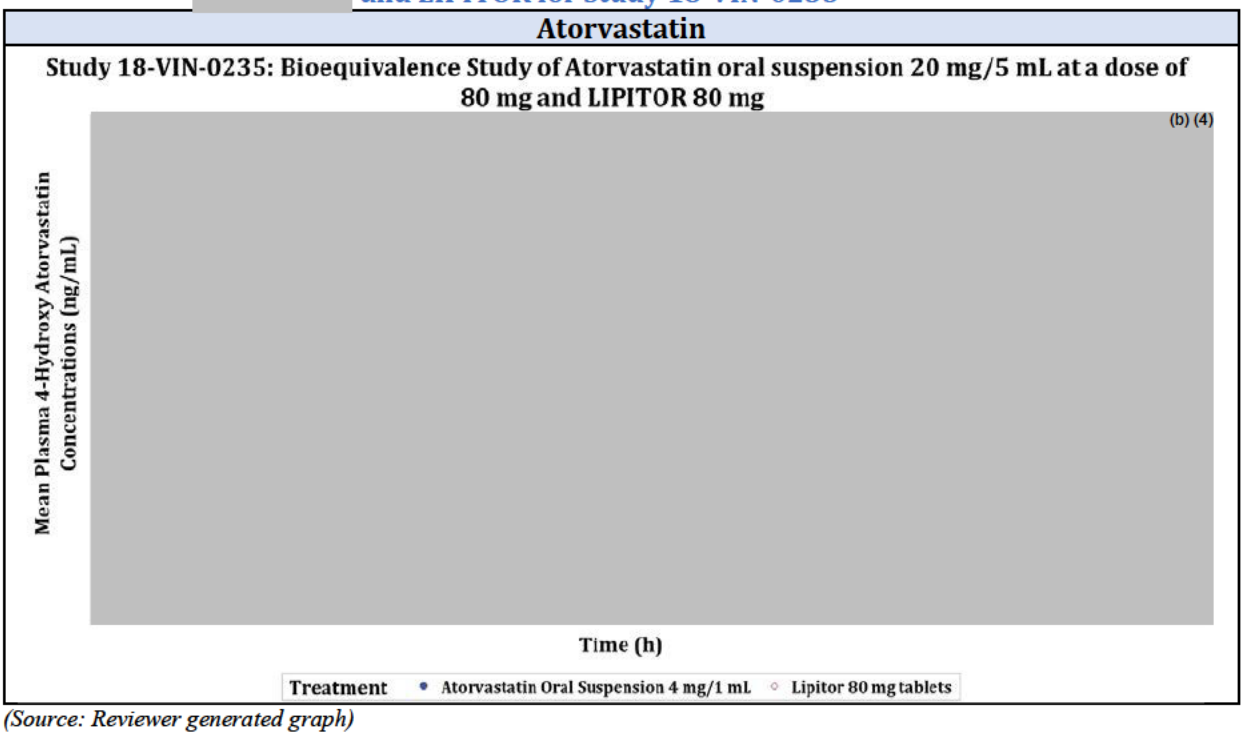
(Source: Reviewer generated graph)

Figure 3 Mean 2-Hydroxy Atorvastatin Concentration (±SD) Versus Time by Treatment (inset showing profiles for the first 8 hours) following 80 mg Doses of (b) (4) and LIPITOR for Study 18-VIN-0235



(Source: Reviewer generated graph)

Figure 4 Mean 4-Hydroxy Atorvastatin Concentration (±SD) Versus Time by Treatment (inset showing profiles for the first 8 hours) following 80 mg Doses of (b) (4) and LIPITOR for Study 18-VIN-0235



(Source: Reviewer generated graph)

Table 3 Summary of Statistical Analysis of Relative Bioavailability Between (b) (4) and LIPITOR

Moiety PK Parameter	Atorvastatin	2-Hydroxy Atorvastatin	4-Hydroxy Atorvastatin
$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	(b) (4)		
$AUC_{(0\text{-}t)}$ (ng.hr/mL)			
C_{max} (ng/mL)			

Results are expressed as the least squares mean ratio of Test (b) (4) Reference (LIPITOR) treatments (90% C.I. limits)

(Source: Reviewer's analysis based on data submitted for Study 18-VIN-0235)

3.3.2 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic or extrinsic factors?

