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APPLICATION NUMBER:

22-363

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Biopharmaceutics Review

NDA:	22-363
Submission Date:	July 6, 2009
Type of Submission:	Amendment #0035 to New Drug Application
Product name:	Pitavastatin Calcium
Trade Name:	Livalo
Dosage Form:	Immediate-Release Tablet
Dosage Strengths:	1 mg, 2 mg, and 4 mg
Sponsor:	Kowa Company Limited

Background

On October 1, 2008, the sponsor submitted a New Drug Application for pitavastatin tablets (1 mg, 2 mg and 4 mg). The proposed dissolution method was sufficiently discriminatory using basket at 35 rpm in 900 mL of pH 6.8 phosphate buffer at 37 °C. However, the proposed specification was not acceptable. Based on the dissolution data provided on the clinical, stability and registration batches for each strength, a single-point dissolution test specification of NLT (b) (4) (Q=(b) (4)) in 30 minutes was recommended.

On June 23, 2009, the Agency requested as a Phase IV commitment that the sponsor revise the dissolution specification within one year from the date of approval. The request was to adopt a single-point dissolution test specification of NLT (b) (4) (Q=(b) (4)) in 30 minutes for all dosage strengths (1 mg, 2 mg, and 4 mg).

On July 6, 2009, the sponsor agreed that within one year following approval to adopt a single-point dissolution test method and specification of NLT (b) (4) (Q=(b) (4)) in 30 minutes.

Comments

It is noted that the sponsor agreed to adopt within one year from the date of approval a single-point dissolution test specification of NLT (b) (4) (Q=(b) (4)) in 30 minutes for all dosage strengths.

Recommendation

The agreement is acceptable and no further action is required at this time.

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Biopharmaceutics Review

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Recommendation

The proposed dissolution method is sufficiently discriminatory using basket at 35 rpm in 900 mL of pH 6.8 phosphate buffer at 37 °C. However, the specification proposed by the sponsor is not acceptable. Based on the dissolution data provided on the clinical, stability and registration batches for each strength, a single-point dissolution test specification of NLT^{(b) (4)} (Q=^{(b) (4)}) in 30 minutes is recommended.

The 1-mg dosage strength is proportionally similar in its active and inactive ingredients to the 2-mg and 4-mg dosage strengths for which BE testing has been conducted. It is worth noting that the film coating solution is not exactly proportional between the three strengths. However, the difference in the film coating solution is small^{(b) (4)} as compared to total target dosage form weight. Accordingly, per SUPAC IR, this is a Level 1 change and none beyond the application dissolution testing is required.

Although, the sponsor stated that pitavastatin would be considered BCS Class I immediate release solid oral dosage form, there was no data submitted to support this claim. However, each SkyePharma and Patheon combination was demonstrated to be similar in vitro by either the dissolution data were too fast (e.g.,^{(b) (4)} by 15 minutes) leading to a fast pass or had an f_2 ^{(b) (4)}. And, the SkyePharma and Patheon biobatches are similar using the proposed dissolution condition. Therefore, a biowaiver for Patheon 1 mg tablets is justifiable.

Background

SkyePharma, France manufactured pitavastatin 1 mg, 2 mg and 4 mg tablets that were used for clinical trials and pivotal Phase 3 trials conducted for the EU and US drug development process. The proposed commercial product in the USA will be manufactured by Patheon, Cincinnati, USA. Although the formulations used for SkyePharma 1 mg, 2 mg and 4 mg tablets and Patheon corresponding tablets are identical and the formulations are proportional, equivalence of SkyePharma tablets used for Phase 3 trials and the tablets manufactured by Patheon requires confirmation. As a result, the sponsor conducted a bioequivalence study [NK-104-1.37US] to compare SkyePharma 2 mg and 4 mg tablets with Patheon 2 mg and 4 mg tablets.

In the bioequivalence study, Batch N906.14 of 2 mg and N905.10 of 4 mg manufactured by SkyePharma were used as the reference batches. Batches 3062493R of 2 mg and 3062496R of 4 mg manufactured by Patheon were used as the test batches. The sponsor stated that results of the bioequivalence study showed similar pharmacokinetics of pitavastatin and pitavastatin lactone for SkyePharma and Patheon tablets, as the 90% CI fell within the acceptance range of 80-125% for AUC and Cmax. Therefore, the SkyePharma 2 mg and 4 mg tablets and Patheon 2 mg and 4 mg tablets are considered bioequivalent.

The sponsor is requesting a biowaiver for the lower dose, 1 mg. To support the biowaiver request, the sponsor provided in vitro dissolution data comparing Patheon 1 mg tablet and Patheon 2 mg tablet using the proposed dissolution method (basket at 35 rpm, 900 mL of pH 6.8 phosphate buffer USP at 37°C), and two additional pH media (pH 1.2 and 4.5).

Dissolution Method Development

Pitavastatin calcium is freely soluble in pyridine, tetrahydrofuran, chloroform or dilute hydrochloric acid; soluble in ethylene glycol; sparingly soluble in octanol; slightly soluble in methanol; very slightly soluble in water or ethanol, and practically insoluble in acetonitrile or diethyl ether. Solubility also varies with pH, pitavastatin calcium is slightly soluble at pH 1.2 and pH 2.0, insoluble at pH 4.0, slightly soluble at pH 6.0 and 6.8 and very slightly soluble at higher pH values.

The solubility of pitavastatin calcium in various solvent is shown in table 1 below.

Table 1: Solubility of Pitavastatin Calcium in Various Solvent (20±5°C)

Solvent	Solvent Volume (mL) for 1 g API	Comment
Pyridine	(b) (4)	Freely soluble
Tetrahydrofuran		Freely soluble
Chloroform		Freely soluble
Ethylene glycol		Soluble
Octanol		Sparingly soluble
Methanol		Slightly soluble
(b) (4) Ethanol		Slightly soluble*
Water		Very slightly soluble
Acetonitrile		Practically insoluble
Diethyl ether		Practically insoluble
10% Hydrochloric acid		Freely soluble

(b) (4) reports in DMF (b) (4) that (b) (4) pitavastatin calcium is "slightly soluble", the table has been changed to reflect this.

The dissolution method was developed using the 2 mg tablet formulation samples as shown in Tables 2 and 3 below

Table 2: Tablets used in Dissolution Method Development

Material	Batch/Lot No	Manufacturer
2-mg Livalo tablets cores	GM	Kowa, Nagoya factory
2-mg Livalo coated tablets	GM	Kowa, Nagoya factory
2-mg(b) (4) cores*	709K	Kowa, Fuji Laboratories
2-mg cores(b) (4)	627T-3	Kowa, Fuji Laboratories

*These batches were manufactured to earlier formulations evaluated during the development of the product and were selected as different formulation controls for this study.

Table3 : Tablet Formulations used in Dissolution Method Development

Ingredient	Livalo Core	Livalo Coated	(b) (4) Core	Cores (b) (4)
	(mg)	(mg)	(mg)	(mg)
Pitavastatin Calcium	(b) (4)			
Lactose monohydrate				
HPMC (b) (4)				
L-HPC				
Magnesium Aluminummetasilicate				
Microcrystalline Cellulose				
Magnesium Stearate				
(b) (4)				
Total	120.00	127.00		(b) (4)

The factors investigated included the effect of using different apparatus: paddle or basket, the effect of using different rotation speed, and the effect of using different dissolution media. In each investigation the ability to detect a difference between film coated tablets and tablet cores was used as the primary measure of discrimination, then alternative tablet core formulations were used to confirm the method was suitably discriminatory.

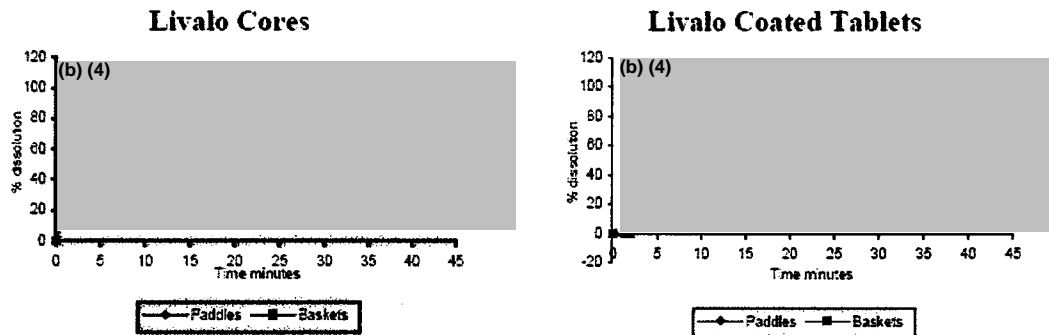
The Effect of Using Different Apparatus: Paddle or Basket

This dissolution study was performed to investigate the effect of using paddle versus basket. The dissolution media was 900 mL of (b) (4) and the rotation speed was 50 rpm. The data provided in table 4 shows the differences in the dissolution of pitavastatin when using a paddle versus a basket. Figure 1 shows the dissolution profiles comparing paddle and basket and their effect on the dissolution of tablet cores and coated tablets.

Table 4: Effect of Paddles or Baskets on Mean Dissolution (n=6)

Dosage Form and Apparatus	Dissolution Time Point							
	2 min	5 min	7 min	10 min	15 min	20 min	30 min	45 min
Livalo Cores	(b) (4)							
Paddles								
Baskets								
Livalo Coated Tablets								
Paddles								
Baskets								

Figure 1: Comparison of Paddle and Basket on the Dissolution of Tablet Cores and Coated Tablets.



The basket data indicates a more rapid release profile compared to the paddle data and a greater difference between the film coated tablets and cores is observed for the basket. This suggests that the use of basket is the more discriminatory technique compared to the use of paddle.

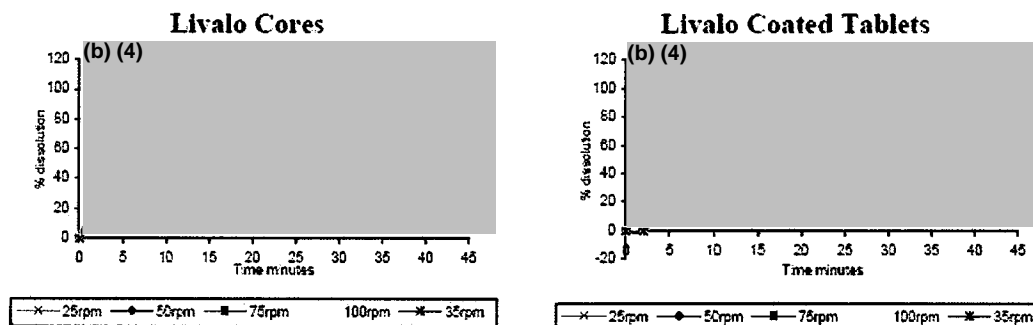
The Effect of Using Different Rotation Speed

Although differences were observed suggesting that basket were the more discriminatory method, no significant difference was observed between paddle and basket at 50 rpm thus the impact of rotation speed between 25 rpm and 100 rpm using (b) (4) as the media was investigated. Data showing the effect of rotation speed on pitavastatin dissolution is provided in Table 5 and Figure 2.

Table 5: Effect of Using Different Rotation Speed on Mean Dissolution (n=6)

Dosage Form and Apparatus	Dissolution Time Point							
	2 min	5min	7 min	10 min	15 min	20 min	30 min	45 min
Livalo Cores	(b) (4)							
25rpm								
35rpm								
50rpm								
75rpm								
100rpm								
Livalo Coated Tablets	(b) (4)							
25rpm								
35rpm								
50rpm								
75rpm								
100rpm								

Figure 2: Comparison of Using Different Rotation Speed on the Dissolution of Tablet Cores and Coated Tablets



The data indicates that the slower the rotation speed the more discriminatory the method becomes for the Livalo coated tablets, but much less so for the Livalo cores. However, this effect is much less pronounced at 75 rpm and 100 rpm. Clearly the most discriminatory speeds are less than 50 rpm. Since the greatest difference between tablet cores and film coated tablets was observed using baskets at 25 rpm, this condition was selected for evaluating a suitable dissolution media.

The Effect of Using Different Dissolution Media

A number of potential media were screened by immersing a single tablet in a glass beaker containing 100 mL of each potential media at 37 °C and observing the disintegration of the tablets over a 30 minute period. Dissolution profiles were then generated, using Basket at 25 rpm in the following media:

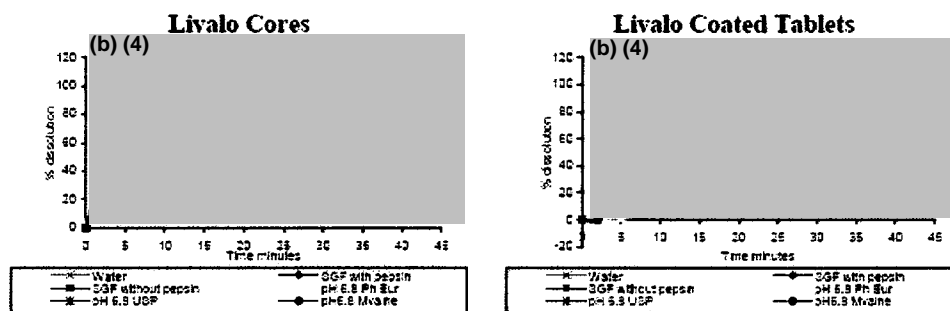
- Purified water,
- Simulated gastric fluid at pH 1.2 with pepsin (as described in the USP),
- Simulated gastric fluid at pH 1.2 without pepsin,
- pH 6.8 phosphate buffer (as described in the Ph. Eur.),
- pH 6.8 phosphate buffer (as described in the USP),
- pH 6.8 MacIlvaine buffer (phosphate-citric acid).

Table 6 and Figure 3 below show the effect of using different media on the dissolution of tablet core and coated tablet.

Table 6: Effect of Media Choice on Mean Dissolution (n=6)

Dosage Form and Apparatus	Dissolution Time Point							
	2 min	5min	7 min	10 min	15 min	20 min	30 min	45 min
Livalo Cores	(b) (4)							
Water								
pH1.2 SGF with pepsin								
pH 1.2 SGF without pepsin								
pH 6.8 phosphate Ph Eur								
pH 6.8 phosphate USP								
pH 6.8 MacIlvaine buffer								
Livalo Coated Tablets								
Water								
pH1.2 SGF with pepsin								
pH 1.2 SGF without pepsin								
pH 6.8 phosphate Ph Eur								
pH 6.8 phosphate USP								
pH 6.8 MacIlvaine buffer								

Figure 3: Media Comparison on the Mean Dissolution of Tablet Cores and Coated Tablets



Strongly acidic media were considered unsuitable for discriminatory dissolution. The dissolution profiles obtained in this study for water demonstrated that the

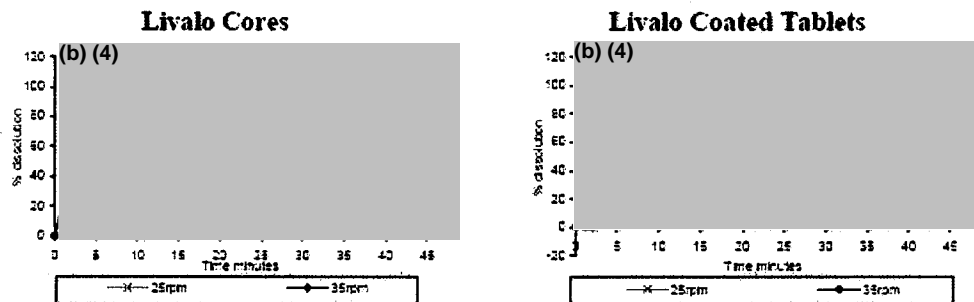
method is able to discriminate between film coated tablets and cores. However, the greatest difference between cores and film coated tablets is observed using the Ph Eur compliant pH 6.8 Phosphate buffer but the film coated tablets fail to reach a suitable plateau value. However, a realistic plateau value is achieved using the USP pH 6.8 Phosphate buffer and the pH 6.8 MacIlvaine buffer.

A comparison was done using the pH 6.8 USP phosphate buffer at different rotation speeds, data is provided in Table 7 and Figure 4. The sponsor stated that the basket rotation at 35 rpm provides a smoother release profile than at 25 rpm, as the 35 rpm could overcome potential mechanical effects associated with dissolution using baskets at very slow rotation speeds. Therefore, the dissolution conditions chosen for this drug product are basket at 35 rpm using pH 6.8 USP phosphate buffer.

