Analytes of Interest and Choice of Dose: Two Important Considerations in the Design of Bioequivalence Studies with Atorvastatin

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Abstract

Atorvastatin is an oral lipid-lowering agent. A Small Tablet (ST) formulation and a Chewable Tablet (CT) formulation have recently been developed and tested in two single-dose bioequivalent (BE) studies (10 mg and 80 mg), each in 76 healthy volunteers. Plasma samples were only analyzed for atorvastatin in ST studies, and simultaneously for both atorvastatin and ortho-hydroxyatorvastatin in CT studies. The results showed the ST and the CT formulations were each bioequivalent to the current Marketed Tablet (MT) formulation, at the lowest (10 mg) and the highest (80 mg) doses. For the CT formulation, both atorvastatin and its metabolite achieved BE at both doses. Although the metabolite BE is not warranted, supportive metabolite data may be needed depending on the degree of divergence in formulations from its MT formulation. Furthermore atorvastatin has linear PK with respect to AUC; however, C_{max} is nonlinear with a greater than dose-proportional increase. Therefore, to ensure the desired sensitivity to detect formulation differences, BE studies with atorvastatin should be conducted at the highest dose.

Keywords: Atorvastatin; Bioequivalence; Marketed tablet; Small Tablet; Chewable tablet

Introduction

Atorvastatin is a lipid-lowering agent, approved for treatment once daily at 10-80 mg doses in adults and at 10-20 mg doses in children aged 10 years or older [15]. Following oral administration, atorvastatin is rapidly absorbed, and maximum plasma concentrations are achieved within 1 to 2 hours. Atorvastatin is extensively metabolized by cytochrome P450 3A4 to active metabolites: ortho- and para-hydroxyatorvastatin. Approximately 70% of the circulating inhibitory activity for HMG-CoA reductase is attributed to these active metabolites [15]. *In vitro* inhibition of HMG-CoA reductase by ortho- and para-hydroxylated metabolites is equivalent to that of atorvastatin. Ortho-hydroxyatorvastatin is the predominant active metabolite in systemic circulation [12,18]. In a single-dose study of 2.5 to 120 mg doses [16] and in multiple-dose studies of 2.5 to 80 mg dose [15], the plasma pharmacokinetics (AUC and C_{max}) of atorvastatin equivalents, measured as all compounds capable of inhibiting HMG-CoA reductase, showed nonlinear increases. However, in a multiple-dose study [25], a greater than dose-proportional increase was observed only in the C_{max} but not in the AUC of either atorvastatin or its active metabolites. In this multiple-dose study, atorvastatin concentrations were assayed by a gas chromatography/mass spectrometry (GC/MS) method. The difference between the atorvastatin-equivalent concentration and atorvastatin concentration represented the sum of the concentrations of active metabolites.

A new Small Tablet (ST) formulation, which is round-shaped, film-coated, and about 33% smaller in size than the Marketed Tablet (MT) formulation, has been developed with the main objective to ease patient administration, particularly the elderly who have swallowing difficulties. Additionally, a Chewable Tablet (CT) formulation has been developed as an alternative formulation of atorvastatin, which is also age-appropriate for use in the pediatric population.

The criteria for establishing bioequivalence (BE) of orally administered drug products include Test/Reference comparisons of both C_{max} and AUC as the indicators of peak and extent of exposures, respectively.

According to EMA [7] in studies to determine bioequivalence after a single dose, the parameters to be analyzed are AUC_{last}, or, when relevant, AUC_{72h}, and C_{max}. In studies with a sampling period of 72 h, and where the concentration at 72 h is quantifiable, AUC_{inf} and residual area do not need to be reported; it is sufficient to report AUC truncated at 72h, AUC_{72h}. A statistical evaluation of T_{max} is not required unless rapid release is claimed to be clinically relevant and of importance for onset of action or is related to adverse events [19,9,11,7]. Regulatory authorities such as United States Food and Drug Administration (FDA), European Medicines Agency (EMA), and Health Canada Therapeutic Products Directorate (TPD) generally recommend that the parent drug released from the dosage form, rather than the metabolites, be used as the basis for BE determination. The rationale for this recommendation is that concentration-time profile of the parent drug is more sensitive to the changes in formulation performance than a metabolite which is more reflective of metabolite formation, distribution, and elimination. In the case of drugs whose metabolites contribute meaningfully to safety and/or efficacy, some regulatory agencies such FDA and TPD require the determination of the BE based on the parent drug as well as the submission of metabolite data as supportive information [13,8]. However, the position of the EMA regarding the consideration of active metabolites for BE assessment has been evolving up to the finalization of the current BE guideline which only requires the analysis of the parent drug in BE studies [5,7]. In the current EMA guidance [7], the EMA clearly specifies the C_{max} of the parent compound is usually more sensitive in detecting differences between formulations in absorption rate rather than the

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C_{max} of a metabolite. It also clarifies further that the active metabolites do not need to be measured unless it is not feasible to measure parent drug concentrations.