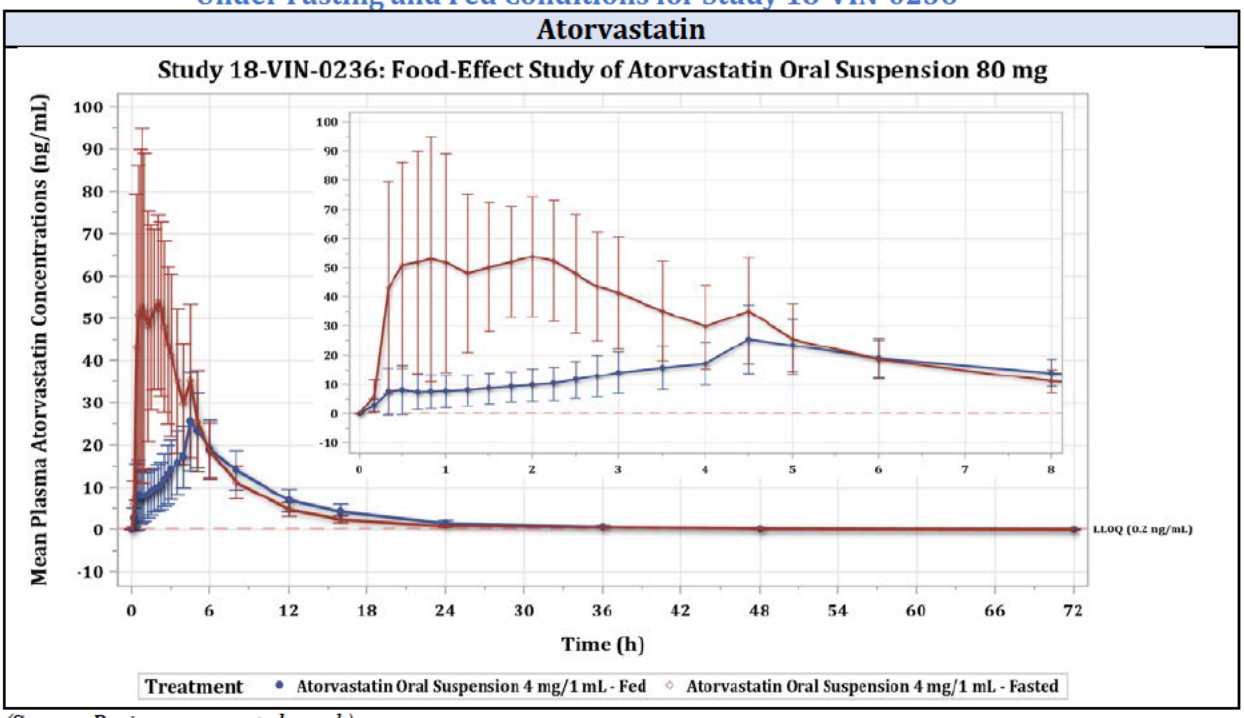
No alternative dosing regimen is recommended based on intrinsic factors, which is in agreement with the listed drug, LIPITOR. The Applicant conducted a food-effect study which demonstrated lower exposure of atorvastatin, 2-hydroxy atorvastatin and 4-hydroxy atorvastatin under fed condition and to a greater extent compared to the effect of food on LIPITOR.

3.3.2.1 Food Effect

The effect of food on systemic exposure of (b) (4) was evaluated in Study 18-VIN-0236 in which a single dose of 80 mg (b) (4) was administered in healthy adult male subjects in a crossover manner under fasting condition and following a high-fat breakfast. Plasma atorvastatin C_{max}, $AUC_{(0\text{-}t)}$ and $AUC_{(0\text{-}inf)}$ were lower by 63%, 30% and 30%, respectively, under fed condition, as compared to fasting condition (Figure 5, Table 4). Similarly, plasma 2-hydroxy atorvastatin C_{max}, $AUC_{(0\text{-}t)}$ and $AUC_{(0\text{-}inf)}$ were lower by 60%, 34% and 33%, respectively, under fed condition, as compared to fasting condition (Figure 6, Table 4). Plasma 4-hydroxy atorvastatin C_{max}, $AUC_{(0\text{-}t)}$ and $AUC_{(0\text{-}inf)}$ were lower by 45%, 21% and 14%, respectively, under fed condition, as compared to fasting condition (Figure 7, Table 4) The product label for LIPITOR specifies that although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether LIPITOR is given with or without food.