Table 7: Effect of Rotation Speed on Mean Dissolution, using Phosphate USP Media pH 6.8

Dosage Form and Apparatus	Dissolution Time Point							
	2 min	5 min	7 min	10 min	15 min	20 min	30 min	45 min
Livalo Cores	(b) (4)							
25rpm								
35rpm								
Livalo Coated Tablets								
25rpm								
35rpm								

Figure 4: The Effect of Rotation Speed on Mean Dissolution, Phosphate USP, pH 6.8

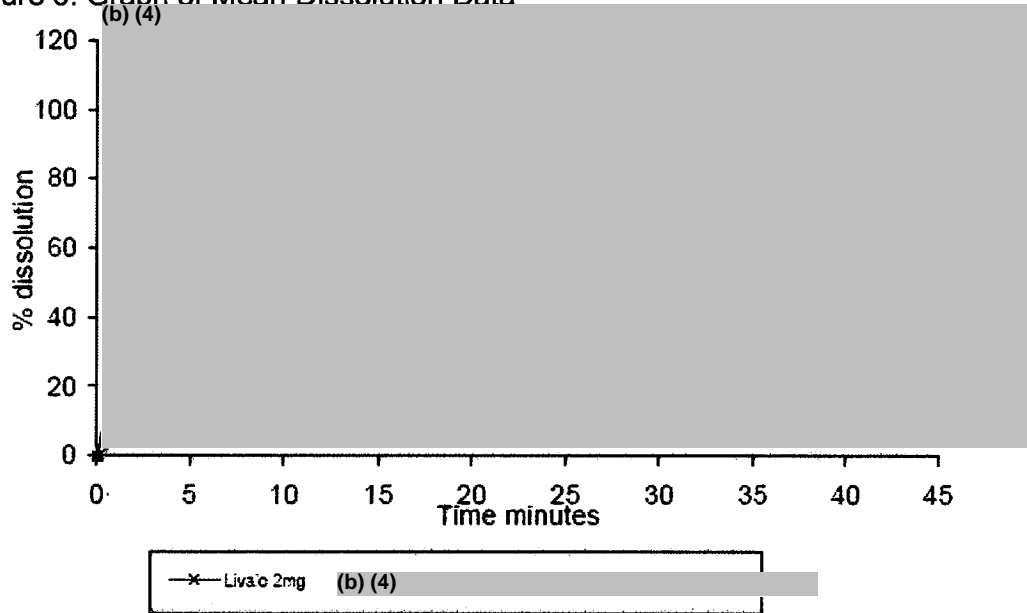


The discriminatory nature of the dissolution test conditions chosen with respect to tablet core formulation was then confirmed by using alternative (b) (4) tablet core formulations. The mean dissolution data of these formulations are shown in Table 8 and Figure 5. The data provided indicates that the alternative formulations can be discriminated against.

Table 8: Mean Dissolution Data on Different Pitavastatin Tablet Core Formulations

Dosage Form and Apparatus	Dissolution Time Point							
	2 min	5min	7 min	10 min	15 min	20 min	30 min	45 min
Livalo cores	(b) (4)							
(b) (4)								
(b) (4)								

Figure 5: Graph of Mean Dissolution Data



The proposed dissolution method is sufficiently discriminatory using basket over paddle at 35 rpm. The medium is 900 mL of pH 6.8 phosphate buffer at 37 °C). The profiles were determined by sampling after 2, 5, 7, 10, 15, 20, 30, and 45 minutes.

Justification of Specification

The sponsor stated that dissolution data to date indicates that dissolution of the product is related to the formulation and rate of disintegration, and to insure the performance of the immediate-release tablet, a single-point dissolution acceptance criterion of $Q = (b) (4)$ at 30 minutes is appropriate.

As seen in Table 9 below the dissolution data for the core and coated tablets of nine registration batches using the proposed dissolution method (Basket, 900 mL Phosphate USP media pH 6.8, 37°C, at 35 rpm) support dissolution test specification of NLT $(b) (4)$ ($Q = (b) (4)$) in 30 minutes as only Batch 3062496R was

the batch that failed Stage 1 dissolution testing though it passed Stage 2 dissolution testing. Additional data supporting this specification are found in the Appendix.

Table 9: Dissolution Data for the Core and Coated Tablets using the Proposed Dissolution Method (Basket, 900 mL Phosphate USP media pH 6.8, 37°C, at 35 rpm)

Dose Strength	Batch	Core Tablets			Coated Tablets		
		Average (n=6, %)	Range (%)	% RSD	Average (n=6, %)	Range (%)	% RSD
1 mg	3062490R	(b) (4)					
	3062491R						
	3062492R						
2 mg	3062493R						
	3062494R						
	3062495R						
4 mg	3062496R						
	3062497R						
	3062498R						

*Note: Dissolution at 30 minute results failed S1 testing per USP requirements. Several results were below Q (b) (4). S2 testing was performed per USP and sample passes S2 testing specs. Average result of N=12 units was (b) (4) and no unit was below Q (b) (4).

Reviewer's Note:

The specification proposed by the sponsor is not acceptable. Based on the dissolution data provided on the clinical and stability and registration batches for each strength, a single-point dissolution test specification of NLT (b) (4) (Q (b) (4)) in 30 minutes is recommended.

Assessing Proportional Similarity:

Pitavastatin calcium tablets are an immediate-release solid oral dosage form of 1.00 mg, 2.00 mg and 4.00 mg of pitavastatin calcium measured as pitavastatin. The proposed dosage forms are immediate-release, film-coated tablets. The composition of pitavastatin tablets are shown in table 10 below.

Table 10: Target Composition of the 1 mg, 2 mg, and 4 mg Pitavastatin Tablets

Component	Reference	Function	Quantity		
			1 mg Tablet (mg)	2 mg Tablet (mg)	4 mg Tablet (mg)
Tablet Core					
Pitavastatin Calcium	DMF (b) (4)	Active	1.045 ¹	2.09 ¹	4.18 ²
Lactose Monohydrate	NF	(b) (4)	(b) (4)		
Low Substituted Hydroxypropyl Cellulose	NF				
Hypromellose (b) (4)	USP				
Magnesium Aluminummetasilicate (b) (4)	NF				
Magnesium Stearate	NF				
(b) (4)	USP				
(b) (4)					
Film Coating (b) (4)					
(b) (4)	DMF (b) (4)				
	USP				
Total			83.00	165.00	329.00

¹ Equivalent to 1.00 mg, 2.00 mg and 4.00 mg of Pitavastatin Calcium

Reviewer's Note:

The 1-mg dosage strength is proportionally similar in its active and inactive ingredients to the 2-mg and 4-mg dosage strengths for which BE testing has been conducted. It is worth noting that the film coating (b) (4) is not exactly proportional between the three strengths. However, the difference in the film coating (b) (4) is small (b) (4) compared to total target dosage form weight. According to SUPAC IR, this is a Level 1 change and none beyond the application dissolution testing is required.

Assessing Dissolution Similarity:

1. Assessing Dissolution Similarity between Patheon 1 mg and 2 mg Tablets in Three Media (pH 1.2, 4.5, and 6.8)

The sponsor submitted *In vitro* dissolution profile comparison data between Patheon 1 mg tablets and Patheon 2 mg tablets in three media (pH 1.2, 4.5 and 6.8).

pH 6.8 Medium

In pH 6.8 medium, the mean release of Patheon 1 mg tablets, and 2 mg tablets, at 15 minutes was at or above (b) (4) as seen in Tables 11 and 12 below. At this pH, the profiles demonstrate "rapid dissolving" characteristics therefore similarity was confirmed visually.

Table 11: Patheon 1 mg Tablet Dissolution Data at pH 6.8

Patheon 1 mg/ 3062490R

Time (min.)	Dissolution rate (%)													mean	RSD
	1	2	3	4	5	6	7	8	9	10	11	12			
0	(b) (4)														
5															
10															
15															
20															
30															
45															

Patheon 1 mg/ 3062491R

Time (min.)	Dissolution rate (%)													
	1	2	3	4	5	6	7	8	9	10	11	12	mean	RSD
0	(b) (4)													
5														
10														
15														
20														
30														
45														

Patheon 1 mg/ 3062492R

Time (min.)	Dissolution rate (%)													
	1	2	3	4	5	6	7	8	9	10	11	12	mean	RSD
0	(b) (4)													
5														
10														
15														
20														
30														
45														

Table 12: Patheon 2 mg Tablet Dissolution Data at pH 6.8 (cont.)

Patheon 2 mg/ 3062493R

Time (min.)	Dissolution rate (%)													mean	RSD
	1	2	3	4	5	6	7	8	9	10	11	12			
0	(b) (4)														
2															
5															
7															
10															
12															
15															
20															
30															
45															

Patheon 2 mg/ 3062494R

Time (min.)	Dissolution rate (%)													mean	RSD
	1	2	3	4	5	6	7	8	9	10	11	12			
0	(b) (4)														
2															
5															
7															
10															
12															
15															
20															
30															
45															

Patheon 2 mg/ 3062495R

Time (min.)	Dissolution rate (%)													mean	RSD
	1	2	3	4	5	6	7	8	9	10	11	12			
0	(b) (4)														
2															
5															
7															
10															
12															
15															
20															
30															
45															

pH 1.2 Medium

In pH 1.2 medium, the degradation of pitavastatin was observed mainly due to the formation of (b) (4). Therefore, dissolution profile was calculated with the sum of pitavastatin and (b) (4) peak area as seen in Tables 13 and 14. With (b) (4) (degradation product) added to the calculation, all lots (Patheon 1 mg and Patheon 2 mg) have release above (b) (4) at 15 minutes, therefore "rapid dissolving" was confirmed and a profile comparison using similarity factor, f_2 , was not necessary.

Table 13: Patheon 1 mg Tablet Dissolution Data at pH 1.2

Patheon 1 mg/ 3062490R

Time (min.)	Dissolution rate (%)													
	Only pitavastatin peak							Pitavastatin (b) (4)						
	1	2	3	4	5	6	mean	1	2	3	4	5	6	Mean
0	(b) (4)													
5														
10														
15														
20														
30														
45														

Patheon 1 mg/ 3062491R

Time (min.)	Dissolution rate (%)													
	Only pitavastatin peak							Pitavastatin (b) (4)						
	1	2	3	4	5	6	mean	1	2	3	4	5	6	Mean
0	(b) (4)													
5														
10														
15														
20														
30														
45														

Patheon 1 mg/ 3062492R

Time (min.)	Dissolution rate (%)													
	Only pitavastatin peak							Pitavastatin (b) (4)						
	1	2	3	4	5	6	mean	1	2	3	4	5	6	Mean
0	(b) (4)													
5														
10														
15														
20														
30														
45														

Table 14: Patheon 2 mg Tablet Dissolution Data at pH 1.2 (cont.)

Patheon 2 mg/ 3062493R

Time (min.)	Dissolution rate (%)													
	Only pitavastatin peak							Pitavastatin (b) (4)						
	1	2	3	4	5	6	mean	1	2	3	4	5	6	mean
0	(b) (4)													
5														
10														
15														
20														
30														
45														

Patheon 2 mg/ 3062494R

Time (min.)	Dissolution rate (%)													
	Only pitavastatin peak							Pitavastatin (b) (4)						
	1	2	3	4	5	6	mean	1	2	3	4	5	6	mean
0	(b) (4)													
5														
10														
15														
20														
30														
45														

Patheon 2 mg/ 3062495R

Time (min.)	Dissolution rate (%)													
	Only pitavastatin peak							Pitavastatin + (b) (4)						
	1	2	3	4	5	6	mean	1	2	3	4	5	6	mean
0	(b) (4)													
5														
10														
15														
20														
30														
45														

pH 4.5 Medium

In pH 4.5 medium, all batches showed dissolution of above (b) (4) in 15 minutes with the exception of 3052495R (2 mg batch). However, the mean release at 15 minutes (n=18) for all three Patheon 2 mg lots (3062493R, 3062494R, 3062495R) was (b) (4) with a %RSD=13 as seen in Tables 15 and 16.

Therefore, the mean dissolution profile for the Patheon 2 mg strength is classified as "rapid dissolving". The mean release at 15 minutes (n=18) for the three 1 mg Patheon lots (3062490R, 3062491R, 3062492R) was (b) (4) with a RSD of 7.3%, demonstrating rapid dissolution characteristics.

Table 15: Patheon 1 mg Tablet Dissolution Data at pH 4.5

Patheon 1 mg/ 3062490R							
Time (min.)	Dissolution rate (%)						
	1	2	3	4	5	6	mean
0	(b) (4)						
5							
10							
15							
20							
30							
45							

Patheon 1 mg/ 3062491R							
Time (min.)	Dissolution rate (%)						
	1	2	3	4	5	6	mean
0	(b) (4)						
5							
10							
15							
20							
30							
45							

Patheon 1 mg/ 3062492R							
Time (min.)	Dissolution rate (%)						
	1	2	3	4	5	6	mean
0	(b) (4)						
5							
10							
15							
20							
30							
45							

Table16: Patheon 2 mg Tablet Dissolution Data at pH 4.5 (cont.)

Patheon 2 mg/ 3062493R

Time (min.)	Dissolution rate (%)						
	1	2	3	4	5	6	mean
0	(b) (4)						
5							
10							
15							
20							
30							
45							

Patheon 2 mg/ 3062494R

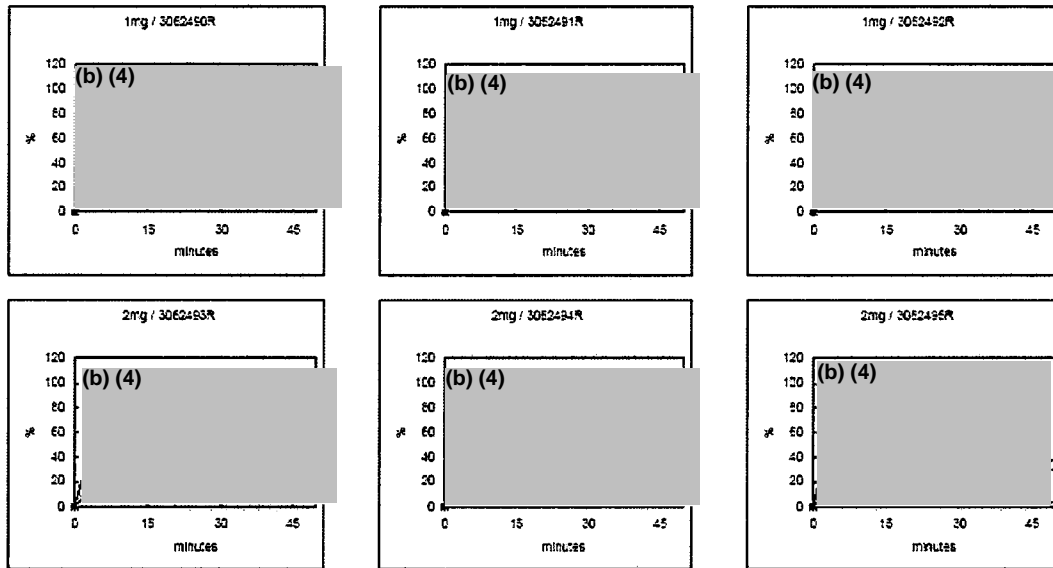
Time (min.)	Dissolution rate (%)						
	1	2	3	4	5	6	mean
0	(b) (4)						
5							
10							
15							
20							
30							
45							

Patheon 2 mg/ 3062495R

Time (min.)	Dissolution rate (%)						
	1	2	3	4	5	6	mean
0	(b) (4)						
5							
10							
15							
20							
30							
45							

Figure 6 below show the *In vitro* dissolution profile comparison between Patheon 1 mg tablets and Patheon 2 mg tablets in the three media (pH 1.2, 4.5 and 6.8)

Figure 6: Patheon 1 mg and 2 mg Tablet Dissolution Profiles at pH 1.2, 4.5 and 6.8



P: pitavastatin only

(b) (4)

Table 17 below shows the average of three batches by strength (1 mg and 2 mg) in the three media (pH 1.2, pH 4.5, and pH 6.8).