Also according to Biopharmaceutics Classification System (BCS) based biowaivers [19,7,9], for the immediate release test products with proportionally formulated strengths, high soluble drugs with or without high permeability (i.e., BCS Class I and III drugs, respectively) can be exempted from *in vivo* BE studies and rely on *in vitro* dissolution methods as surrogates. For other BCS Class of drugs (e.g., BCS Class II and IV drugs), to demonstrate BE for all strengths, it is required to conduct one clinical BE study (the one which is most sensitive to formulation differences), provided that certain conditions for the test product are met. The EMA and TPD do not have specific BE guidance for atorvastatin. Also their general positions regarding the selection of the dose strengths for BE studies have been evolving until recently. The EMA's BE guideline was finalized in January 2010 [5,6]. The TPD nonlinear drug guidance issued 2003 [10], and the TPD draft BE guidance issued January 2010 [11]. In the EMA draft guidance [5,6], a linear pharmacokinetic was defined as a proportional increase in AUC and C_{max} with the increased dose over the therapeutic dose range. It also recommended that in the case of a linear PK that could not be concluded from the available data, the Sponsors need to conduct BE studies at both the lowest dose using the lowest strength and the highest dose using the highest strength. Similarly, in the current TPD BE guideline [9] it specifies "for some of the complicated drugs --such as those with …non-linear kinetics….--the bioavailability of each strength of the drug should be established," whereas in the TPD non-linear draft guidance [10], a detailed decision tree toward various non-linear pharmacokinetic situations was specified.

Global regulatory opinions on the measurement of active metabolites and on the selection of the dose strength(s) to be studied for BE assessments were still evolving during the time when the studies to support the development of atorvastatin ST and CT formulations were conducted. During this period, there are many examples of other drugs, including pioglitazone and risperidone, where both parent and active metabolites were evaluated in the BE studies [24,1]. The pharmacokinetics of ortho-hydroxyatorvastatin, the principal active metabolite of atorvastatin, were analyzed in the BE studies for the CT formulation, but not in studies for the ST formulation. This paper presents the analyses that were used to determine whether metabolite data provide additional informative value in the assessment of the BE of new atorvastatin formulations. Additionally, we assessed the linearity of atorvastatin pharmacokinetics to determine the need to adopt a bracketing approach for establishing the atorvastatin for new formulations at several strengths, i.e., the need to evaluate atorvastatin BE at the lowest (10 mg) and the highest (80 mg) strengths.

Materials and Methods

Study design

There were four individual BE studies; each conducted as an open-label, single-dose, randomized, 2-way crossover study, with a 14-day washout period between doses. Eligible adult subjects were admitted to the clinical research unit on Day 0 of each period. On Day 1 of each period, following an overnight 8-hour fast, subjects received a single dose of the atorvastatin reference tablets or the test tablets with 240 mL of ambient temperature water according to a randomization schedule. Study treatment was administered under the supervision of investigator

site personnel. For the CT formulations, subjects must chew the study treatment and then drink water. For the ST and MT formulations, subjects were to swallow the study treatment whole with water. The oral cavity of each subject was examined following dosing to ensure the study treatment was completely ingested. Subjects must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 8 hours prior to the start of pharmacokinetic sample collections. Water was permitted until 1 hour prior to study medication administration. Water may be consumed without restriction beginning 1 hour after dosing. Lunch and dinner were provided approximately 4 and 9-10 hours after dosing, respectively. The total daily nutritional composition was approximately 50% carbohydrate, 35% fat and 15% protein. The daily caloric intake per subject was less than 3200 kcal. In order to standardize the conditions on PK sampling days, all subjects were required to refrain from lying down during the first 4 hours after dosing.