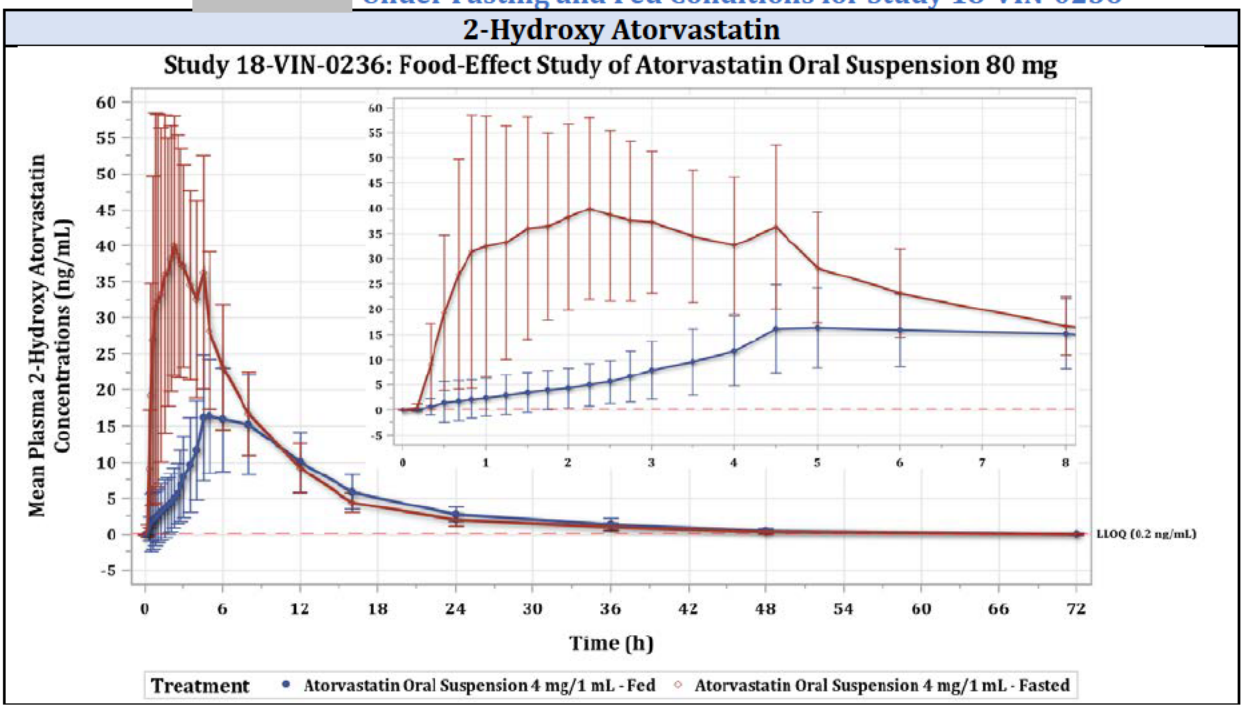
Reference ID: 4667680

Figure 5 **Mean Atorvastatin Concentration (±SD) Versus Time by Treatment (inset showing profiles for the first 8 hours) following 80 mg Doses of (b) (4) Under Fasting and Fed Conditions for Study 18-VIN-0236**