Table 17: Average of 3 Batches by Strength

Time (min.)	1 mg								2 mg							
	pH 1.2				pH 4.5				pH 1.2				pH 4.5			
	P		P+L						P		P+L					
	Mean n=18	RSD	Mean n=18	RSD	Mean n=18	RSD	Mean n=36	RSD	Mean n=18	RSD	Mean n=18	RSD	Mean n=18	RSD	Mean n=36	RSD
0	(b) (4)	0.0	(b) (4)	0.0	(b) (4)	0.0	(b) (4)	0.0	(b) (4)	0.0	(b) (4)	0.0	(b) (4)	0.0	(b) (4)	0.0
5		19.3		19.4		24.8		24.6		14.2		13.9		18.0		21.2
10		2.7		2.6		12.1		12.4		4.4		4.2		15.3		14.3
15		2.6		2.7		7.3		7.6		3.4		3.3		12.6		10.1
20		2.5		2.5		5.4		4.8		3.1		3.1		10.9		7.2
30		2.4		2.5		3.7		2.0		2.8		2.8		8.3		3.8
45		3.1		3.1		2.3		1.4		2.3		2.4		6.8		1.5

(b) (4)

Reviewer's Note:

Both strengths could be classified as rapid dissolving, thus, a mathematical comparison using similarity factor f_2 was not necessary. Similarity was confirmed visually.

2. Assessing Dissolution Similarity between the 2 mg and 4 mg Manufactured at Patheon and SkyePharma

To support the different manufacturer used in the clinical trials and the commercial manufacturing, a human bioequivalence study was done on the 2 mg and 4 mg pitavastatin calcium tablets manufactured at SkyePharma and Patheon. In addition to the in-vivo study, an in vitro study was done comparing the 1-mg, 2-mg and 4-mg strengths from SkyePharma and Patheon. To avoid any batch selection issues, batches were chosen as injudiciously as possibly. Where it was possible, pivotal clinical batches were used. However, for SkyePharma batches, by this time, most were exhausted. In addition, there is the concern of bias using only very old (>4 years) batches which may not be representational of tablets used in pivotal clinical trials. Therefore, SkyePharma batches were chosen to bracket all possibilities. If possible, batches from the pivotal clinical studies, the old 'I' series and the newest batch were used. All batches were manufactured using identical process and equipment from the 'I' series to the pivotal clinical batches and through the most latest batches. Table 18 below lists the batches that were used for the in vitro comparison experiment.

Table 18: Batch Listing for In Vitro Comparison Experiment

Manufacturer	Strength	Batch No.	Manufacturing date
SkyePharma	1 mg tablet	P246.05	March 2007
		I433	April 2004
	2 mg tablet	N906.14*	March 2007
		M219	December 2007
		I428	April 2004
	4 mg tablet	N905.10*	March 2007
		M207	September 2005
		I355	April 2004
Patheon Pharmaceuticals	1 mg tablet	3062490R	October 2007
		3062491R	October 2007
		3062492R	October 2007
	2 mg tablet	3062493R*	October 2007
		3062494R	October 2007
		3062495R	October 2007
	4 mg tablet	3062496R*	October 2007
		3062497R	October 2007
		3062498R	October 2007

*Used in the in-vivo study, see Section 2.7.1

For the clinical manufacturing site, SkyePharma, the following batches were used:

- For the 1-mg strength, unfortunately the biobatch K351 was not available at the time, so two batches were used, the latest SkyePharma manufactured batch P246.05 and a much earlier batch I433.
- For the 2-mg strength, the biobatch M219, the most recent manufactured batch N906.14, and the much earlier batch I428 were used.
- For the 4-mg strength, the biobatch M207, the older I355 batch, and the most recent N905.10 were used.

For the commercial manufacturing site, Patheon Pharmaceuticals Inc. all nine exhibit/registration batches were used.

The dissolution profiles were generated using the proposed dissolution conditions and dissolution assay test method. The sampling points are 5, 10, 15, 20, 30, 45 minutes. The dissolution of the two products compared were judged equivalent when f_2 value was (b) (4).

SkyePharma to Patheon graphical comparisons are provided in Figures 7-14 below. For each strength, the worst representative Patheon batch was chosen for the comparison between each SkyePharma batch. The results are provided from lowest to highest strength. The time points that were used in the f_2 comparisons are bolded for ease of review. Lastly, there is the complete tabular list of each SkyePharma to Patheon comparison for the 1 mg, the 2 mg and the 4 mg. Also, the raw dissolution data for each of the batches and each strengths is provided in the Appendix.

1-mg Strength

Figure 7: Dissolution Profiles Comparison of **1 mg, SkyePharma P246.05** and **Patheon 3062490R** using the Proposed Dissolution Method (Basket, 900 mL Phosphate USP media pH 6.8, 37°C, at 35 rpm)

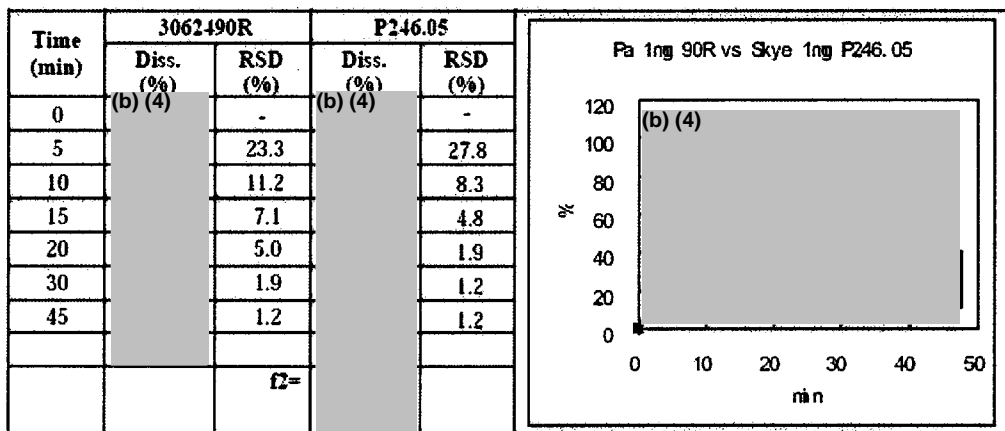
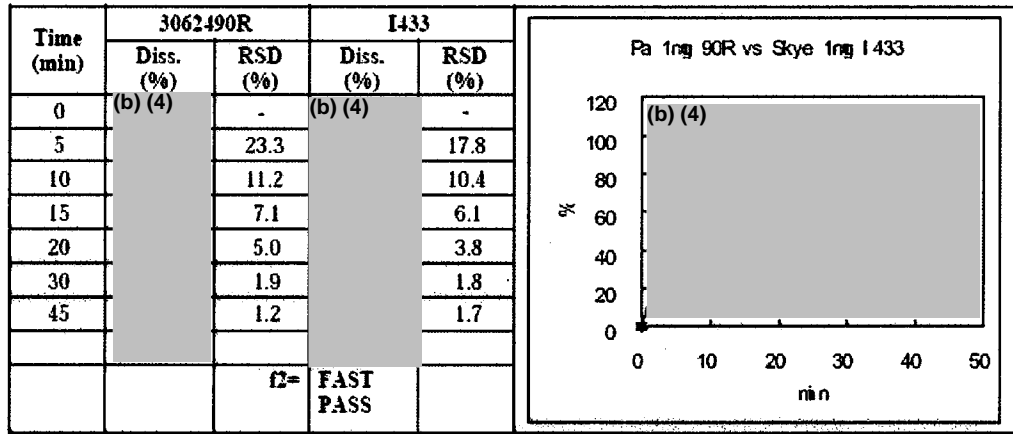


Figure 8: Dissolution Profiles Comparison of 1 mg, **SkyePharma I433** and **Patheon 3062490R** using the Proposed Dissolution Method (Basket, 900 mL Phosphate USP media pH 6.8, 37°C, at 35 rpm)



2-mg Strength

Figure 9: Dissolution Profiles Comparison of 2 mg, **SkyePharma N906.14** and **Patheon 3062493R** Using the Proposed Dissolution Method (Basket, 900 mL Phosphate USP media pH 6.8, 37°C, at 35 rpm)

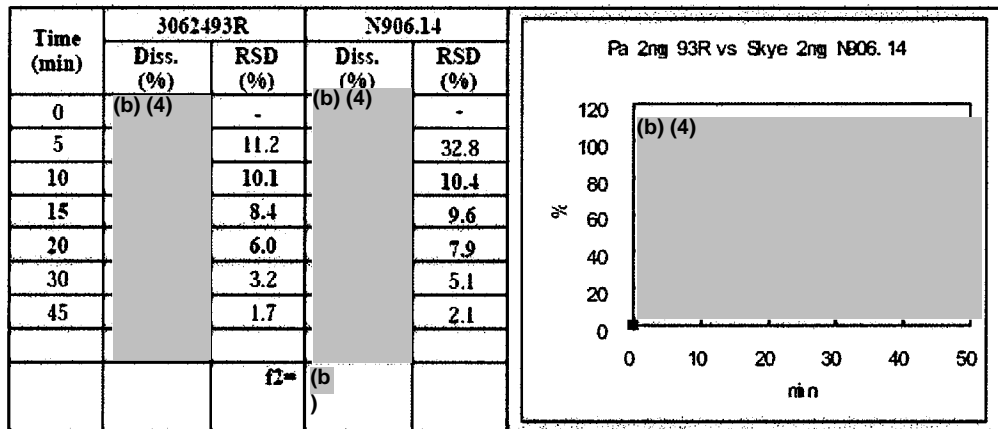


Figure 10: Dissolution Profiles Comparison of 2 mg, **SkyePharma I428** and **Patheon 3062493R** Using the Proposed Dissolution Method (Basket, 900 mL Phosphate USP media pH 6.8, 37°C, at 35 rpm)

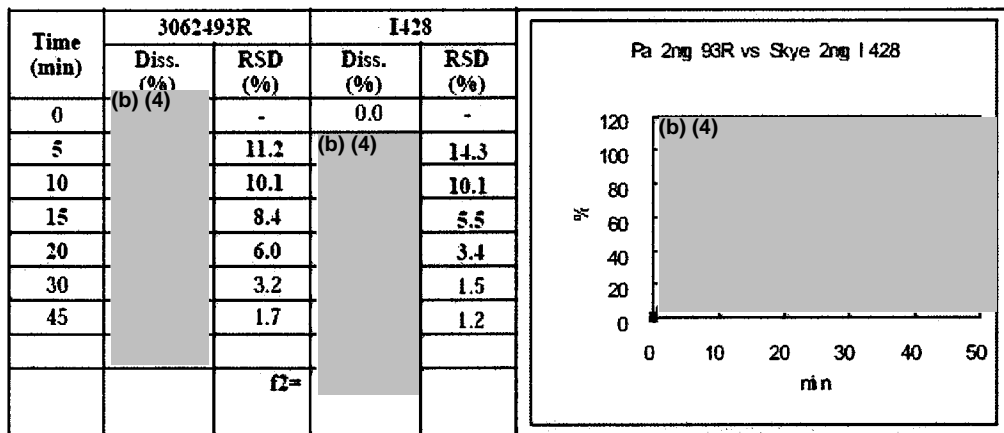
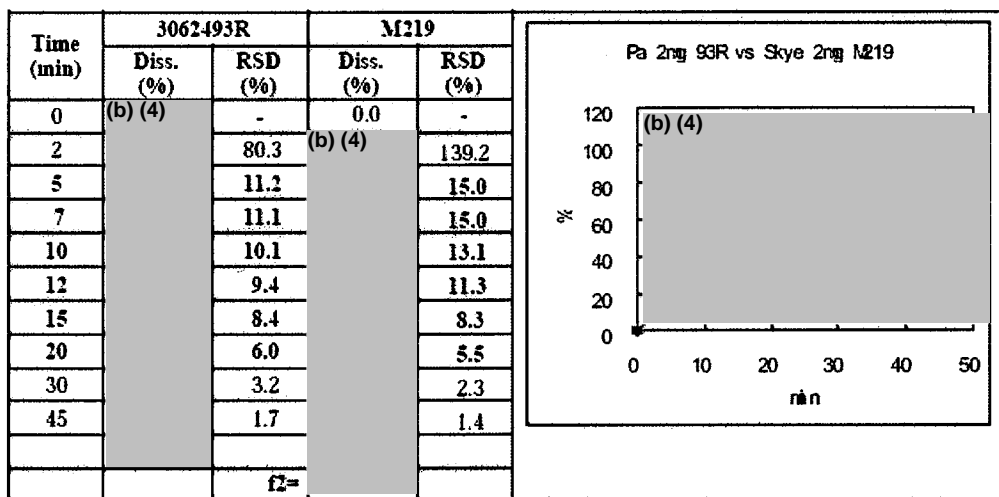


Figure 11: Dissolution Profiles Comparison of 2 mg, **SkyePharma M219** and **Patheon 3062493R** Using the Proposed Dissolution Method (Basket, 900 mL Phosphate USP media pH 6.8, 37°C, at 35 rpm)



4-mg Strength

Figure 12: Dissolution Profiles Comparison of **4 mg, SkyePharma N905.10** and **Patheon 3062496R** Using the Proposed Dissolution Method (Basket, 900 mL Phosphate USP media pH 6.8, 37°C, at 35 rpm)

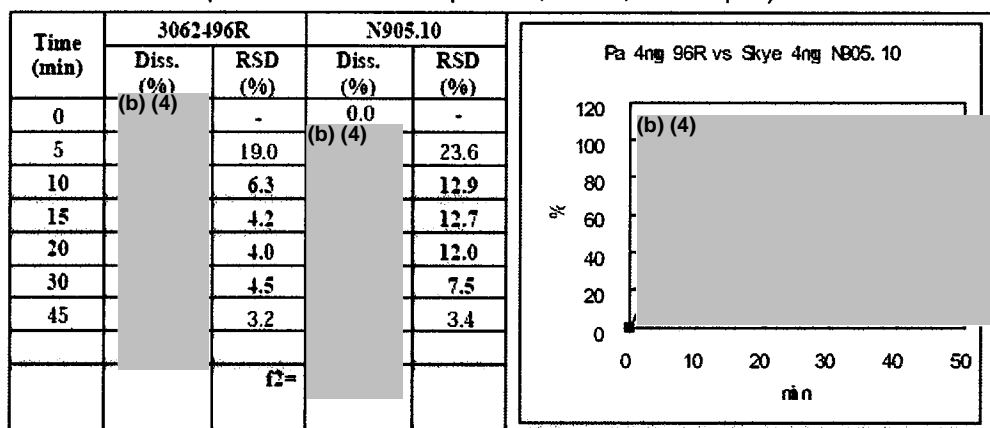


Figure 13: Dissolution Profiles Comparison of **4 mg, SkyePharma I355** and **Patheon 3062496R** Using the Proposed Dissolution Method (Basket, 900 mL Phosphate USP media pH 6.8, 37°C, at 35 rpm)

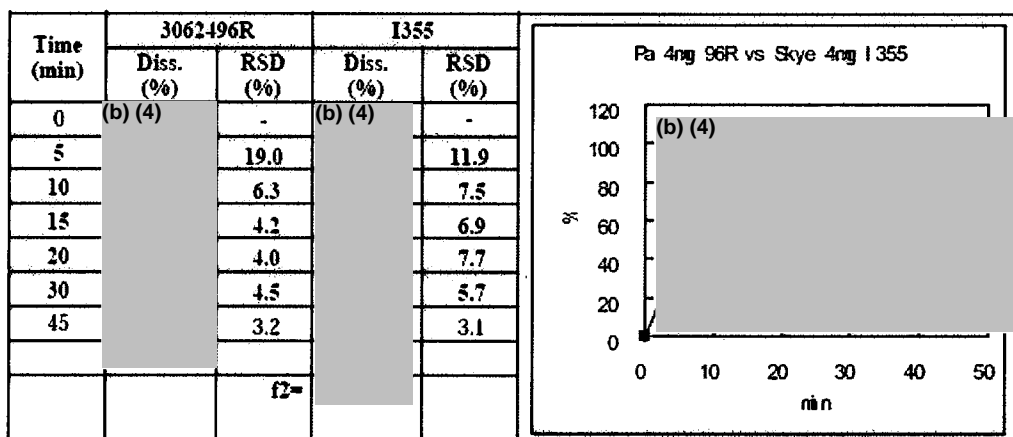
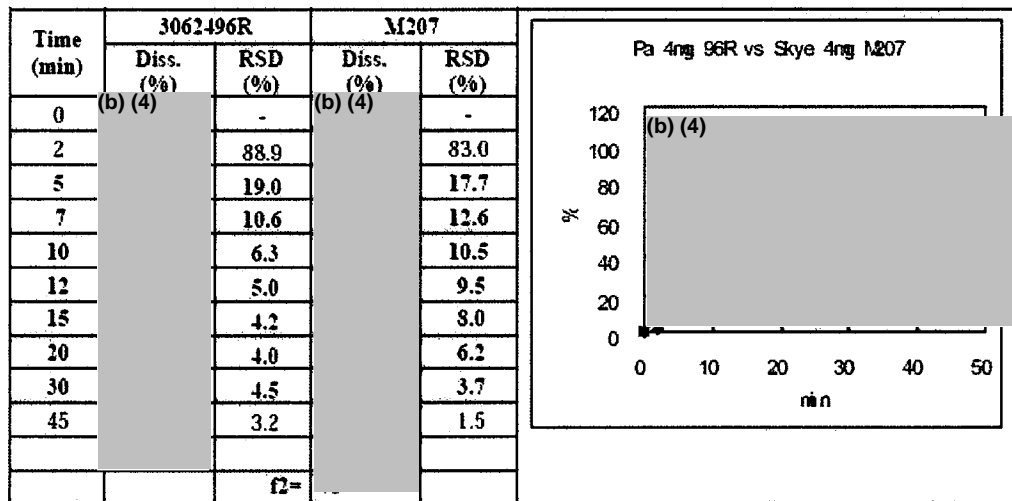


Figure 14: Dissolution Profiles Comparison of **4 mg, SkyePharma M207** and **Patheon 3062496R** Using the Proposed Dissolution Method (Basket, 900 mL Phosphate USP media pH 6.8, 37°C, at 35 rpm)



Each SkyePharma and Patheon combination was demonstrated to be similar in vitro. This was demonstrated by either the dissolution data were too fast (e.g., (b) (4) by 15 minutes) leading to a fast pass or had an f_2 (b) (4). For completion, Tables 19-21 below are provided with the entire comparative set of data for each comparison between SkyePharma and Patheon. The f_2 values range from the lowest of (b) (4) to the highest (b) (4) (not including any fast passes).