The test products were atorvastatin ST at the doses of 1X10 mg (batch No. 08-066359, production date Apr. 2008, expiration date Apr. 2009) in Study A and 1X80 mg (batch No. 08-066360, production date Apr. 2008, expiration date Apr. 2009) in Study B; or atorvastatin CT at the doses of 1X10 mg (batch No. 08-069701, production date Mar. 2008, expiration date Mar. 2012) in Study C, and 2X40 mg (80 mg) (batch No. 08-069700, production date Mar. 2008, expiration date Nov. 2010) in Study D. The reference product was atorvastatin MT at the respective 1X10 mg (batch No. 08-064783, expiration date Nov. 2010) or 1X80 mg (batch No. 08-064786, expiration date Nov. 2010) dose in ST studies as well as 1X10 mg (batch No. 08-066007, expiration date Feb. 2012) or 1X80 mg (batch No. 08-064786, expiration date Nov. 2010) dose in CT studies. Blood samples for PK analyses were obtained pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, 36, 48, and 72 hours after each dose.
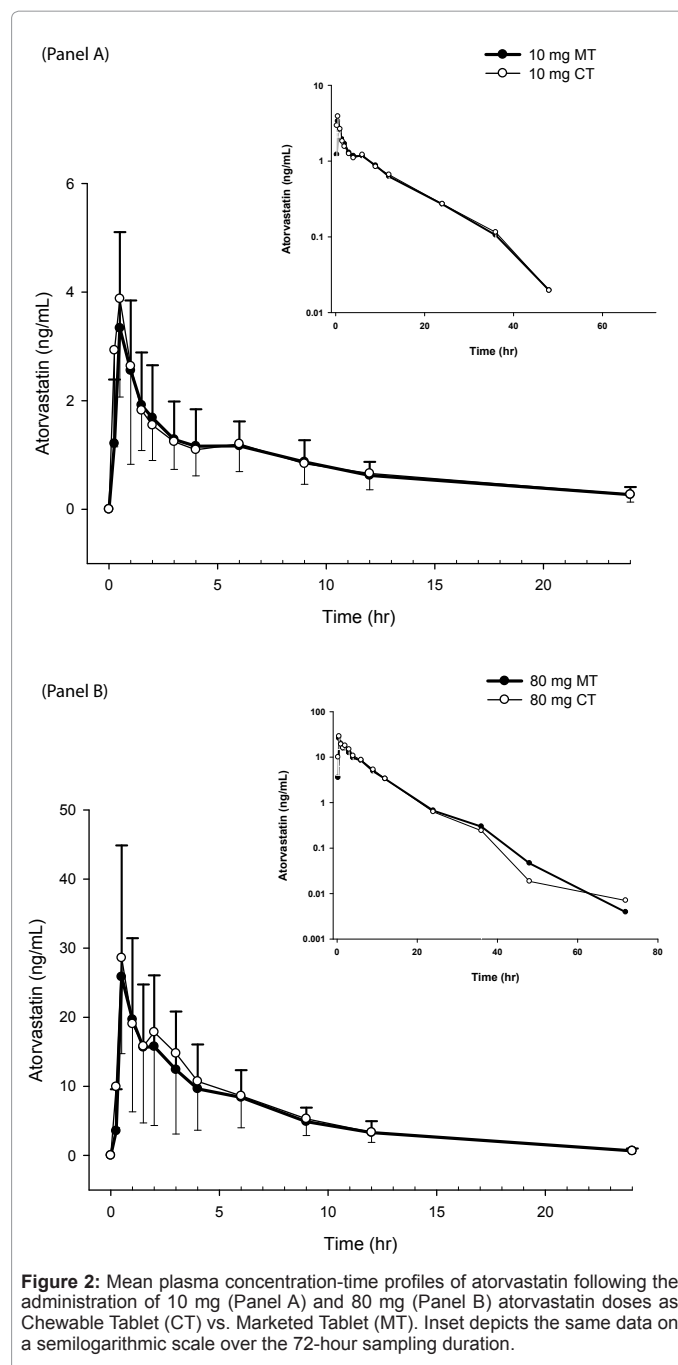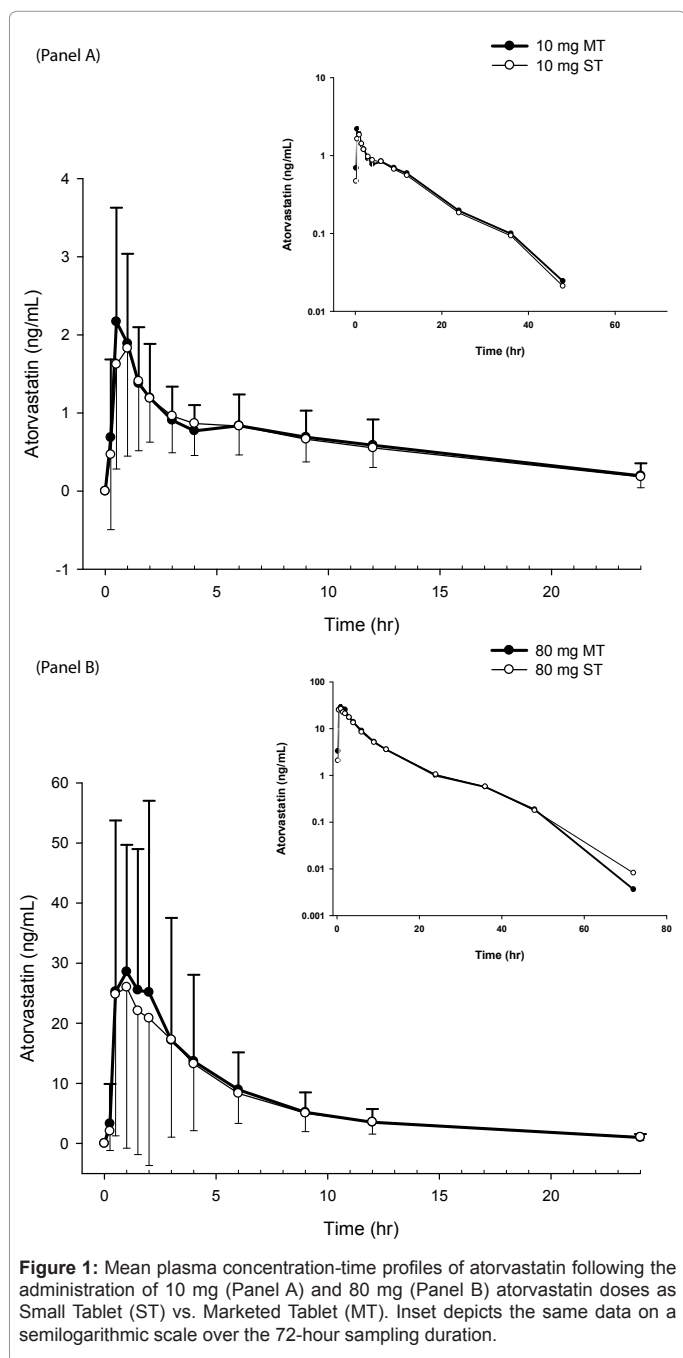
Subjects