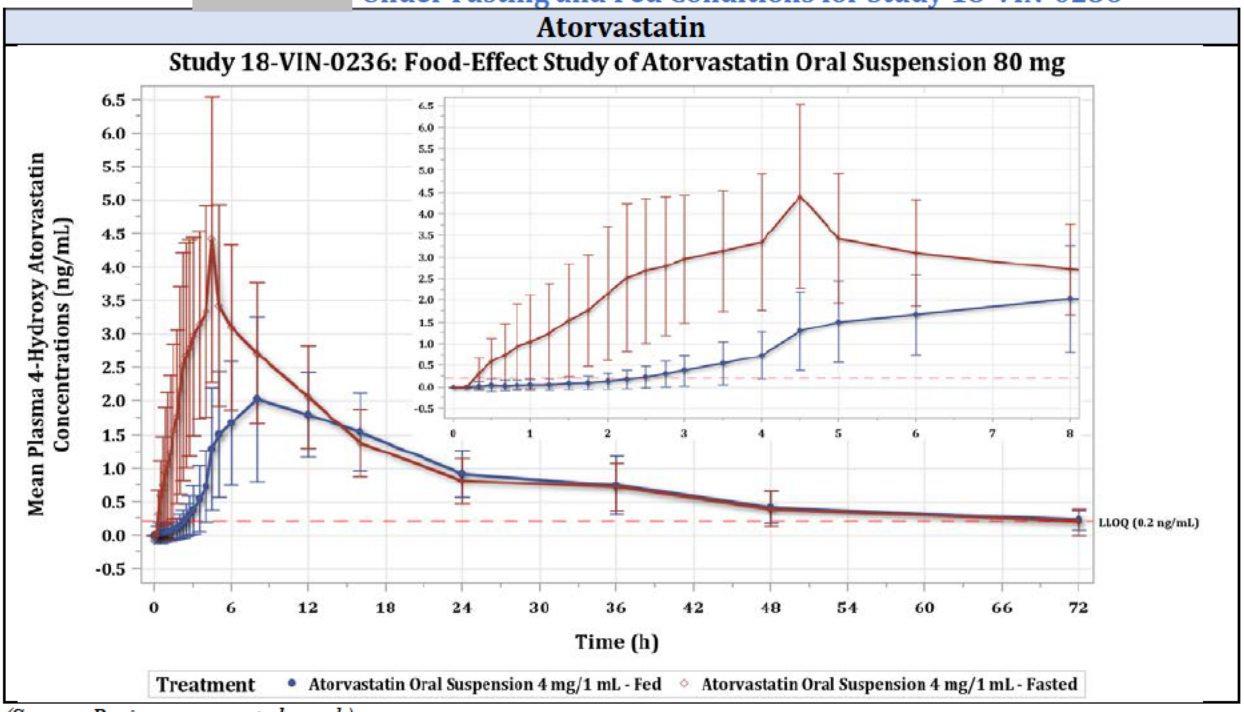
(Source: Reviewer generated graph)

Figure 6 **Mean 2-Hydroxy Atorvastatin Concentration (±SD) Versus Time by Treatment (inset showing profiles for the first 8 hours) following 80 mg Doses of (b) (4) Under Fasting and Fed Conditions for Study 18-VIN-0236**



(Source: Reviewer generated graph)

Figure 7 **Mean 4-Hydroxy Atorvastatin Concentration (±SD) Versus Time by Treatment (inset showing profiles for the first 8 hours) following 80 mg Doses of (b) (4) Under Fasting and Fed Conditions for Study 18-VIN-0236**



(Source: Reviewer generated graph)

Table 4 **Summary of Statistical Analysis of Relative Bioavailability Between Fed and Fasting Conditions Following Administration of (b) (4) 80 mg**

Moiety PK Parameter	Atorvastatin	2-hydroxy atorvastatin	4-hydroxy atorvastatin
AUC_{0-t}	70.48 (63.44, 78.30)	67.03 (61.28, 73.32)	85.93 (76.35, 96.71)
$AUC_{0-\infty}$	70.00 (62.93, 77.85)	66.26 (60.34, 72.77)	79.14 (69.08, 90.66)
C_{max}	37.19 (28.69, 48.21)	39.62 (31.99, 49.06)	54.95 (42.05, 71.81)

Results are expressed as the least squares mean ratio of Fed/Fast treatments (90% C.I. limits)

(Source: Reviewer's analysis based on data submitted for Study 18-VIN-0236)

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

4.1.1 How are atorvastatin, 2-hydroxy atorvastatin and 4-hydroxy atorvastatin identified and what are the analytical methods used to measure them in plasma?