Table 19: **1-mg** SkyePharma to Patheon f_2 Comparisons

SkyePharma Batches	Patheon Batches
	(b) (4)
P246	
I433	

Table 20: 2-mg SkyePharma to Patheon *f*₂ Comparisons

SkyePharma Batches	Patheon Batches
	(b) (4)
N906.14	
I428	
M219	

Table 21: 4-mg SkyePharma to Patheon *f*₂ Comparisons

SkyePharma Batches	Patheon Batches
	(b) (4)
N905.10	
I355	
M207	

Reviewer's Note:

The *f*₂ values over (b) (4), demonstrates that the Patheon batches are similar to the SkyePharma batches using the proposed dissolution condition.

3. Assessing Dissolution Similarity between the 2 mg and 4 mg Manufactured at Patheon and SkyePharma and Used in the In-Vivo Bioequivalence Study

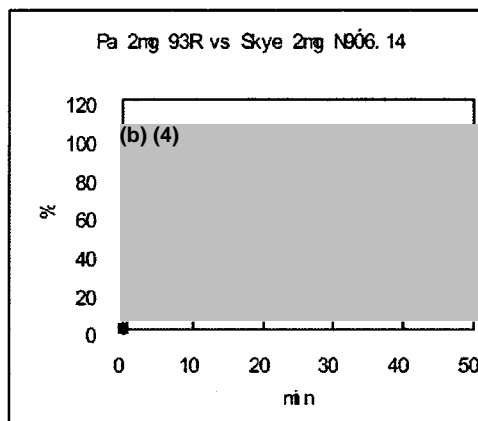
For the in vivo bioequivalence (BE) study, SkyePharma N906.10 and Patheon 3062493R were compared for the 2-mg tablet, and SkyePharma N905.10 and Patheon 3062496R were compared for the 4-mg tablet. These batches were compared using the proposed dissolution test (basket at 35 rpm, 900 mL of pH 6.8 phosphate buffer USP at 37°C) and are shown in tables 22-23. *f*₂ values comparisons between batches N906.14 vs. 3062493R (2mg) and batches N905.10 vs. 3062496R (4mg) were (b) (4)

2-mg Strength Used In Vivo BE Study

Table 22: f_2 Comparison between 3062493R and N906.14 (2 mg tablets, n=12)

Time (min)	3062493R (Pantheon 2 mg)		N906.14 (SkyePharma 2 mg)	
	Diss. (%)	RSD (%)	Diss. (%)	RSD (%)
0	(b)	-	(b)	-
5	(b)	11.2	(b)	32.8
10	(b)	10.1	(b)	10.4
15	(b)	8.4	(b)	9.6
20	(b)	6.0	(b)	7.9
30	(b)	3.2	(b)	5.1
45	(b)	1.7	(b)	2.1

$f_2 =$ (b)

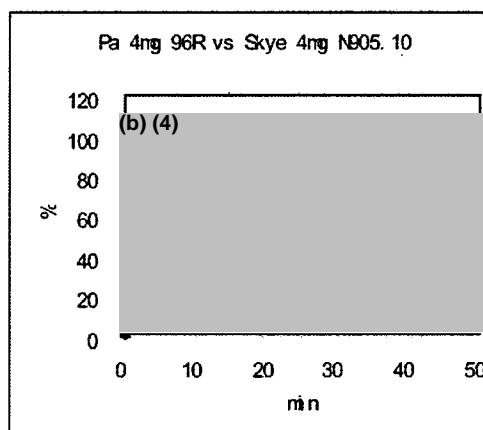


4 mg Strength Used In Vivo BE Study

Table 23: f_2 Comparison between 3062496R and N905.10 (4 mg tablets, n=12)

Time (min)	3062496R (4 mg Patheon)		N905.10 (4 mg SkyePharma)	
	Diss. (%)	RSD (%)	Diss. (%)	RSD (%)
0	(b)	-	(b)	-
5	(b)	19.0	(b)	23.6
10	(b)	6.3	(b)	12.9
15	(b)	4.2	(b)	12.7
20	(b)	4.0	(b)	12.0
30	(b)	4.5	(b)	7.5
45	(b)	3.2	(b)	3.4

$f_2 =$ (b)



Reviewer's Note:

The 2-mg SkyePharma batch N906.14 and Patheon batch 3062493R, and 4-mg SkyePharma batch N905.10 and Patheon batch 3062496R used in the in-vivo BE study are similar using the proposed dissolution condition.

Analytical Method:

The HPLC assay with UV detection at 245 nm was used to determine pitavastatin calcium content in the dissolution samples. The assay was validated for linearity, accuracy, precision, specificity.

Method Validation	
Sample Linearity	(b) (4)
Mean Accuracy%	101.0%-102.2%
Precision(%RSD)	(b) (4)
Intermediate Precision (%RSD)	
Reproducibility (%RSD)	
Stability	Stable for NMT 24 hours

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Appendix

The raw dissolution data using the proposed dissolution method (Basket, 900 mL Phosphate USP media pH 6.8, 37°C, at 35 rpm) for each SkyePharma and Patheon batches for the 1-mg, 2-mg, and 4-mg is provided immediately below in Tables 1-17.

Table 1: Dissolution Data of **SkyePharma 1 mg Batch P246.05**

Time (min.)	Dissolution rate (%)													mean	RSD
	1	2	3	4	5	6	7	8	9	10	11	12			
0	(b) (4)													-	
5														27.8	
10														8.3	
15														4.8	
20														1.9	
30														1.2	
45														1.2	

Table 2: Dissolution Data of **SkyePharma 1 mg Batch I433**

Time (min.)	Dissolution rate (%)													mean	RSD
	1	2	3	4	5	6	7	8	9	10	11	12			
0	(b) (4)													-	
5														17.8	
10														10.4	
15														6.1	
20														3.8	
30														1.8	
45														1.7	

Table 3: Dissolution Data of **SkyePharma 2 mg Batch N906.14**

Time (min.)	Dissolution rate (%)												mean	RSD
	1	2	3	4	5	6	7	8	9	10	11	12		
0	(b) (4)												-	
5													32.8	
10													10.4	
15													9.6	
20													7.9	
30													5.1	
45													2.1	

Table 4: Dissolution Data of **SkyePharma 2 mg Batch I428**

Time (min.)	Dissolution rate (%)													mean	RSD
	1	2	3	4	5	6	7	8	9	10	11	12			
0	(b) (4)														-
2	(b) (4)														
5	(b) (4)														14.3
7	(b) (4)														
10	(b) (4)														10.1
15	(b) (4)														5.5
20	(b) (4)														3.4
30	(b) (4)														1.5
45	(b) (4)														1.3

Table 5: Dissolution Data of **SkyePharma 2 mg Batch M219**

Time (min.)	Dissolution rate (%)													
	1	2	3	4	5	6	7	8	9	10	11	12	mean	RSD
0	(b) (4)													-
2														139.2
5														15.0
7														15.0
10														13.1
12														11.3
15														8.3
20														5.5
30														2.3
45														1.4

Table 6: Dissolution Data of **SkyePharma 4 mg Batch N905.10**

Time (min.)	Dissolution rate (%)													mean	RSD
	1	2	3	4	5	6	7	8	9	10	11	12			
0	(b) (4)														-
5															23.6
10															12.9
15															12.7
20															12.0
30															7.5
45															3.4

Table 7: Dissolution Data of **SkyePharma 4 mg Batch I355**

Time (min.)	Dissolution rate (%)													mean	RSD
	1	2	3	4	5	6	7	8	9	10	11	12			
0	(b) (4)														-
2															
5															11.9
7															
10															7.5
15															6.9
20															7.7
30															5.7
45															3.1

Table 8: Dissolution Data of **SkyePharma 4 mg Batch M207**

Time (min.)	Dissolution rate (%)													mean	RSD
	1	2	3	4	5	6	7	8	9	10	11	12			
0	(b) (4)													-	
2														83.0	
5														17.7	
7														12.6	
10														10.5	
12														9.5	
15														8.0	
20														6.2	
30														3.7	
45														1.5	

Table 9: Dissolution Data of **Patheon 1 mg Batch 3062490R**

Time (min.)	Dissolution rate (%)													mean	RSD
	1	2	3	4	5	6	7	8	9	10	11	12			
0	(b) (4)														-
5															23.3
10															11.2
15															7.1
20															5.0
30															1.9
45															1.2

Table 10: Dissolution Data of **Patheon 1 mg Batch 3062491R**

Time (min.)	Dissolution rate (%)													
	1	2	3	4	5	6	7	8	9	10	11	12	mean	RSD
0	(b) (4)													-
5														31.1
10														15.4
15														9.0
20														5.4
30														1.8
45														1.2

Table 11: Dissolution Data of **Patheon 1 mg Batch 3062492R**

Time (min.)	Dissolution rate (%)													
	1	2	3	4	5	6	7	8	9	10	11	12	mean	RSD
0	(b) (4)													-
5														20.2
10														11.3
15														7.2
20														4.3
30														2.3
45														1.8

Table 12: Dissolution Data of **Patheon 2 mg Batch 3062493R**

Time (min.)	Dissolution rate (%)													
	1	2	3	4	5	6	7	8	9	10	11	12	mean	RSD
0	(b) (4)													-
2														80.3
5														11.2
7														11.1
10														10.1
12														9.4
15														8.4
20														6.0
30														3.2
45														1.7

Table 13: Dissolution Data of **Patheon 2 mg Batch 3062494R**

Time (min.)	Dissolution rate (%)													mean	RSD
	1	2	3	4	5	6	7	8	9	10	11	12			
0	(b) (4)													-	
2														88.7	
5														26.9	
7														21.3	
10														16.3	
12														14.2	
15														11.6	
20														8.5	
30														5.0	
45														1.9	

Table 14: Dissolution Data of **Patheon 2 mg Batch 3062495R**

Time (min.)	Dissolution rate (%)													mean	RSD
	1	2	3	4	5	6	7	8	9	10	11	12			
0	(b) (4)													-	
2	(b) (4)													128.8	
5	(b) (4)													22.8	
7	(b) (4)													20.5	
10	(b) (4)													15.9	
12	(b) (4)													13.3	
15	(b) (4)													10.4	
20	(b) (4)													7.3	
30	(b) (4)													3.5	
45	(b) (4)													0.6	

Table 15: Dissolution Data of **Patheon 4 mg Batch 3062496R**

Time (min.)	Dissolution rate (%)													mean	RSD
	1	2	3	4	5	6	7	8	9	10	11	12			
0	(b) (4)														-
2															88.9
5															19.0
7															10.6
10															6.3
12															5.0
15															4.2
20															4.0
30															4.5
45															3.2

Table 16: Dissolution Data of **Patheon 4 mg Batch 3062497R**

Time (min.)	Dissolution rate (%)														mean	RSD
	1	2	3	4	5	6	7	8	9	10	11	12				
0	(b) (4)														-	
2															-	
5															21.4	
7															14.0	
10															13.0	
12															12.1	
15															11.8	
20															11.1	
30															9.6	
45															5.8	

Table 17: Dissolution Data of **Patheon 4 mg Batch 3062498R**

Time (min.)	Dissolution rate (%)														
	1	2	3	4	5	6	7	8	9	10	11	12	mean	RSD	
0	(b) (4)														-
2	(b) (4)														125.0
5	(b) (4)														26.3
7	(b) (4)														15.3
10	(b) (4)														14.3
12	(b) (4)														13.7
15	(b) (4)														12.5
20	(b) (4)														11.1
30	(b) (4)														8.8
45	(b) (4)														5.6

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CLINICAL PHARMACOLOGY REVIEW

NDA	22-363; N-000 BB; N-000 BM; N-000 BM
Submission Dates	October 1, 2008; February 6, 2009; April 14, 2009; July 13, 2009
Brand Name	LIVALO®
Generic Name	Pitavastatin calcium
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader (Acting)	Wei Qiu, Ph.D.
Pharmacometric Reviewers	Justin Earp, Ph.D.; Manoj Khurana, Ph.D.
Pharmacometric Team Leader	Christoffer Tornøe, Ph.D.
OCP Division	Clinical Pharmacology 2 (HFD 870)
OND Division	Metabolism and Endocrinology Products (HFD 510)
Sponsor	Kowa Company Limited
Formulation; Strength	Immediate release oral tablets; 1, 2, and 4 mg
Relevant IND	60,492
Indication	Adjunct therapy to diet to reduce elevated lipid concentrations

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1 Executive Summary

Pitavastatin is a new molecular entity and is a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor. Currently, 6 HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, and rosuvastatin) are marketed in the U.S. to treat patients with elevated lipid disorders. NDA 22-363 seeks approval for the once daily oral administration of a 1, 2, or 4 mg pitavastatin tablet as an adjunct therapy to reduce elevated lipid concentrations. Pitavastatin is

marketed in Japan as LIVALO® (1 and 2 mg tablets) since September 2003, approved in Korea on January, 2005 and in Thailand on November, 2007. It is currently pending approval in China.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA 22-363's Clinical Pharmacology and Biopharmaceutics information and finds it acceptable provided that the sponsor agrees to the Clinical Pharmacology labeling recommendations. The sponsor should receive the recommendations and Post Marketing Requirement details.

1.2 Post Marketing Requirement

Effect of the lopinavir and ritonavir combination on pitavastatin exposure

Protease inhibitors are indicated to treat patients with human immunodeficiency virus infection and are well known to elevate lipid concentrations. Statins are commonly used to treat protease inhibitors induced hyperlipidemia. The combination of lopinavir and ritonavir increases rosuvastatin AUC and C_{max} to 2 and 5 fold, respectively, as compared to those of rosuvastatin alone administration [Kiser et al. *J Acquir Immune Defic Syndr* 47:570-8 (2008)]. This interaction results in the rosuvastatin dose being limited to 10 mg once daily (the dose range is 5 – 40 mg once daily) when receiving the combination of lopinavir and ritonavir [rosuvastatin labeling].