These studies were each conducted in healthy adult male and female subjects aged 18 to 55 years (inclusive) with a body mass index between 18 and 30 kg/m² (inclusive). The protocol for each study was approved by the Independent Review Board of the clinical site and the studies were conducted in full compliance with the principles of the Declaration of Helsinki and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines.

Pharmacokinetic and statistical analyses

Plasma concentrations of atorvastatin and/or ortho-hydroxyatorvastatin were determined at Advion Bioservices, Ithaca, NY, by liquid chromatography tandem mass spectrometric (LC/MS/MS) method, as previously described [2]. Currently there are two validated LC/MS/MS assays, each with different assay ranges and limit of quantification (LOC). The assay with a linear range of 0.100 ng/mL to 10.0 ng/mL and a lower limit of quantification (LLOQ) of 0.100 ng/mL was used in the 10 mg ST and CT studies (Study A and Study C). The assay with a linear range of 0.250 to 100 ng/mL and LLOQ of 0.250 ng/mL was used in the 80 mg ST and CT studies (Study B and Study D).

Noncompartmental pharmacokinetic analyses which do not require the assumption of a specific compartmental model were performed on the plasma concentration–time profiles of individual subjects. The PK parameters analyzed include area under plasma concentration-time profile from time zero extrapolated to infinite time (AUC_{inf}), area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (AUC_{last}), and maximum plasma

concentration (C_{max}). The estimation of AUC was completed by linear/log trapezoidal method which use the linear trapezoidal rule during the ascending phase to the first occurrence of C_{max} and the log trapezoidal rule during the descending phase. Natural-log transformed AUC_{inf}, AUC_{last}, and C_{max} were analyzed by analysis of variance (ANOVA) using a mixed effects model with sequence, period, and treatment as fixed effects and subject-within-sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals (CIs) were obtained, and the adjusted mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. The BE of the Test to Reference

Figure 1: Mean plasma concentration-time profiles of atorvastatin following the administration of 10 mg (Panel A) and 80 mg (Panel B) atorvastatin doses as Small Tablet (ST) vs. Marketed Tablet (MT). Inset depicts the same data on a semilogarithmic scale over the 72-hour sampling duration.