Atorvastatin, 2-hydroxy atorvastatin and 4-hydroxy atorvastatin concentrations in plasma were determined using validated liquid chromatography with electrospray ionization and tandem mass spectrometry (LC-ESI-MS/MS). (b) (4) A summary of validation parameters for the quantitation of atorvastatin, 2-hydroxy atorvastatin and 4-hydroxy atorvastatin in plasma are shown in Table 5, Table 6 and Table 7, respectively.

OSIS Inspection:

The Office of Study Integrity and Surveillance (OSIS) inspection was requested for the clinical and bioanalytical sites of the pivotal clinical pharmacology studies 18-VIN-0235 and 18-VIN-0236. The Division of New Drug Study Integrity (DNDSI) within OSIS determined that an inspection was not warranted for the clinical and bioanalytical sites. The rationale for this decision was that the clinical and analytical inspections occurred in (b) (4) which fell within the requested surveillance interval. The final classification for the inspections was No Action Indicated (NAI), and therefore, an inspection was not warranted at this time (*See memo from Folaremi Adeyemo, Reference ID: 4577533, dated 19 Mar 2020 in DARRTS*).

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Reference ID: 4667680

4.2 Biopharmaceutics

(b) (4) is formulated as an oral suspension of 20 mg atorvastatin/5 mL, to be administered in a 20 mL volume for an atorvastatin dose of 80 mg. The unit formula for (b) (4) 80 mg is provided in Table 8.

Table 8 Unit Formula of the (b) (4) 80 mg Drug Product

Ingredient	Amount	
	% w/v	Quantity/mL (mg/mL)
Atorvastatin Calcium ((b) (4)), USP	0.400	4.000
Carboxymethylcellulose Sodium, USP	(b) (4)	
Magnesium Aluminum Silicate, NF		
Methylparaben, NF		
Ethylparaben, NF		
Propylparaben, NF		
Sucralose, NF		
Acesulfame Potassium, NF		
Orange Flavor ((b) (4))		
(b) (4) Water, USP		
Total	100.0%	1 mL

(Source: Module 2.7.1: Summary of Biopharmaceutics Studies and Associated Analytical Methods, Table 1, Page 4)

4.3 Clinical PK Assessments

Study 18-VIN-0235: ***Fasting bioequivalence comparison between*** (b) (4) ***and LIPITOR in healthy male subjects***

(b) (4)

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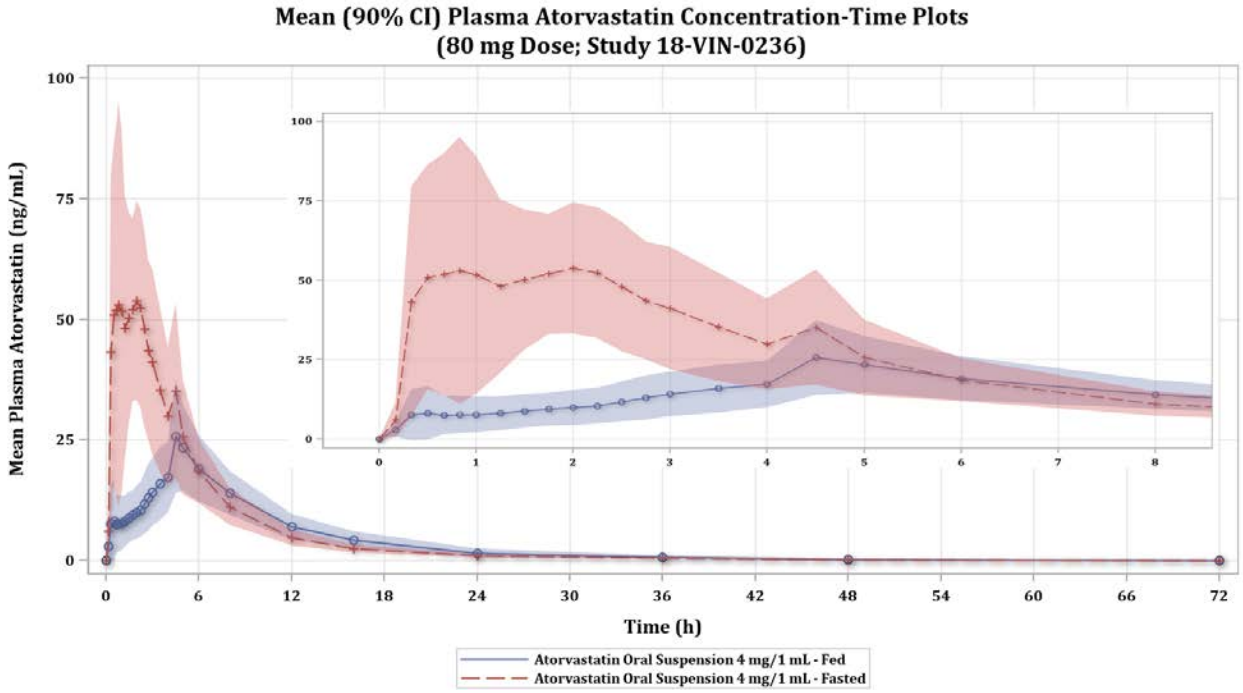
Study 18-VIN-0236: ***Effect of Food on the pharmacokinetics of*** [redacted] ***in healthy male subjects***