Pitavastatin shares many metabolic, excretory, and transporter pathways as those of rosuvastatin. Because of the lopinavir and ritonavir combination's potential to increase pitavastatin exposure upon coadministration and thereby causes safety concern, you should conduct a drug interaction study with the combination of lopinavir and ritonavir per the draft Drug Interaction Guidance [<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072101.pdf>] to characterize this potential interaction.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The sponsor conducted 5 placebo-controlled and 7 active-controlled key clinical efficacy and safety studies and 41 clinical pharmacology and biopharmaceutics studies to support NDA 22-363.

Pitavastatin Pharmacology in Humans

Absorption

Upon oral administration of a single 4 mg pitavastatin tablet, the mean pitavastatin C_{max} , AUC_{0-inf} , and t_{max} (median) are 82 ng/mL, 209 ng·h/mL, and 0.75 hour, respectively. Pitavastatin is well absorbed in the proximal jejunum and distal jejunum/proximal ileum. Geometric mean pitavastatin absolute oral bioavailability of an oral solution is 51%. A high fat meal decreases pitavastatin C_{max} and AUC 43.1 and 11%, respectively, but the decrease in pitavastatin AUC is not significant. Pitavastatin pharmacokinetics (PK) is approximately dose-proportional for both oral single and multiple doses from 1 – 24 mg. Pitavastatin AUC_{0-24} at steady state is 1.5 times that after a single dose.

Distribution

The mean pitavastatin volume of distribution is 211.4 L. Pitavastatin is 99.5 – 99.6% plasma protein bound. Pitavastatin primarily binds to serum albumin but also binds to α_1 -acid glycoprotein. Pitavastatin lactone is 98.95 – 99.33% plasma protein bound. Association of pitavastatin and/or its metabolites with blood cells is minimal.

Metabolism

UDP-glucuronosyl transferase (UGT) 1A3 and 2B7 primarily metabolize pitavastatin to pitavastatin glucuronide, which in turn forms pitavastatin lactone. Pitavastatin also undergoes oxidative metabolism to form 8-hydroxy pitavastatin via cytochrome P450 (CYP) 2C9. Pitavastatin lactone and

8-hydroxy pitavastatin are the major and minor metabolite in the systemic circulation, respectively. Another minor oxidative metabolite is dihydroxy pitavastatin.

In vitro data show that CYPs 2C9 and 1B1 metabolize pitavastatin, whereas, CYPs 3A4, 2D6, 2C19, 2B6, 1A2, and 1A1 metabolize pitavastatin lactone. Pitavastatin inhibits CYP2C8 but does not inhibit CYPs 1A1, 1A2, 1B1, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4 in vitro, whereas pitavastatin lactone does not inhibit CYPs 2C9 and 3A4 in vitro. There is no information on pitavastatin lactone's effect on other CYP isozymes.

Pitavastatin lactone's HMG-CoA reductase inhibition status is inconclusive per the submitted data.

Chiral inversion of pitavastatin via metabolism to its optical isomers may be very low per the dog and rat data.

Excretion

In a mass-balance study, a mean of 15.1 and 78.6% of the dose was excreted in the urine and feces, respectively, with a mean total of 93.7% of the radioactive dose recovered in the excreta during 7 days postdose. The percentage of dose excreted in urine for pitavastatin, dihydroxy pitavastatin, pitavastatin glucuronide, pitavastatin lactone, and an unknown metabolite is 3, 4.1, 3.8, 0.8, and 1.2, respectively. The percentage of dose excreted in feces for pitavastatin, dihydroxy pitavastatin, pitavastatin lactone, 8-hydroxy pitavastatin, and an unknown metabolite is 42.9, 7.3, 2.6, 7.2, and 4.7, respectively.

Organic anion transporting polypeptide (OATP) 1B1 and 1B3 are responsible for the hepatic uptake of pitavastatin in vitro. The sponsor showed that pitavastatin is not a substrate of multidrug-resistance protein 1 (MDR1, alias P-gp) and multidrug resistance-associated protein 2 (MRP2) but is a substrate of breast cancer resistance protein (BCRP) in vitro. However, another research group showed that MDR1, MRP2, and BCRP are responsible for pitavastatin biliary excretion in vitro. Thus, the P-glycoprotein substrate status is inconclusive. The sponsor also showed that pitavastatin lactone is not a substrate of MRP2 and BCRP but is a substrate of MDR1 in vitro. Pitavastatin is neither a P-gp inhibitor nor a P-gp inducer in vivo.

Pharmacodynamics

The differences in lipid lowering are not significant between morning and evening pitavastatin dosing. Morning vs. evening dosing does not affect pitavastatin exposure.

A pitavastatin dose and low-density lipoprotein cholesterol (LDL-C) reduction relationship exists over the 1 – (b) (4) mg pitavastatin once daily oral dose range. There is a relationship between pitavastatin dose and myalgia rate as well as between pitavastatin dose and rhabdomyolysis rate over the 1 – (b) (4) mg pitavastatin once daily oral dose range. A drug concentration and muscle related adverse events (blood CPK elevation and myalgia) relationship is not apparent in the 4 (b) (4) mg pitavastatin dose groups (only available data). Plasma pitavastatin and pitavastatin lactone C_{troughs} for the (b) (4) patients with no muscle related adverse events are comparable to those of patients with blood CPK elevation and to those of myalgic patients. For rhabdomyolysis, the plasma pitavastatin and plasma pitavastatin lactone average C_{troughs} appear to be higher than those of patients with no muscle related adverse events, blood elevated CPK, and myalgia suggesting an exposure-response relationship. However, the data is limited to draw a definite conclusion (2 cases in the (b) (4) mg dose group).

QT Prolongation

A thorough QT study does not detect the 4 (b) (4) mg pitavastatin once daily oral doses have QT prolongation effect.

Pharmacogenomics

This submission does not contain any pharmacogenomic data.

Specific Populations

Hepatic Impairment

Moderate hepatically impaired (Child-Pugh B disease) patients' pitavastatin AUC_{inf} and C_{max} increases 275 and 169%, respectively, as compared to those of healthy volunteers. Mild hepatically impaired (Child-Pugh A disease) patients' pitavastatin AUC_{inf} and C_{max} increases 57 and 34%, respectively, as compared to those of healthy volunteers.

Renal Impairment

Moderate renally impaired (GFR 30 – < 50 mL/min/1.73 m²) patients' pitavastatin AUC_{inf} and C_{max} increases 79.5 and 59.7%, respectively, as compared to those of healthy volunteers. Hemodialysis patients' pitavastatin AUC_{inf} and C_{max} increases 86.3 and 40.5%, respectively, as compared to those of healthy volunteers. Per the Phase 3 clinical studies data, there is a pitavastatin dose-dependent increase in muscle adverse events frequency in participants with normal renal function and mild renal impairment. In the same analysis, the mild renal impairment group showed similar percentage of participants with muscle adverse events in comparison to that of the normal renal function group with each of the dose groups (1, 2, and 4 mg pitavastatin once daily).

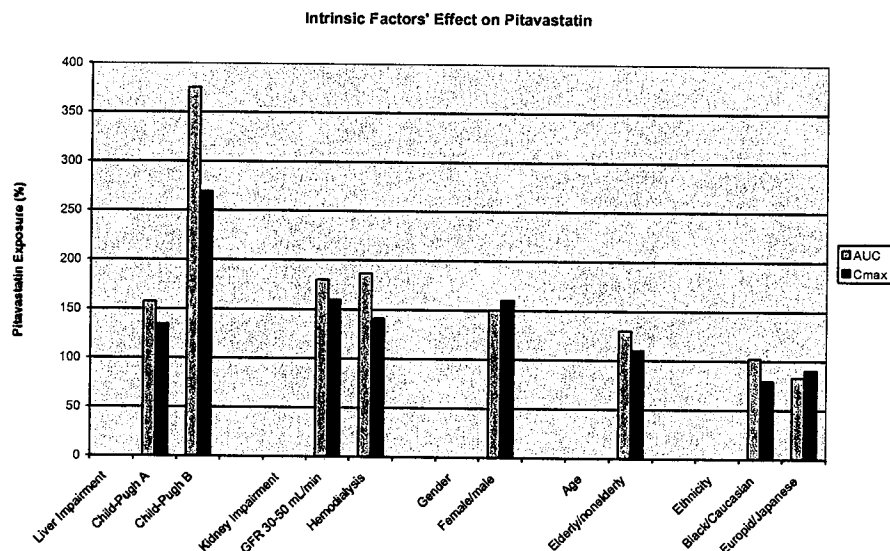
Gender, Age, and Ethnicity

Women's pitavastatin AUC_{0-inf} and C_{max} are 54 and 60% higher than that of men, respectively.

Elderly's pitavastatin AUC_{0-inf} and C_{max} are 30 and 10% higher than that of nonelderly, respectively.

African American's pitavastatin AUC_{0-inf} is 2% higher and pitavastatin C_{max} is 21% lower than those of Caucasian American, respectively. Europid's pitavastatin AUC_{0-inf} and C_{max} are 17 and 10% lower than that of Japanese, respectively.

This submission does not contain any population or model-based data for analysis.



100% Pitavastatin Exposure = no intrinsic effect

Drug-Drug Interactions

The following highlights the significant drug-drug interactions. See the rest in the chart below.

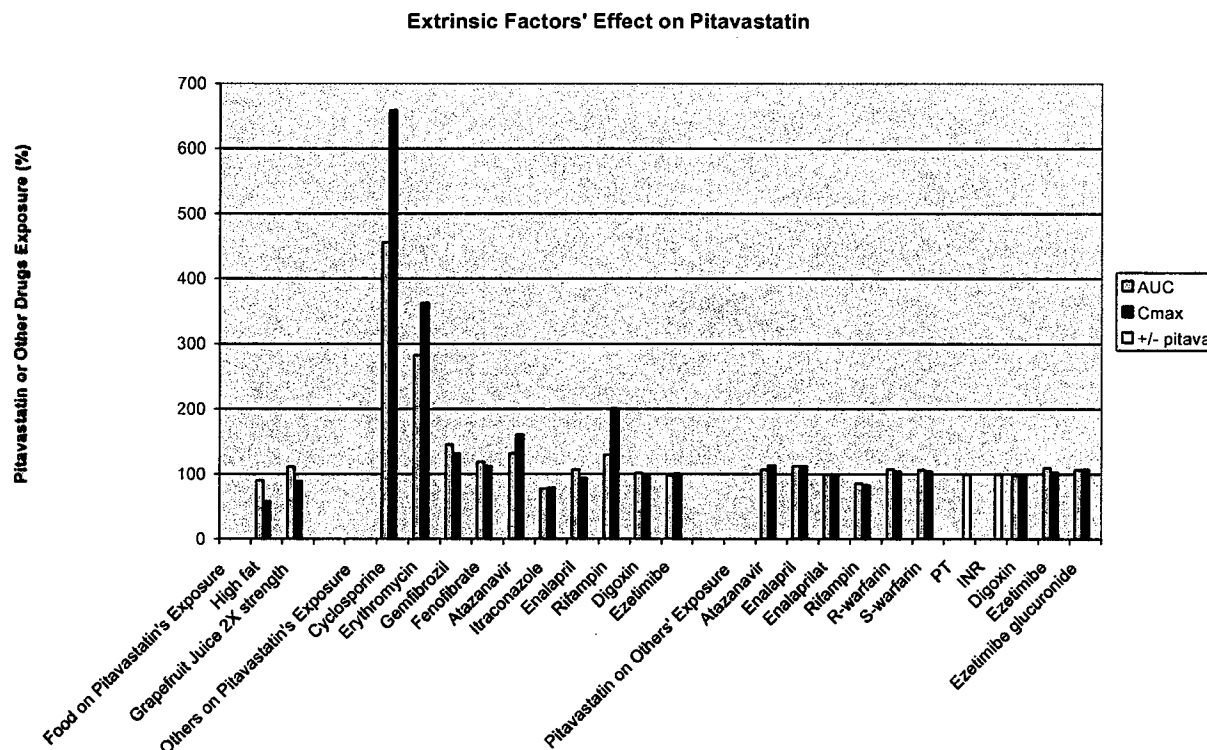
Effects of Other Drugs on Pitavastatin

Cyclosporine increases pitavastatin AUC₀₋₂₄ and C_{max} 355 and 558%, respectively. Erythromycin increases pitavastatin AUC_{0-t} and C_{max} 182 and 262%, respectively. Gemfibrozil increases pitavastatin

AUC₀₋₂₄ and C_{max} 45 and 31%, respectively. Atazanavir increases pitavastatin AUC₀₋₂₄ and C_{max} 31 and 60%, respectively. Itraconazole decreases pitavastatin AUC_{0-t} and C_{max} 23 and 22%, respectively. Rifampin increases pitavastatin AUC₀₋₂₄ and C_{max} 29 and 100%, respectively.

Effects of Pitavastatin on Other Drugs

Pitavastatin decreases rifampin AUC₀₋₂₄ and C_{max} 15 and 18%, respectively.



100% Exposure = no extrinsic effect

Biopharmaceutics

Pitavastatin calcium's Biopharmaceutics Classification System class status is unknown.

Formulation

The clinically-tested 2 and 4 mg pitavastatin tablets are bioequivalent to the to-be-marketed 2 and 4 pitavastatin tablets, respectively.

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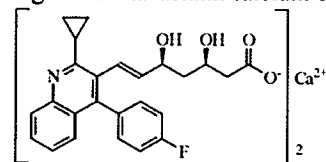
A Required Inter-Division Clinical Pharmacology Briefing for NDA 22-363 was conducted on June 23, 2009; participants included D. Gortler, K. Johnson, L. Elmore, S. Naraharisetti, P. Roy, L. Velazquez, D. Bashaw, S. Choe, P. Ji, S. Chung, M. Packanowski, K. Reynolds, E. Reese, I. Zdrojewski, Y. Harigaya, T. Ong, Z. Li, S. Doddapaneni, C. Sahajwalla, M. Khurana, W. Qiu, and J. Lau as well as C. Tornøe, I. Chowdhury, and E. Colman via telephone conference.

2 Question-Based Review

2.1 General Attributes

2.1.1 What are pitavastatin calcium's key physicochemical properties?

Figure 1. Pitavastatin calcium's molecular structure.



Pitavastatin calcium has a molecular weight of 880.98, empirical formula of $C_{50}H_{46}CaF_2N_2O_8$, and is very slightly soluble in water. Pitavastatin calcium has a pKa of 5.31 and octanol:water partition coefficient (log P) of 0.08 at pH 6.2.

2.1.2 What is the formulation for the to-be-marketed pitavastatin calcium oral tablets?

Table 1. To-be-marketed pitavastatin calcium immediate-release oral tablets' formulation.

Pitavastatin Calcium Immediate Release Oral Tablets Formulation:				
Component	Function	Quantity (mg)		
		1 mg Tablet	2 mg Tablet	4 mg Tablet
Tablet Core				
Pitavastatin Calcium	Active	1.045	2.09	4.18
Lactose Monohydrate	(b) (4)			
Low Substituted Hydroxypropyl Cellulose				
Hypromellose (b) (4)				
Magnesium				
Aluminometasilicate (b) (4)				
Magnesium Stearate				
(b) (4)				
(b) (4)				
Film Coating (b) (4)				
(b) (4)				
(b) (4)				
Total		83.00	165.00	329.00

2.1.3 How does pitavastatin calcium work?

Pitavastatin competitively inhibits HMG-CoA reductase, which is a rate-limiting enzyme in cholesterol biosynthesis in the liver. As a result, the expression of LDL-receptors followed by the uptake of LDL from blood to liver is accelerated, and then the plasma total cholesterol decreases. Further, the sustained inhibition of cholesterol synthesis in the liver decreases very low density lipoprotein secretion into blood and plasma triglyceride concentrations.

2.1.4 What are the sponsor's proposed indication and dosage regimen for pitavastatin calcium?

Patients with primary hyperlipidemia and mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein (Apo) B, non-high-density lipoprotein cholesterol (non-HDL-C), triglycerides (TG), TC/HDL-C, and Apo-B/Apo-A1 ratio and to increase HDL-C and Apo-A1. Pitavastatin can be taken with or without food, at any time of day with the dose range of 1 mg to 4 mg once daily.