Figure 2: Mean plasma concentration-time profiles of atorvastatin following the administration of 10 mg (Panel A) and 80 mg (Panel B) atorvastatin doses as Chewable Tablet (CT) vs. Marketed Tablet (MT). Inset depicts the same data on a semilogarithmic scale over the 72-hour sampling duration.

was to be concluded if the 90% CIs for the ratios (Test/Reference) of adjusted geometric means for AUC_{inf}, AUC_{last}, and C_{max} of atorvastatin fell entirely within (80%, 125%).

A sample size of 74 subjects was determined to provide 99% and 91% power that the 90% CI for the ratio of Test to Reference treatment for AUC_{inf} and C_{max}, respectively, would lie within the acceptance region of (80%, 125%) This estimate was based on the assumption that the true ratio between Test and Reference treatments for both AUC_{inf} and C_{max} was 1.05 and also assumed within-subject standard deviations (SD) of 0.185 and 0.35 for loge AUC_{inf} and loge C_{max}, respectively, as obtained from the average of 10 previous studies.
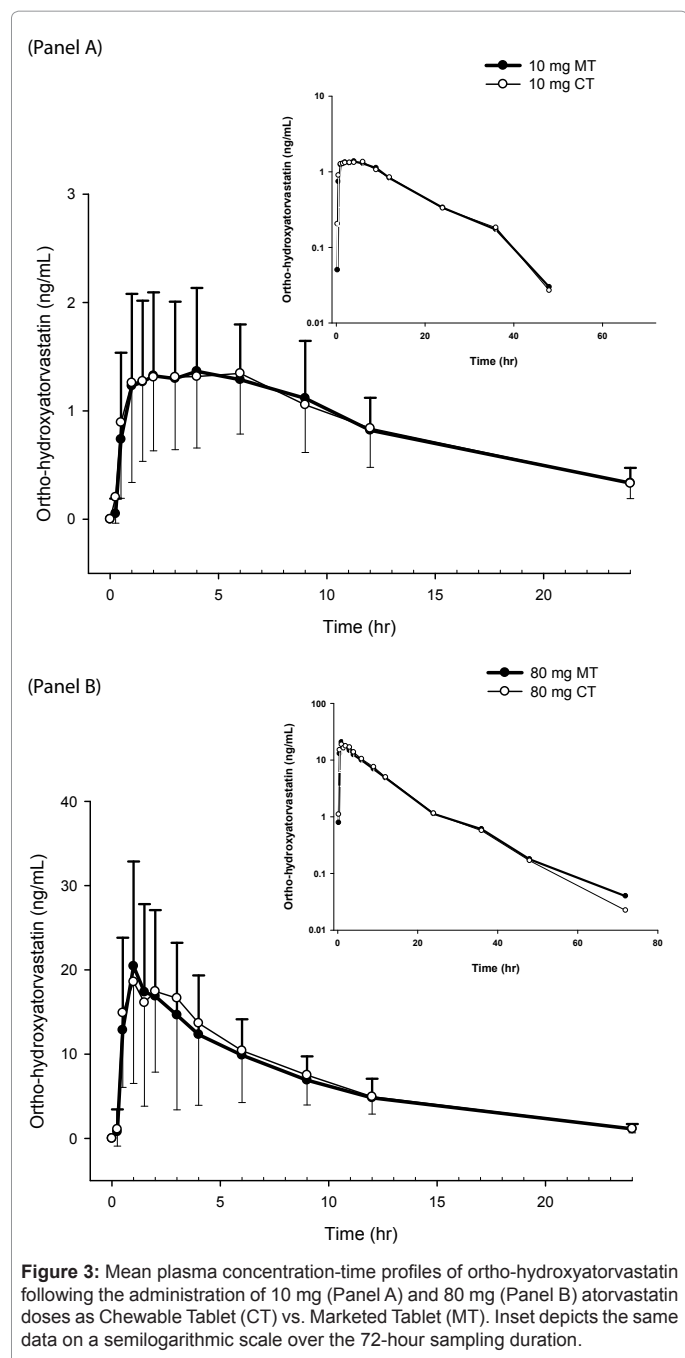
Figure 3: Mean plasma concentration-time profiles of ortho-hydroxyatorvastatin following the administration of 10 mg (Panel A) and 80 mg (Panel B) atorvastatin doses as Chewable Tablet (CT) vs. Marketed Tablet (MT). Inset depicts the same data on a semilogarithmic scale over the 72-hour sampling duration.

Safety

The safety and tolerability was evaluated by vital signs monitoring, physical examinations, 12-lead ECGs, and subject interviews on adverse events (AEs).