Comparison of the PK of atorvastatin and its metabolites, 2-hydroxy atorvastatin and 4-hydroxy atorvastatin following a single 80 mg dose of [redacted] (20 mL of 4 mg/mL suspension) following fasting and fed conditions was carried out in a Phase 1, open label, balanced, randomized, single-dose, one-treatment, two-period, two-sequence, crossover oral bioavailability study in healthy, adult, male subjects. A total of 14 healthy male Asian subjects, aged between 22 and 44 years (mean = 33.1 years), participated in this study. The mean body weight of the population was 59.1 kg and the mean BMI was 21.9 kg/m^2.

Serial blood samples were taken for the PK measurement of atorvastatin, 2-hydroxy atorvastatin and 4-hydroxy atorvastatin.

The mean atorvastatin, 2-hydroxy atorvastatin and 4-hydroxy atorvastatin exposure following administration of single 80 mg doses of [redacted] under fed and fasting conditions are presented in Figure 11, Figure 12 and Figure 13, respectively.

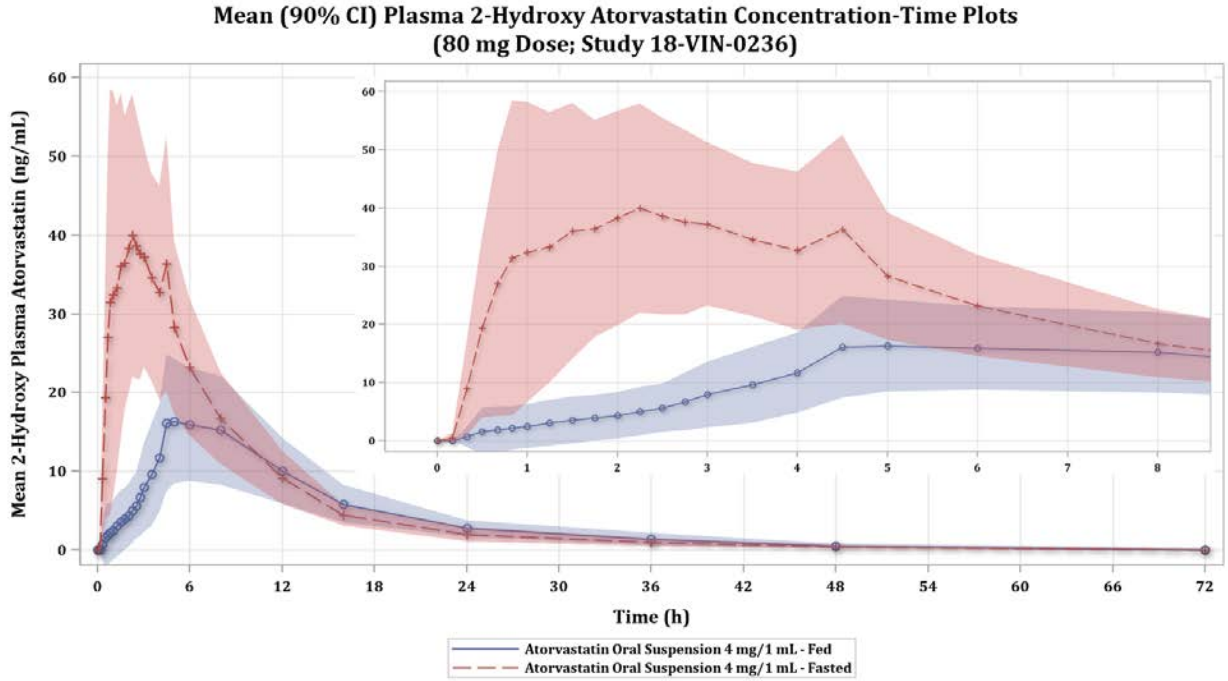
Figure 11 **Mean atorvastatin concentration (90% C.I) versus time (inset - for the first 8 hours) by treatment following 80 mg doses of** [redacted] **under Fasting and Fed Conditions**