2.2 General Clinical Pharmacology

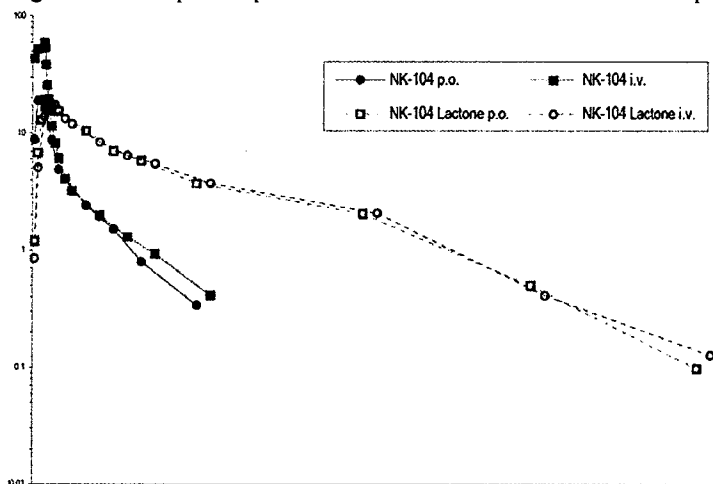
Most clinical studies' numbers have the "NK or NKS" prefix to signify the pitavastatin development program. For simplicity, this review does not show the "NK or NKS" prefix.

2.2.1 What are pitavastatin's clinical pharmacokinetic (PK) characteristics?

Absorption

In a single-dose, randomized, 2-period crossover study (Study 1.02.EU) with 18 healthy Caucasian men (fasted for 10 hours) received either 2 mg pitavastatin IV infusion (0.02 mg/mL) or 2 mg pitavastatin oral solution (0.02 mg/mL) in Period 1. After a 7-day washout between doses, fasted volunteers received the alternate treatment in Period 2. Serial plasma and urine samples were collected predose and for 48 hours postdose to determine pitavastatin and its lactone via LC/MS/MS analyses.

Figure 2. Mean plasma pitavastatin and its lactone concentrations upon single oral and IV doses of 2 mg pitavastatin



Tables 2 (left). Summary of pitavastatin PK parameters in plasma. Table 3 (right). Summary of pitavastatin lactone PK parameters in plasma.

Parameter	Statistics	NK-104 2 mg p.o.	NK-104 2 mg i.v.
AUC_{0-48} [ng·h/mL]	N	18	18
	Mean (SD)	37.72 (20.18)	78.63 (21.11)
	Geomean (geom. SD)	33.57 (1.63)	76.07 (1.30)
$AUC_{0-\infty}$ [ng·h/mL]	N	18	18
	Mean (SD)	47.40 (22.32)	86.91 (23.45)
	Geomean (geom. SD)	42.95 (1.58)	83.90 (1.32)
AUC_R	N	18	18
	Mean (SD)	0.80 (0.15)	0.91 (0.04)
	Geomean (geom. SD)	0.78 (1.23)	0.91 (1.05)
C_{max} [ng/mL]	N	18	18
	Mean (SD)	21.43 (13.02)	60.85 (11.34)
	Geomean (geom. SD)	18.58 (1.70)	59.83 (1.21)
MRT [h]	N	18	18
	Mean (SD)	5.66 (4.58)	2.67 (1.57)
	Geomean (geom. SD)	4.55 (1.87)	2.18 (2.03)
T_{max} [h]	N	18	18
	Mean (SD)	0.68 (0.19)	0.99 (0.03)
	Median (Min-Max)	0.75 (0.5–1.0)	0.97 (0.97–1.03)
$T_{1/2}$ [h]	N	18	18
	Mean (SD)	5.24 (4.82)	4.59 (2.47)
	Geomean (geom. SD)	3.91 (2.09)	3.90 (1.86)
$Vd/F, Vd$ [L]	N	18	18
	Mean (SD)	308.8 (193.7)	148.1 (65.9)
	Geomean (geom. SD)	258.7 (1.85)	133.2 (1.64)
$CL/F, CL$ [mL/min]	N	18	18
	Mean (SD)	837.7 (367.0)	409.5 (118.7)
	Geomean (geom. SD)	764.2 (1.56)	394.5 (1.32)
F	N	18	—
	Mean (SD)	0.53 (0.14)	—
	Geomean (geom. SD)	0.51 (1.31)	—

Parameter	Statistics	NK-104 2 mg p.o.	NK-104 2 mg i.v.
AUC_{0-48} [ng·h/mL]	N	18	18
	Mean (SD)	144.2 (53.5)	147.1 (50.9)
	Geomean (geom. SD)	137.5 (1.34)	140.2 (1.36)
$AUC_{0-\infty}$ [ng·h/mL]	N	18	18
	Mean (SD)	168.7 (56.5)	172.5 (47.1)
	Geomean (geom. SD)	161.9 (1.32)	167.2 (1.28)
AUC_R	N	18	18
	Mean (SD)	0.85 (0.04)	0.84 (0.07)
	Geomean (geom. SD)	0.85 (1.05)	0.84 (1.09)
C_{max} [ng/mL]	N	18	18
	Mean (SD)	18.98 (7.43)	21.19 (5.18)
	Geomean (geom. SD)	17.86 (1.41)	20.59 (1.28)
MRT [h]	N	18	18
	Mean (SD)	14.50 (3.00)	14.80 (2.67)
	Geomean (geom. SD)	14.21 (1.23)	14.58 (1.20)
T_{max} [h]	N	18	18
	Mean (SD)	1.28 (0.38)	1.41 (0.29)
	Median (Min-Max)	1.25 (0.75–2.00)	1.29 (1.03–2.00)
$T_{1/2}$ [h]	N	18	18
	Mean (SD)	11.62 (2.88)	11.97 (2.55)
	Geomean (geom. SD)	11.29 (1.29)	11.73 (1.23)
$Vd/F, Vd$ [L]	N	18	18
	Mean (SD)	206.4 (54.6)	211.4 (69.5)
	Geomean (geom. SD)	200.0 (1.29)	201.2 (1.38)
$CL/F, CL$ [mL/min]	N	18	18
	Mean (SD)	211.5 (50.4)	203.7 (46.6)
	Geomean (geom. SD)	204.7 (1.32)	198.2 (1.28)

The mean and geometric mean of pitavastatin absolute oral bioavailability is 53 and 51%, respectively. The pitavastatin lactone exposure is similar between IV and PO administration, which suggests that pitavastatin:

- is completely absorbed from the gastrointestinal tract

- shows high 1st pass effect before reaching systemic circulation

Study 104A2115 examined pitavastatin's regio-specific absorption in 6 healthy participants' (5 men and 1 woman) intestines. This was a single-dose, randomized, and crossover study. Each fasted participant orally received the following treatments of 8 mg pitavastatin:

- Treatment A: an immediate release pitavastatin tablet
- Treatment B: an (b) (4) capsule to deliver pitavastatin to the proximal jejunum (small bowel's 1st meter)
- Treatment C: an (b) (4) capsule to deliver pitavastatin to the distal/proximal ileum (small bowel's 3rd – 4th meter)
- Treatment D: an (b) (4) capsule to deliver pitavastatin to the terminal ileum (small bowel's last meter)
- Treatment E: an (b) (4) capsule to deliver pitavastatin to the ascending colon

A washout of a minimum of 5 days separated each treatment period. Serial plasma samples were collected predose and 48 hours postdose to determine pitavastatin and its lactone via a validated LC/MS/MS bioanalytical assay.

Figure 3 (left). Mean plasma pitavastatin concentrations vs. time plots. Figure 4 (right). Mean plasma pitavastatin lactone concentrations vs. time plots.

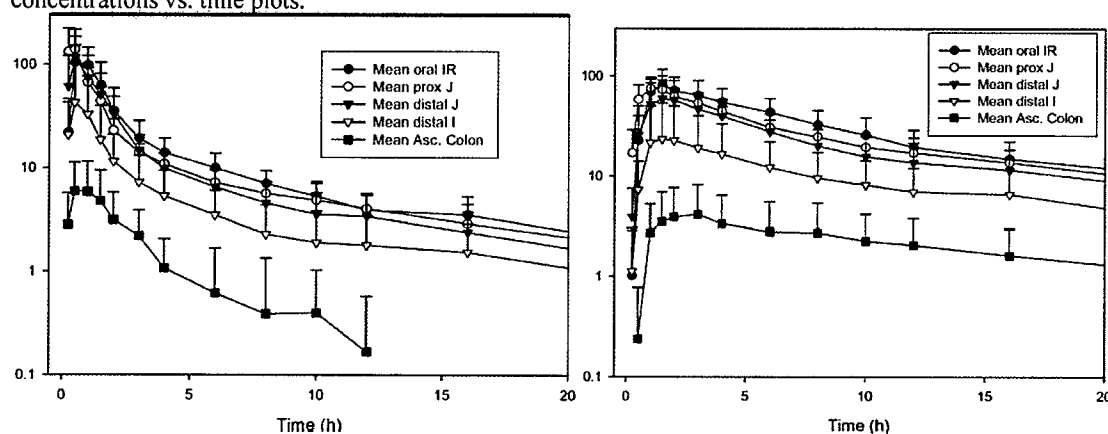


Table 4. Pitavastatin and its lactone PK parameters analyses.

Analyte	Treatment	PK parameter	Estimated ratio of geometric means	lower 90% CI	upper 90% CI
Pitavastatin	B: proximal jejunum	AUC _{0-t} (ng.h/mL)	0.89	0.37	2.16
		C _{max} (ng/mL)	1.21	0.54	2.74
	C: distal jejunum/proximal ileum	AUC _{0-t} (ng.h/mL)	0.92	0.38	2.23
		C _{max} (ng/mL)	0.71	0.31	1.60
	D: terminal ileum	AUC _{0-t} (ng.h/mL)	0.28	0.11	0.71
		C _{max} (ng/mL)	0.22	0.09	0.53
	E: ascending colon	AUC _{0-t} (ng.h/mL)	0.03	0.01	0.08
		C _{max} (ng/mL)	0.05	0.02	0.10
Pitavastatin Lactone	B: proximal jejunum	AUC _{0-t} (ng.h/mL)	0.81	0.46	1.41
		C _{max} (ng/mL)	0.89	0.48	1.66
	C: distal jejunum/proximal ileum	AUC _{0-t} (ng.h/mL)	0.60	0.34	1.06
		C _{max} (ng/mL)	0.59	0.32	1.10
	D: terminal ileum	AUC _{0-t} (ng.h/mL)	0.23	0.13	0.43
		C _{max} (ng/mL)	0.19	0.10	0.38
	E: ascending colon	AUC _{0-t} (ng.h/mL)	0.09	0.05	0.17
		C _{max} (ng/mL)	0.07	0.03	0.14

When compared with the oral immediate release administration (Treatment A), both pitavastatin and its lactone C_{max} and AUC_{0-t} indicate that pitavastatin is well absorbed in the proximal jejunum and distal jejunum/proximal ileum, and less so in the terminal ileum with the ascending colon being the least absorption site. The sponsor conducted Study 104A2115 to examine pitavastatin's absorption data so as to optimize the pitavastatin delivery via modified release formulation.

Distribution

Per Study 1.02.EU, mean (SD) pitavastatin volume of distribution is 211.4 (69.5) L. Pitavastatin (0.1 – 1 µg/mL) is 99.5 – 99.6% bound in human plasma via in vitro equilibrium dialysis (Fujino et al. *Xenobio Metabol Dispos* 14:415-24 [1999]). Pitavastatin is primarily bound to human serum albumin and binding to α₁-acid glycoprotein is also strong. Pitavastatin lactone (0.3 – 3 µg/mL) is 98.95 – 99.33% bound in human plasma via in vitro ultracentrifugation per Study RI107017.

Per Study SNY 419/013926 below, radioactivity concentrations in whole blood mirror those in plasma and are generally about 50 – 60% of the corresponding plasma concentrations suggesting that association of pitavastatin and/or its metabolites with blood cells is minimal.

Metabolism and Excretion

Study SNY 419/013926 examined the mass balance of a single dose of ¹⁴C-pitavastatin 32 mg (2.4 MBq/65 µCi; fluorophenyl-U-¹⁴C radiolabel) in purified water upon oral administration to 6 overnight-fasted healthy men (5 Caucasian and 1 Negroid). Serial whole-blood, plasma, urine, and fecal samples were collected predose and for 168 hours postdose to determine pitavastatin and its metabolites. Pitavastatin and its lactone in plasma were determined via an HPLC-UV method. The 8 OH-

pitavastatin (M-13) metabolite in plasma was determined via an LC-MS/MS method. Radioactivity in whole blood, plasma, urine, and fecal samples were detected via liquid scintillation counting. The metabolites profiles in plasma, urine, and feces were analyzed via HPLC with radioactivity and UV detections.

Figure 5. Proposed pitavastatin metabolic pathways in humans [Fujino et al. *Xenobiotica* 33:27-41 (2003)].

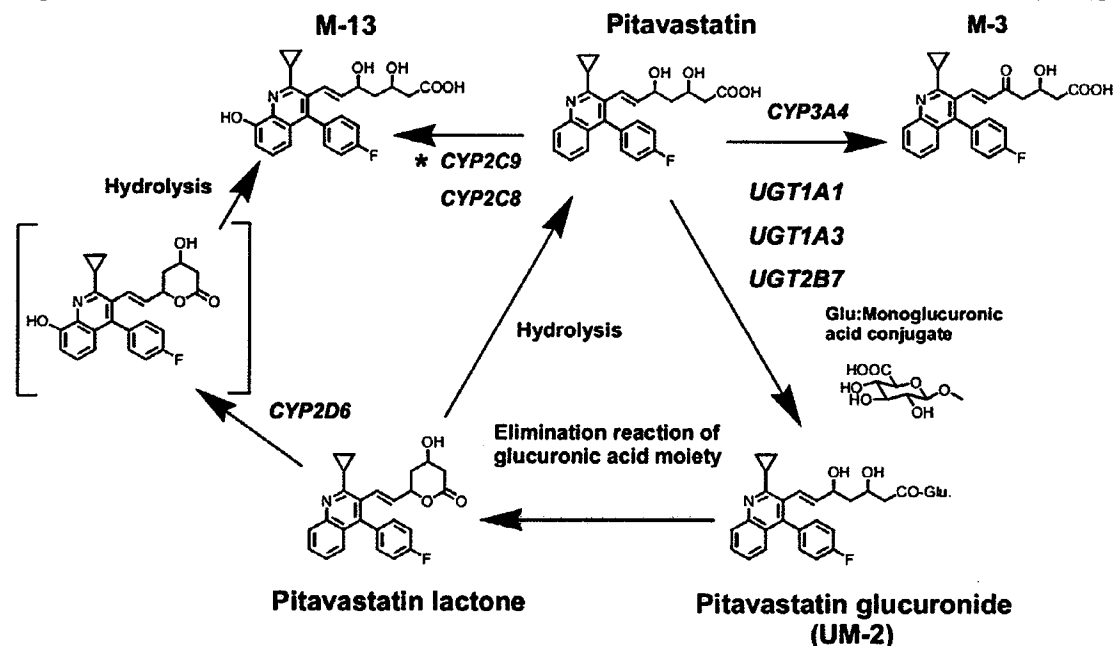


Figure 6 (left). Mean concentrations of radioactivity, unchanged pitavastatin and its lactone in plasma upon oral administration of ^{14}C -pitavastatin to 6 healthy men. Figure 7 (right). Mean cumulative excretion of radioactivity in urine and feces during 7 day postdose upon oral administration of ^{14}C -pitavastatin to 6 healthy men.