Results

Subject characteristics

A total of 76 healthy volunteers were assigned to receive study treatment in each study, and a total of 74, 73, 72, and 70 subjects completed Study A, Study B, Study C, and Study D, respectively. The ST studies (Study A; Study B) conducted at the same study center in

United States had comparable demographic characteristics: number of male/female subjects (38/38; 41/35); mean age, years (37; 41), mean weight, kg (71; 74), and race (White 93%; White 93%). In contrast, the CT studies (Study C; Study D) conducted at different study centers in different countries had somewhat different demographic characteristics: number of male/female subjects (70/6; 59/17), mean age, years (28; 36), mean weight kg (66; 79), and race (Asian 75%; Black/White: 46%/16%).

Pharmacokinetics

The mean plasma concentration-time profiles of atorvastatin following the administration of 10 mg and 80 mg given as ST or CT formulations, were superimposable on those following the administration of MT formulation at the respective dose (Figure 1 and Figure 2), respectively. Median T_{max} [hour (range)] were similar between ST vs MT: 10 mg [1.0 (0.25-9.0) vs 0.5 (0.25-4.0)], 80 mg [1.0 (0.5-4.0) vs 1.0 (0.5-4.0)] as well as between CT vs MT treatments: 10 mg [0.5 (0.25-1.5) vs 0.5 (0.4-4.0)], 80 mg [0.5 (0.25-6.0) vs 0.5 (0.5-6.0)]. Similar results were obtained for ortho-hydroxyatorvastatin in the CT studies (Figure 3). Median T_{max} [hour (range)] of ortho-hydroxyatorvastatin were similar between CT vs MT treatments: 10 mg [4.0 (0.5-9.0) vs 3.5 (0.5-9.0)], 80 mg [1.0 (0.5-6.0) vs 1.0 (0.5-6.0)]. Of note, following the administration of 10 mg ST or CT formulations, plasma concentrations of atorvastatin and ortho-hydroxyatorvastatin were mostly not quantifiable at 72 h. Thus AUC_{inf}, instead of AUC_{72h} was reported in these studies. A statistical summary of treatment comparisons of AUC_{inf}, AUC_{last}, and C_{max} is presented in Table 1. The 90% CIs for the ratio of the adjusted geometric means for AUC_{inf}, AUC_{last}, and C_{max} of atorvastatin were completely within (80%, 125%), the acceptance range for concluding BE. In addition, the corresponding 90% CIs for ortho-hydroxyatorvastatin measurements in the CT studies were also completely within the bioequivalent limits.

For the assessment of dose-relationship of the exposures of atorvastatin and its principal metabolite, when compared across 10 mg and 80 mg of ST and CT studies, as shown in Table 1, a greater than dose-proportional increase is generally seen in C_{max} but not AUC. In the ST studies with the 8-fold increase in dose, the AUC shows proportional increase (about 9-fold) whereas C_{max} of atorvastatin exhibits a greater than proportional increase (about 14- to 16-fold) in both groups. In the CT studies, with the 8-fold increase in dose, the AUC of both atorvastatin and ortho-hydroxyatorvastatin increased proportionally (about 6.5-fold); the C_{max} of ortho-hydroxyatorvastatin, however, shows a greater than proportional increase (about 15-fold). In addition, when compared across studies, the AUC ratios of ortho-hydroxyatorvastatin vs. atorvastatin for both groups in the CT studies are about 1.1-1.3, with no apparent dose relationship.

Safety

Both 10 mg and 80 mg dose given as ST, CT, and MT formulations were generally safe and well-tolerated in adult healthy volunteers. Overall, the AE profiles were consistent with the product label of atorvastatin. There were no deaths or serious AEs reported in these studies. There were no study discontinuations due to an AE that considered treatment related.

Discussion

The results of these four studies showed that the ST and the CT formulations of atorvastatin were each bioequivalent to the current MT formulation, at the lowest (10 mg) and the highest (80 mg) doses.