(Source: Reviewer generated graph)

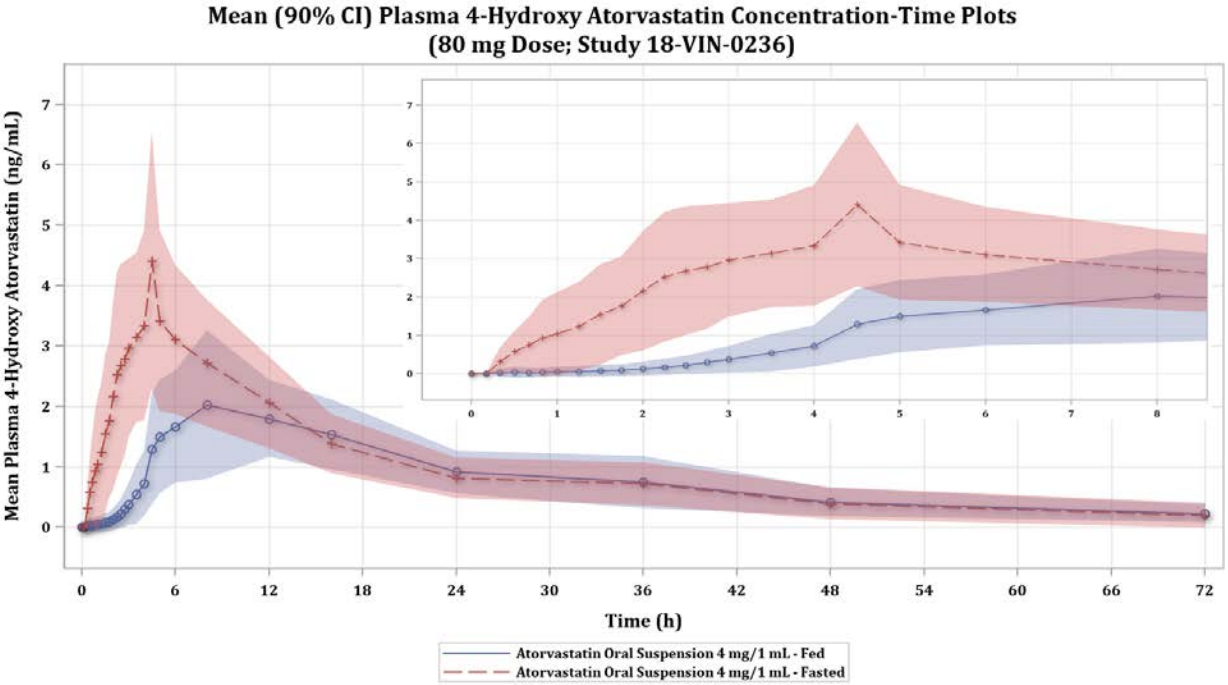
Reference ID: 4667680

Figure 12 **Mean 2-hydroxy atorvastatin concentration (90% C.I) versus time (inset - for the first 8 hours) by treatment following 80 mg doses of (b) (4) under Fasting and Fed Conditions**



(Source: Reviewer generated graph)

Figure 13 **Mean 4-hydroxy atorvastatin concentration (90% C.I) versus time (inset - for the first 8 hours) by treatment following 80 mg doses of (b) (4) under Fasting and Fed Conditions**



(Source: Reviewer generated graph)

Pharmacokinetics:

Following doses of 80 mg [redacted] the median time to peak (T_{max}) atorvastatin levels was 4.5 hours under fed conditions compared to 1.5 hours under fasting conditions. (Figure 11, Table 10). There was a significant effect of food on the PK of [redacted] with a reduction in the peak (C_{max}) and total (AUC) atorvastatin exposure by 63% and 30%, respectively (Table 10).