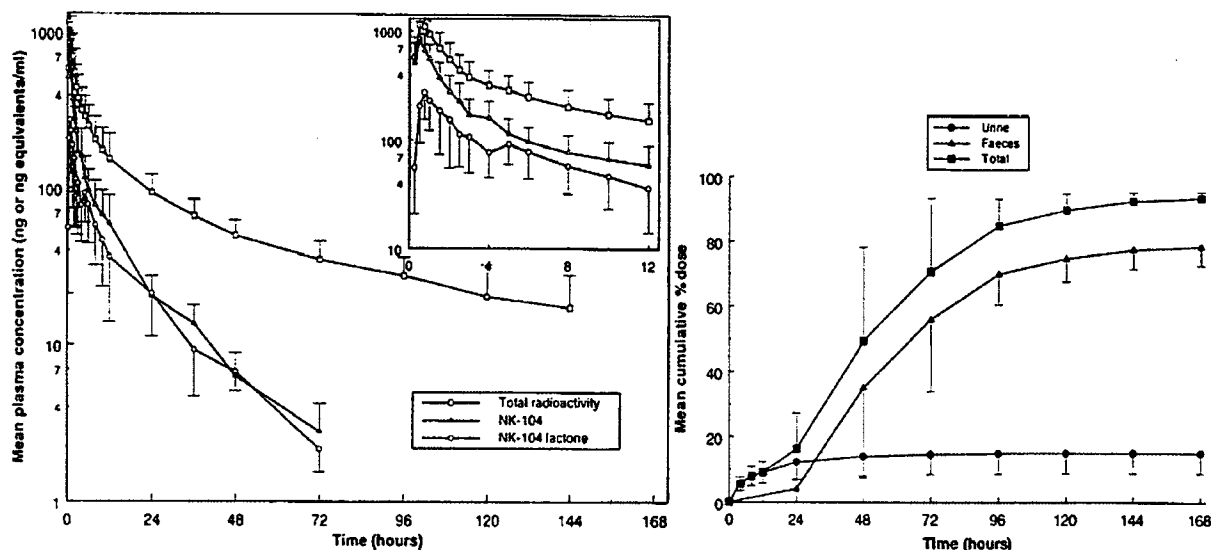


Table 5. Mean PK parameters for pitavastatin, its lactone, and 8-hydroxy pitavastatin for 6 healthy men.

Parameter	Radioactivity (Mean \pm SD)	Pitavastatin (Mean \pm SD)	Lactone (Mean \pm SD)	8-OH Pitavastatin (M13; Mean \pm SD)
C _{max} (ng/mL)	1169 \pm 456	857.7 \pm 379.7	274.2 \pm 117.7	2.99 \pm 0.74
T _{max} (h) ^a	0.5	0.5	0.75	1.25
AUC _{0-t} (ng*h/mL)	10268 \pm 3683	2991 \pm 1136	1818 \pm 804	12 \pm 4
λ_z (h ⁻¹)	0.0103 \pm 0.0044	0.0486 \pm 0.0034	0.0428 \pm 0.007	0.1782 \pm 0.0931
t _{1/2} (h) ^b	67.6	14.3	16.2	3.9
AUC _{0-∞} (ng*h/mL)	12299 \pm 4772	3175 \pm 1205	2074 \pm 653	16 \pm 4
CL/F (mL/min)	-	183 \pm 71	-	-
V _d /F (L)	-	226 \pm 87	-	-

^aMedian value. ^bCalculated as $\ln 2/\text{mean } \lambda_z$ via non-rounded data. λ_z – terminal elimination rate constant.

Pitavastatin and its lactone exposure accounted for almost 1/2 of the total pitavastatin derived systemic exposure to 168 hours postdose. Pitavastatin and its lactone had similar t_{1/2}, which suggests that the lactone formation may be the rate-limiting step for the lactone kinetics. The M-13 metabolite (8-OH pitavastatin) accounted for < 1% of the plasma radioactivity at all sampling times. Dihydrodiol pitavastatin (M-14) is another minor metabolite.

A mean of 15.1 and 78.6% of the dose was excreted in the urine and feces, respectively, with a mean total of 93.7% of the radioactive dose recovered in the excreta during 7 days postdose.

Table 6. Pitavastatin and its major metabolites excreted (% of dose) in urine for the 48 hours postdose and in feces* for 96 hours postdose.

	Urine, % dose	Feces, % dose
Pitavastatin	3.0	42.9
Dihydroxy pitavastatin	4.1	7.3
Pitavastatin glucuronide	3.8	-
Pitavastatin lactone	0.8	2.6
8-hydroxy pitavastatin	-	7.2
Unknown	1.2 (H6)	4.7 (H7)
Others	each < 0.3	each < 2

*Feces were collected during 12 hours predose and at 24 hours intervals postdose for 7 days. Only 1 participant had fecal sample from 0 – 24 hours postdose. Most of the analytes were below quantitation limits from 96 hours – 7 days postdose.

For unknown reason, the ratio of pitavastatin lactone AUC_{0-∞} to pitavastatin AUC_{0-∞} is less than 1 for this mass-balance study, which is different from that (2 – 3) of other studies such as the absolute bioavailability, food effect, and drug interaction studies.

Study AE2544 examined the in vitro incubation of pitavastatin (0.5 and 2.5 μ M) and its lactone (0.5 μ M) in microsomes generated from lymphoblastoid cell lines expressing human CYPs with NADPH at 37°C for 2 hours. Pitavastatin and its metabolites are analyzed via LC/MS methods.

Table 7. Results of in vitro incubation with CYP isozymes.

P450 isozyme	Remaining ratio (% of control)		
	Pitavastatin Lactone 0.5 μ M	Pitavastatin 0.5 μ M	Pitavastatin 2.5 μ M
control*	100	100	100
CYP1A1	86.9	91.6	105
CYP1A2	80.5	99.8	104
CYP1B1	97.0	87.4	108
CYP2A6	104	113	104
CYP2B6	85.0	111	98.8
CYP2C8	99.5	102	111
CYP2C9-Arg	101	83.1	101
CYP2C9-Cys	107	104	100
CYP2C19	82.4	100	92.5
CYP2D6-Val	83.0	90.5	108
CYP2D6-Met	81.7	104	91.3
CYP2E1	97.2	99.4	117
CYP3A4	81.0	114	114

* control microsomes are reductase or control vector

Per the incubation results above, CYPs 2C9 and 1B1 metabolize pitavastatin, whereas CYPs 3A4, 2D6, 2C19, 2B6, 1A2, and 1A1 metabolize pitavastatin lactone.

Study AE2544 also examined the in vitro inhibition of pitavastatin (0.025, 0.25 and 2.5 μ M) on the metabolic activity of model substrate for CYP isozyme via microsomes generated from lymphoblastoid cell lines expressing human CYPs with NADPH at 37°C for a designated time. The metabolites concentrations were determined via fluorescence spectrophotometry or HPLC.

Table 8. Pitavastatin's inhibition effect on CYPs

P450 isozyme	Relative activity (% of control)			Positive Control**
	0.025 μ M	Pitavastatin 0.25 μ M	2.5 μ M	
reference*	100	100	100	
CYP1A1	107	108	106	61.7
CYP1A2	105	105	103	21.0
CYP1B1	103	105	98.0	26.6
CYP2A6	97.4	106	100	55.5
CYP2B6	102	113	107	14.4
CYP2C8	96.0	84.8	69.6	22.3
CYP2C9-Arg	98.8	92.2	95.4	52.3
CYP2C9-Cys	103	97.9	95.3	62.3
CYP2C19	101	99.4	101	15.9
CYP2D6-Val	105	99.3	101	0.0
CYP2D6-Met	91.9	97.9	96.7	0.741
CYP2E1	91.0	90.1	90.1	5.81
CYP3A4	99.1	101	100	9.02

*Without test article; **Concentration of positive control: CYP1A1, 1A2, 1B1: α -Naphthoflavone 5 μ mol/L; CYP2E1:

Diethyldithiocarbamate 100 μ mol/L; other CYPs: SKF-525A 300 μ mol/L.

Substrate for CYP1A1, 1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 activity: 7-ethoxyresorufin, 7-ethoxyresorufin, 7-ethoxyresorufin, coumarin, 7-ethoxy-4-trifluoro-methylcoumarin, 5-chloro-methylfluorescein diethylether, diclofenac, S-mephenytoin, bufuralol, chlorzoxazone and testosterone.

Of all the tested CYPs inhibition above, pitavastatin only inhibits CYP2C8.

Fujino et al. showed that pitavastatin lactone does not inhibit CYPs 2C9 and 3A4 in vitro [*Xenobiotica* 33:27-41 (2003)]. Fujino et al. also showed that UGTs 1A3 and 2B7 primarily metabolize pitavastatin in vitro, then pitavastatin glucuronide eliminates the glucuronide moiety and a water molecule and then forms pitavastatin lactone [*Xenobiotica* 33:27-41 (2003)]. Fujino et al. showed that pitavastatin undergoes a minor degree of metabolism via CYP2C9, but the rate of metabolism is very slow and CYP mediated metabolism does not play an important role in pitavastatin's elimination [*Drug Metabol Drug Interact* 20:25-42 (2004)]. UGTs 1A3 and 2B7 isozymes are polymorphic [Kiang et al. *Pharmacol Ther* 106:97-132 (2005)]. CYP2C9 isozyme is polymorphic [Kirchheiner et al. *Clin Pharmacol Ther* 77:1-16 (2005)].

Fujino et al. later showed that CYPs 3A4 and 2D6 metabolize pitavastatin lactone [*Xenobiotica* 34:961-71 (2004)].

(b) (4)

At least, pitavastatin lactone is active to cause muscle adverse effects. In general, the lactone forms of statins are more potent than the acid forms in human to cause skeletal muscle effects in vitro [Skottheim et al. *Eu J Pharm Sci* 33:317-25 (2008)].

Study R101030 showed pitavastatin lactone's effect on the inhibition of HMG-CoA reductase in rat liver microsomes. The sponsor incubated both pitavastatin and pitavastatin lactone (5 and 10 nM each) at 37°C for about 60 minutes and measured the inhibition of HMG-CoA reductase activity. They also studied the rate of change of pitavastatin to pitavastatin lactone via incubating pitavastatin lactone (200 nM and 1 µM) only in the microsomal system.

Figure 8. Inhibition of HMG-CoA reductase by pitavastatin and its lactone on the dependency of preincubation time. Each bar in the figure denotes the mean \pm standard error (n = 3).

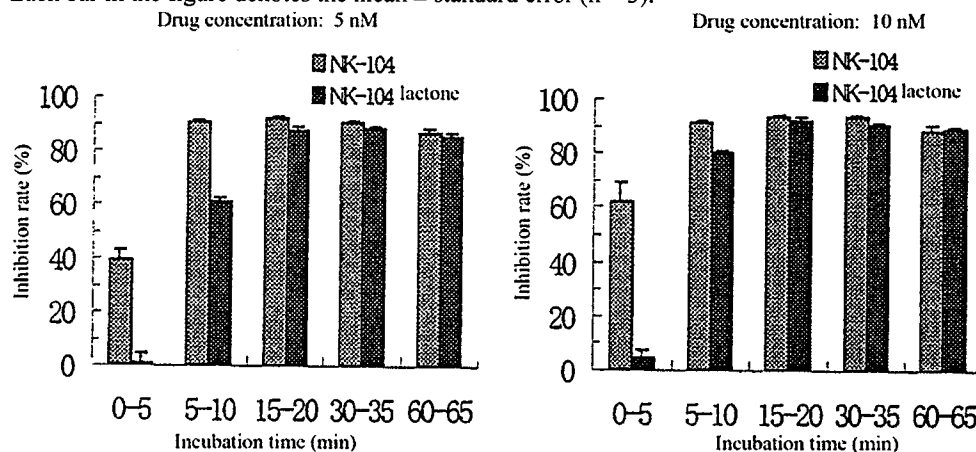
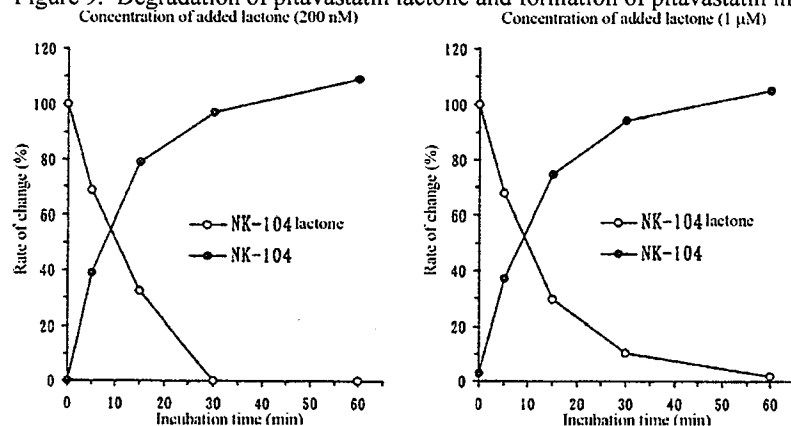


Figure 9. Degradation of pitavastatin lactone and formation of pitavastatin in the rat liver microsomal system.



The sponsor showed that inhibition of HMG-CoA reductase is absent when only pitavastatin lactone is present (0 – 5 minutes incubation). When pitavastatin is formed from its lactone then the pitavastatin lactone incubation showed inhibition of HMG-CoA reductase and eventually matches that of the pitavastatin incubation.

The sponsor showed the data that is consistent with their claim that pitavastatin lactone is not active in inhibiting HMG-CoA reductase but has not definitively proved this claim (see Dr. Elmore's Pharmacology/Toxicology review).

The sponsor also showed the potency of pitavastatin, 8-hydroxy pitavastatin, (b) (4) on HMG-CoA Reductase.

Table 9. Inhibitory Effect of Pitavastatin and Pitavastatin Related Substances on HMG-CoA Reductase.

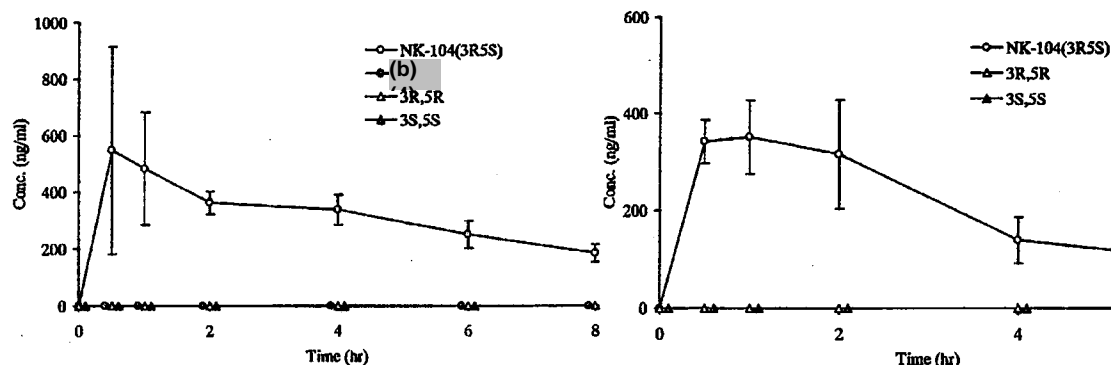
Test Substance	IC ₅₀ (nmol/L)	Relative Potency*
Pitavastatin	5.5	1
Pitavastatin 8-hydroxide (M-13)	3.5	1.6
(b) (4)		

* Relative potency where pitavastatin = 1; n = 4

Optical isomer inversion via in vivo metabolism:

Pitavastatin has 2 chiral carbon centers and is the 3R,5S specific isomer. Thus, pitavastatin has 3 other optical isomers: (b) (4) Study R98054 examined pitavastatin exposure, its (b) (4) isomers' exposure in rats (3 mg/kg single dose) and dogs (1 mg/kg single dose) via a chiral stationary-phase HPLC/UV bioanalytical assay.

Figure 10 (left). Mean (SE) plasma pitavastatin and its optical isomers concentration – time profile in 4 dogs. Figure 11 (right). Mean (SE) plasma pitavastatin and its optical isomers concentration – time profile in 4 rats.



Study R98054 did not detect inversion of pitavastatin to any of the 3 optical isomers in 4 dogs and did not detect the inversion of pitavastatin to its 3R,5R and 3S,5S optical isomers in 4 rats. However, an unknown metabolite interfered the detection of 3S,5R isomer in rats for Study R98054.

Optical isomerization of both asymmetric centers is necessary for the inversion of pitavastatin (3R,5S) (b) (4) whereas optical isomerization of 1 of the 2 asymmetric centers is necessary for the inversion to an epimer. Other 3R,5S statins (pravastatin, fluvastatin, cerivastatin, atorvastatin, and rosuvastatin) have not been reported for chiral inversion via metabolism. Chiral inversion of pitavastatin via in vivo metabolism to its optical isomers is possible but the inversion may be very low per the dog and rat data.

(b) (4)

Per the transporter-expressing HEK293 cells and human cryopreserved hepatocytes, the OATP1B1 and OATP1B3 transporters account for almost all the observed pitavastatin uptake clearance into human hepatocytes and OATP1B1 accounts for about 90% of the clearance [Hirano et al. *J Pharmacol Expt Ther* 311:139-46 (2004)]. Because OATP2B1 also localizes in the hepatic basolateral membrane, Hirano et al. further confirm that OATP2B1 contributes to less than 1% of pitavastatin hepatic uptake clearance as compare to those of OATP1B1 and OATP1B3 [*Drug Metab Dispos* 34:1229-36 (2006)]. OATPs 1B1 and 1B3 transporters are polymorphic [Miyagawa et al. *J Pharmacol Expt Ther* 329:551-7 (2009)].