Study	Dose (mg)	Parameter (units)	Analyte	Adjusted Geometric Mean (SD) Min; Max		Ratio (Test/Reference) of Adjusted Geometric Mean (%)	90% Confidence Intervals (%)	
				Test	Reference		Lower	Upper
ST vs. MT	10	AUC_{inf} (ng.h/mL)	ATV	16.73 (8.26) 5.90; 42.20	17.55 (8.80) 5.68; 51.40	95.34	91.33	99.52
		AUC_{last} (ng.h/mL)	ATV	14.02 (7.89) 4.42; 39.50	17.55 (8.72) 4.73; 48.20	95.79	91.07	100.76
		C_{max} (ng/mL)	ATV	2.34 (1.45) 0.78; 8.23	2.56 (1.23) 0.96; 5.97	91.41	83.39	100.20
ST vs. MT	80	AUC_{inf} (ng.h/mL)	ATV	151.03 (100.78) 66.00; 794.00	152.88 (120.19) 57.90; 864.00	98.79	94.57	103.20
		AUC_{last} (ng.h/mL)	ATV	144.94 (100.57) 58.40; 786.00	146.81 (119.71) 51.80; 856.00	98.72	94.41	103.23
		C_{max} (ng/mL)	ATV	36.38 (31.71) 9.34; 193.00	34.76 (36.47) 7.25; 224.00	104.66	95.73	114.42
CT vs. MT	10	AUC_{inf} (ng.h/mL)	ATV	22.78 (9.73) 9.05; 61.70	22.13 (9.68) 9.83; 65.80	102.91	99.02	106.96
			O-ATV	24.46 (9.52) 10.10; 72.40	24.30 (9.67) 10.40; 70.50	100.64	97.51	103.88
		AUC_{last} (ng.h/mL)	ATV	20.48 (9.57) 7.31; 60.10	19.80 (9.26) 7.00; 64.30	103.48	99.34	107.79
			O-ATV	16.73 (9.59) 7.52; 70.60	16.73 (9.71) 8.52; 68.40	101	97.68	104.44
		C_{max} (ng/mL)	ATV	3.80 (2.22) 1.45; 14.30	3.51 (1.58) 1.13; 8.70	108.13	98.75	118.40
			O-ATV	1.49 (0.86) 0.48; 5.32	1.52 (0.91) 0.57; 5.54	97.98	92.34	103.96
CT vs. MT	80	AUC_{inf} (ng.h/mL)	ATV	131.13 (58.71) 64.20; 364.00	124.03 (53.83) 60.00; 317.00	105.73	100.69	111.02
			O-ATV	163.8 (75.99) 54.90; 514.00	156.5 (69.81) 64.70; 472.00	104.65	100.40	109.08
		AUC_{lst} (ng.h/mL)	ATV	127.49 (59.13) 60.60; 363.00	120.79 (53.36) 57.60; 313.00	105.55	100.34	111.03
			O-ATV	159.16 (74.69) 51.20; 492.00	151.88 (69.19) 61.40; 461.00	104.79	100.41	109.37
		C_{max} (ng/mL)	ATV	29.24 (15.88) 7.02; 91.50	28.85 (16.15) 9.27; 99.20	101.37	92.39	111.23
			O-ATV	22.52 (15.82) 7.29; 95.30	22.28 (12.22) 6.60; 63.20	101.11	93.08	109.84

ATV=atorvastatin acid; O-ATV=ortho-hydroxyatorvastatin acid

Table 1: Statistical summary of pharmacokinetic parameters of atorvastatin and ortho-hydroxyatorvastatin in healthy subjects following single-dose administration of 10 and 80 mg doses as Small Tablet (ST) or Chew Tablet (CT) vs. Marketed Tablet (MT).

For the CT formulation, both atorvastatin and its metabolite were analyzed, and the two moieties led to the same conclusion of BE at both doses. However, for the ST formulation BE was determined only for atorvastatin, as the analyses were only done on atorvastatin. In the ST formulation BE would also be predicted for the metabolite, due to the fact that the ST and CT formulations are remarkably similar and furthermore the ST formulation is closer in composition to MT as compared to ST. Even though excipients are known to influence the drug dissolution and/or absorption [12,7], as stated above the similarities in formulations would not support alterations in BE for the metabolite among these formulations. Especially, the ST formulation was a lower-weight and 33% smaller-size tablet made of essentially the same granulation as the reference MT formulation. The 80 mg ST used the same drug substance and excipients contained in the MT; the 10, 20, and 40 mg ST also used the same percentages of drug substance and excipients as the MT formulation (10, 20 and, 40 mg), with exception of candelilla wax. This type of formulation change is unlikely to affect the metabolite formation. As a result the level of formulation modification in the ST formulation compared to that involved in the CT formulation was considered unlikely to affect the metabolite formation or to result in different BE outcomes of ortho-hydroxyatorvastatin; therefore, ortho-hydroxyatorvastatin was not analyzed in the ST studies.