The median time to peak (T_{max}) 2-hydroxy atorvastatin levels was 5.5 hours under fed conditions compared to 2.1 hours under fasting conditions. (Figure 12, Table 10). Under fed conditions, there was a reduction in the peak (C_{max}) and total (AUC) 2-hydroxy atorvastatin exposure by 60% and 33%, respectively (Table 10), compared to fasting conditions.

The median time to peak (T_{max}) 4-hydroxy atorvastatin levels was 10.0 hours under fed conditions compared to 4.5 hours under fasting conditions. (Figure 13, Table 10). Under fed conditions, there was a reduction in the peak (C_{max}) and total (AUC) 2-hydroxy atorvastatin exposure by 45% and 14%, respectively (Table 10), compared to fasting conditions.

Table 10 Summary of Pharmacokinetic Parameters and Statistical Analysis of Relative Bioavailability of [redacted] Under Fed and Fasting Conditions

Treatment	PK Parameter	N	Geometric Means (C.I.)	Fed/Fasting Ratio (90% C.I.)
Atorvastatin				
[redacted] (Fed)	$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	14	217.11 (182.41, 258.43)	70.48 (63.44, 78.30)
[redacted] (Fasting)		14	308.06 (258.81, 366.67)	
[redacted] (Fed)	$AUC_{(0\text{-}t)}$ (ng.hr/mL)	14	213.01 (178.62, 254.02)	70.00 (62.93, 77.85)
[redacted] (Fasting)		14	304.31 (255.18, 362.89)	
[redacted] (Fed)	C_{max} (ng/mL)	14	26.47 (20.85, 33.59)	37.19 (28.69, 48.21)
[redacted] (Fasting)		14	71.16 (56.06, 90.33)	
[redacted] (Fed)	T_{max}[a] (h)	14	4.50 (0.50, 8.00)	
[redacted] (Fasting)		14	1.50 (0.33, 3.00)	
2-Hydroxy Atorvastatin				
[redacted] (Fed)	$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	14	223.75 (181.49, 275.85)	67.03 (61.28, 73.32)
[redacted] (Fasting)		14	333.80 (270.76, 411.53)	
[redacted] (Fed)	$AUC_{(0\text{-}t)}$ (ng.hr/mL)	14	217.51 (176.34, 268.29)	66.26 (60.34, 72.77)
[redacted] (Fasting)		14	328.25 (266.11, 404.89)	
[redacted] (Fed)	C_{max} (ng/mL)	14	17.89 (13.72, 23.33)	39.62 (31.99, 49.06)
[redacted] (Fasting)		14	45.17 (34.63, 58.90)	
[redacted] (Fed)	T_{max}[a] (h)	14	5.50 (4.50, 12.0)	
[redacted] (Fasting)		14	2.13 (0.83, 4.50)	
4-Hydroxy Atorvastatin				
[redacted] (Fed)	$AUC_{(0\text{-}inf)}$ (ng.hr/mL)	14	56.81 (42.71, 75.58)	85.93 (76.35, 96.71)
[redacted] (Fasting)		14	66.12 (49.70, 87.96)	
[redacted] (Fed)	$AUC_{(0\text{-}t)}$ (ng.hr/mL)	14	45.72 (35.07, 59.60)	79.14 (69.08, 90.66)
[redacted] (Fasting)		14	57.77 (44.31, 75.31)	
[redacted] (Fed)	C_{max} (ng/mL)	14	2.11 (1.56, 2.87)	54.95 (42.05, 71.81)
[redacted] (Fasting)		14	3.85 (2.83, 5.22)	
[redacted] (Fed)	T_{max}[a] (h)	14	10.0 (5.00, 16.0)	
[redacted] (Fasting)		14	4.50 (2.00, 8.00)	

[a]T_{max} reported as median (range)

(Source: Reviewer's analysis based on data submitted for Study 18-VIN-0236)

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