Based on single- and multiple-dose studies, it can be concluded that the atorvastatin AUC increases proportionally with dose, and its nonlinearity is associated with C_{max} only. The multiple-dose study described in the literature [25] was a sequential dose-escalation design, which showed a greater than dose-proportional increase in C_{max} but not in the AUC of atorvastatin as well as its active metabolites. The four ST and CT studies described here were conducted using similar single-dose, two-way crossover study design and were analyzed similarly, allowing for between-study assessment of dose proportionality. For the 8-fold dose increment between the 10- and 80-mg doses given as ST, CT and MT formulations across these four studies, the C_{max} and AUC ratios were 7.7-15.5 and 5.6-9.0 fold, respectively, indicating dose-proportional AUC and greater-than-proportional C_{max}, consistent with the multiple-dose study results of dose proportionality.

Furthermore the analyses of the metabolite/parent ratios of AUC across the CT studies showed no apparent dose relationship in the AUC ratios of ortho- hydroxyatorvastatin/atorvastatin for both formulation groups (i.e., 1.1 and 1.3 at 10 mg and 80 mg atorvastatin doses, respectively). These results are also consistent with those of the multiple-dose study [25] in which the metabolite/parent ratios did not appear dose-related (2.1, 2.4, 1.5, and 2.7 following 10, 20, 40, and 80 mg atorvastatin doses, respectively). These results imply that the metabolic clearance of atorvastatin is not saturable across the 10-80 mg doses; any differences in metabolite exposures due to a formulation change will be reflected in the systemic exposures of the parent drug.

Atorvastatin exhibits a complex pharmacokinetic profile: a greater

than proportional increase in C_{max} only, high intra-subject variability in C_{max}, and its active metabolites contribute significantly to safety and efficacy. It is a BCS Class II drug (low solubility, high permeability drug) [23] and the FDA has recently specified the required studies to support abbreviated new drug applications (ANDA) of 10-80 mg doses of generic atorvastatin [20]. The guidance requires atorvastatin BE study at the highest dose, with a provision of biowaiver for 10 mg, 20 mg, and 40 mg atorvastatin, the generic companies need to show (1) acceptable clinical BE studies on the 80 mg strength, (2) proportionally similar across all strengths, and (3) acceptable *in vitro* dissolution testing of all strengths. In general, the product-specific BE guidelines by FDA require BE studies at the highest dose strength permissible by safety in healthy subjects and also emphasize the measurement of metabolites for products which derive significant pharmacological effects from active metabolite(s). For example, it requires BE evaluation under both fasting and fed conditions with 80 mg (highest strength) simvastatin and to provide beta-OH metabolite data as supportive evidence of a comparable therapeutic outcome [21]. Similarly it is required to conduct BE with 45 mg (highest strength) pioglitazone and to provide M-IV metabolite data [22].

Although statin therapy is generally safe and well tolerated, the increased systemic exposures associated with high doses may increase the risk for relatively common muscular side effects, such as myalgia, and for rare but potentially severe AEs such as myopathy and rhabdomyolysis [4]. There is a clear dose-response relationship for lipid-lowering effects of atorvastatin. Thus, to ensure equivalence of therapeutic outcomes of new generic formulations, it is important to assess bioequivalence of all relevant active moieties under the most sensitive conditions that can detect potential formulation differences. Both AUC and C_{max} are essential measures of BE [19,7], and further that C_{max} is the most sensitive PK parameter to detect differences between formulations [7]. The sources of non-linearity for these measures can be found at different kinetic levels of absorption, distribution, and/or elimination [14]. Specifically, non-linearity of AUC can be related to dose-dependent elimination and/or bioavailability; non-linearity of C_{max} can be related to dose-dependent bioavailability, volume, elimination and/or absorption [17]; in many cases the nonlinearity of AUC would also be manifested in C_{max}. However, non-linear C_{max} may be independent of AUC, if the nonlinearity is driven by absorption rate or distribution volume, and the former driver of C_{max} nonlinearity is of particular interest in BE assessment. When exposure increases more than dose proportionally, for the same difference in dose delivered due to formulation bioavailability differences, a larger difference in exposure will be seen at higher doses, and the highest dose strength will have the largest sensitivity in detecting differences between two products. The development of atorvastatin by Pfizer as the product innovator has been supported by BE studies at both the lowest and highest doses and include PK analyses for active metabolites.

In conclusion, although metabolite BE is not required, supportive metabolite data may be warranted depending on the degree of divergence in formulations from the marketed atorvastatin formulation. Atorvastatin has linear PK with respect to AUC; however, atorvastatin is clearly nonlinear with respect to C_{max}. In light of the nonlinearity of C_{max}, BE studies of new atorvastatin formulations should be conducted at the highest dose.

Acknowledgements

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