Hirano et al. showed that significant basal-to-apical transport of pitavastatin in Madin-Darby canine kidney II cells occurred with OATP1B1/MDR1, OATP1B1/MRP2, and OATP1B1/BCRP, which

indicate involvement of multiple transporters in pitavastatin biliary excretion in humans [*Mol Pharmacol* 68:800-7 (2005)].

Fujino et al. showed that the solute carrier (SLC) transporters are not responsible for the hepatic uptake of pitavastatin lactone via SLC transporters expressing *Xenopus laevis* oocytes [*J Pharm Pharmacol* 57:1305-11 (2005)]. Fujino et al. also showed via ATPase hydrolysis analysis of ABC transporters that pitavastatin is not a substrate of MDR1 and MRP2 but is a substrate of BCRP as well as pitavastatin lactone is not a substrate of MRP2 and BCRP but pitavastatin lactone is a substrate of MDR1 [*J Pharm Pharmacol* 57:1305-11 (2005)].

Inconsistency exists between Hirano and Fujino's data in that pitavastatin is a substrate of MDR1 and MRP2 from Hirano's data and pitavastatin is not a substrate of MDR1 and MRP2 from Fujino's data. This inconsistency is also noted in Shitara and Sugiyama's [*Pharmacol Ther* 112:71-105 (2006)] as well as Neuvonen et al.'s [*Clin Pharmacol Ther* 80:565-81 (2006)] review articles.

In addition, Study P100064 (Report R101068) examined the uptake of mdr1 transporter in mice's (wild type and knockout) different organs via whole body radiography. The report showed that the ratio of concentration of radioactivity in mdr1a/b (-/-) to in mdr1a/b (+/+) at the liver is 3.76 at 1 hour and 0.88 at 6 hours, which would lead to the conclusion that pitavastatin is an mdr1 substrate especially per the 1 hour data. However, Fujino et al. published Study P100064's results with the ratio only at 6 hours (0.88), which would lead to the conclusion that pitavastatin is not an mdr1 substrate [*Drug Metab Pharmacokin* 17:449-56 (2002)].

Per Study NK-104-1.26 (Section 2.4.2.14), pitavastatin is neither a P-gp inhibitor nor a P-gp inducer because of no in vivo interaction between pitavastatin and digoxin (acceptable P-gp substrate per the draft Drug Interaction Guidance) in humans.

(b) (4)

Due to the inconsistent results discussed above, the P-glycoprotein and MRP2 substrate statuses for pitavastatin are inconclusive.

2.2.2 Is pitavastatin calcium PK dose-proportional upon oral administration?

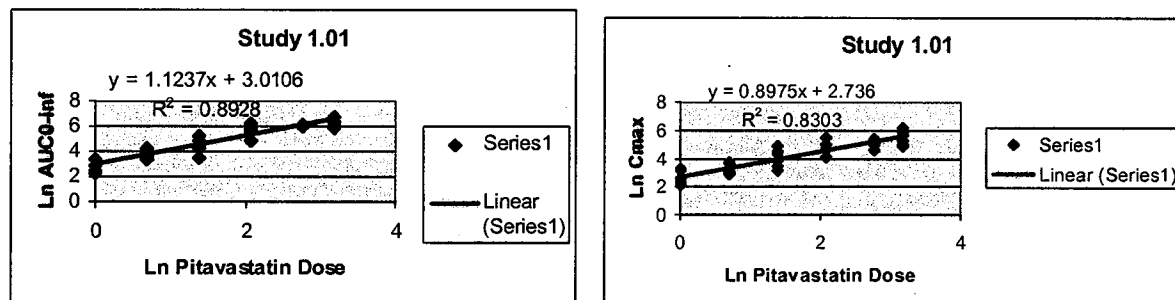
Study PKH/NKN98389N/NK104.1.01 was a parallel, oral single and multiple rising dose (1, 2, 4, 8, 16, and 24 mg pitavastatin) study in 48 healthy Caucasian men. Each dose group consisted of 8 participants (6 on pitavastatin and 2 on placebo).

Participants received the oral multiple once daily doses for 21 days. On Day 1, participants orally received the doses after fasting. On Days 8 and 21, participants orally received their respective doses under fed condition. Serial plasma samples were collected predose and 24 postdose on Days 1, 8, and 21 to determine pitavastatin and its lactone PK via a validated HPLC/UV bioanalytical assay. Per the power model to assess dose-proportionality (C_{\max} or $AUC_{0-\infty} = \alpha \cdot [Dose]^{\beta}$; α depends on the subject and error; β is the dose-proportionality factor; after transformation, $\ln C_{\max}$ or $\ln AUC_{0-\infty} = \ln \alpha + \beta \cdot \ln$ Oral Dose; $\beta = 1$ when dose-proportional). This reviewer performed the subsequent power model analyses.

For Day 1 the slope, β , and its (90% CI) for $\ln AUC_{0-\infty}$ vs. \ln Oral Dose plot and $\ln C_{\max}$ vs. \ln Oral Dose plot were 1.124 (1.01 – 1.24) and 0.90 (0.78 – 1.02), respectively. For Day 8 the slope, β , and its (90% CI) for $\ln AUC_{0-\infty}$ vs. \ln Oral Dose plot and $\ln C_{\max}$ vs. \ln Oral Dose plot were 0.98 (0.89 – 1.07) and 0.91 (0.79 – 1.03), respectively. For Day 21 the slope, β , and its (90% CI) for $\ln AUC_{0-\infty}$ vs. \ln

Oral Dose plot and $\ln C_{\max}$ vs. \ln Oral Dose plot were 1.08 (0.97 – 1.20) and 0.91 (0.81 – 1.02), respectively. Hence, pitavastatin PK is approximately dose proportional for both single and multiple oral doses from 1 – 24 mg.

Figures 13 (left) and 14 (right). Pitavastatin's $\ln AUC_{0-\infty}$ or $\ln C_{\max}$ vs. \ln Dose plots on Day 1, respectively, just for demonstration to only show the single-dose plots.



This reviewer did not review Study HPC/NKN 00435N/NK-104.1.19 ^{(b) (4)}

which is not relevant to the proposed 1, 2, and 4 mg pitavastatin doses.

2.2.3 Does chronic oral dosing alter pitavastatin calcium PK?

Per Study PKH/NKN98389N/NK104.1.01 above, median pitavastatin AUC_{0-24} at Day 21 and Day 1 is 153 and 103 ng.h/mL, respectively, and their ratio is 1.49. Per this $\left[Accumulation = \frac{1}{(1 - e^{-(k\tau)})} \right]$

relationship, $k = \frac{0.693}{12} \text{ hr}^{-1}$, and $\tau = 24$ hours. Thus, the estimated accumulation factor is 1.33.

This reviewer did not review Study HPC/NKN 00435N/NK-104.1.19 ^{(b) (4)}

which may not be relevant to the proposed 1, 2, and 4 mg pitavastatin oral doses.

2.2.4 How are the proposed daily oral pitavastatin calcium doses determined?

Study -209 is a dose-ranging study of oral 8, 16, 32, and 64 mg pitavastatin once daily doses vs. placebo on pitavastatin's efficacy and safety for 8 weeks in 396 patients receiving active treatment and 53 patients receiving placebo. The sponsor observed rhabdomyolysis requiring hospitalization at the doses of 32 and 64 mg daily for 3/34 patients and 3/33 patients, respectively.

Study 2204 is another dose-ranging study of oral 4 and 8 mg pitavastatin once daily doses vs. placebo as well as oral 10, 20, and 40 mg atorvastatin once daily doses on pitavastatin's efficacy and safety for 12 weeks in 400 patients receiving active treatment and both 50 patients receiving placebo and positive controls (atorvastatin). The sponsor observed 2 reports of creatinine kinase (CK) > 10 times the upper limit of normal (ULN) associate with myalgia and elevated myoglobin concentrations in the 8 mg pitavastatin dose group, and 1 of them is suspicious for rhabdomyolysis.

Per the Japanese Phase 3 program, post-marketing experience and the European/US Phase 2 program, the sponsor chose the 2 and 4 mg pitavastatin once daily doses to be studied in the Phase 3 development program with the 1 mg dose to be studied in the elderly population to determine the benefit to risk ratio.

2.2.5 What is pitavastatin calcium's exposure-efficacy relationship to reduce elevated lipid concentrations?

Reduction of LDL-C is the primary efficacy endpoint for pitavastatin. The sponsor did not collect blood samples to determine pitavastatin concentrations for the clinical efficacy and safety studies in

patients. Thus, we cannot conduct pitavastatin concentration-efficacy relationship analysis. However, a pitavastatin once daily oral dose and LDL-C reduction relationship exists.

Table 10. Effects of Pitavastatin on LDL-C, after 12 Weeks of Treatment, Compared to Placebo in 5 Studies

Endpoint LDL-C (mmol/L)	Placebo	Pitavastatin (QD)			(b) (4)
		1 mg	2 mg	4 mg	
HEC/NK98402N/NK-104.2.02					
N	51	52	49	50	
Adjusted mean % change	-4.0	-33.3 ¹	-38.2 ¹	-46.5 ¹	
HEC/NKN98403N/NK-104.2.03					
N	50	49	50	48	
Adjusted mean % change	-1.6	-27.0 ¹	-31.4 ¹	-41.5 ¹	
NKS104A2204²					
N	35	Not included	Not Included	70	
Adjusted mean % change	-2.4	Not included	Not Included	-42.1 ¹	
NK-104-209²					
N	39	Not included	Not included	Not included	
Mean % change	8.0	Not included	Not included	Not included	
NK-104-210²					
N	16	Not included	Not included	28	
Mean % change	0.3	Not included	Not included	-36.9	

¹ - Significantly superior to placebo. NC- Not calculated as dose level stopped. ²Terminated studies

2.2.6 What is pitavastatin calcium's exposure-safety relationship with respect to muscle adverse events?

The major pitavastatin safety related issue is muscle adverse events since rhabdomyolysis was observed during pitavastatin's clinical development. Drs. Manoj Khurana and Justin Earp performed the exposure-safety relationship analyses as the following:

Objectives

Pitavastatin's use in clinical trials was associated with skeletal muscle related adverse effects (AE) of myalgia and rhabdomyolysis. Therefore, exposure safety assessment was focused to answer following key questions:

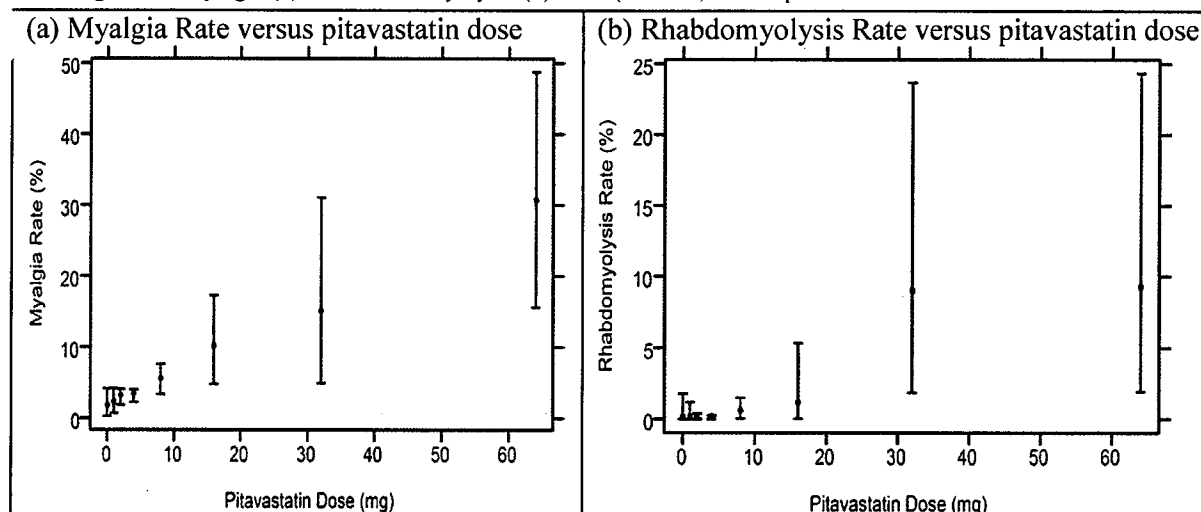
- Is there a dose-AE relationship for pitavastatin with regards to skeletal muscle effects?
- Is there a concentration-AE relationship for pitavastatin with regards to skeletal muscle effects?
- Is there a significant overlap in the exposures achieved with 4 and 8 mg?

Results

Question 1: Is there a dose-AE relationship for Pitavastatin with regards to skeletal muscle effects?

Myalgia rate increased with the pitavastatin dose, based on the data from integrated summary of safety. However, rhabdomyolysis occurred with doses above 4 mg. as shown in the Figure 15 below:

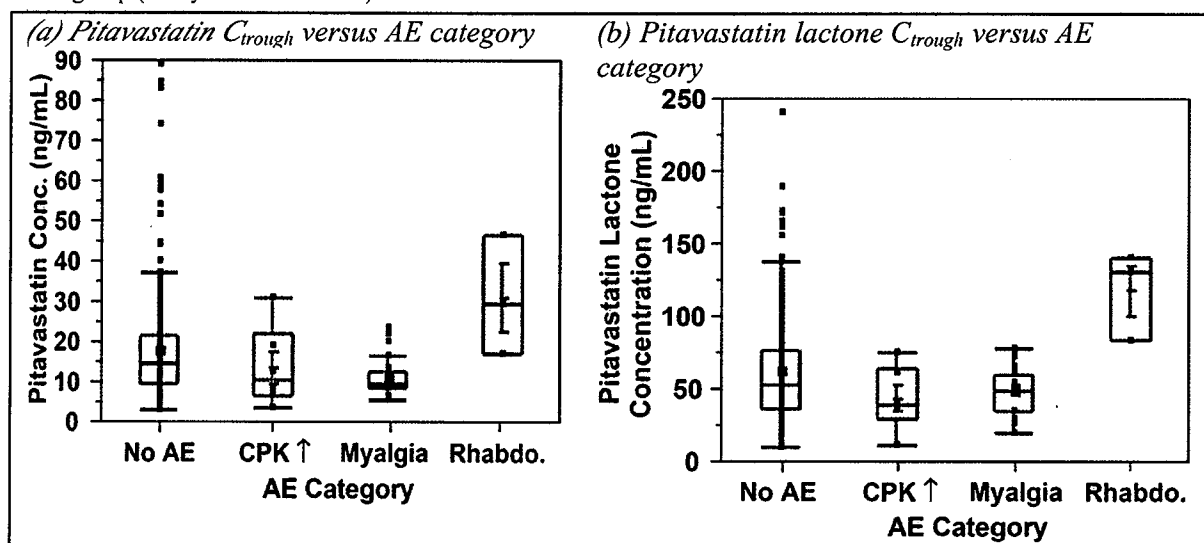
Figure 15. Myalgia (a) and Rhabdomyolysis (b) rates (95% CI) versus pitavastatin dose



Question 2: Is there a concentration-AE relationship for Pitavastatin with regards to skeletal muscle effects?

In order to determine the concentration-AE relationship, safety and pitavastatin concentration data available from only one 12 week Phase 2 study (NKS104A2204) was utilized. The average C_{trough} (Pitavastatin and Lactone) were compared among each AE categories; 1) no muscle related AE, 2) blood CPK elevation, 3) myalgia and 4) rhabdomyolysis. The results showed that concentration-AE was not apparent for pitavastatin and lactone in both 4 and 8 mg dose groups as the pitavastatin and lactone exposures were comparable among the patients with muscle related AEs versus those with no muscle related AEs. Pitavastatin and lactone average C_{trough} appeared to be higher (25th - 75th percentiles) in patients with rhabdomyolysis (16). However, the data is limited to draw any definite conclusion (only 2 cases of rhabdomyolysis in the 8 mg dose group).

Figure 16. (Left) Pitavastatin and (Right) pitavastatin lactone trough concentrations versus AE categories in 8 mg dose group (Study NKS104A2204)

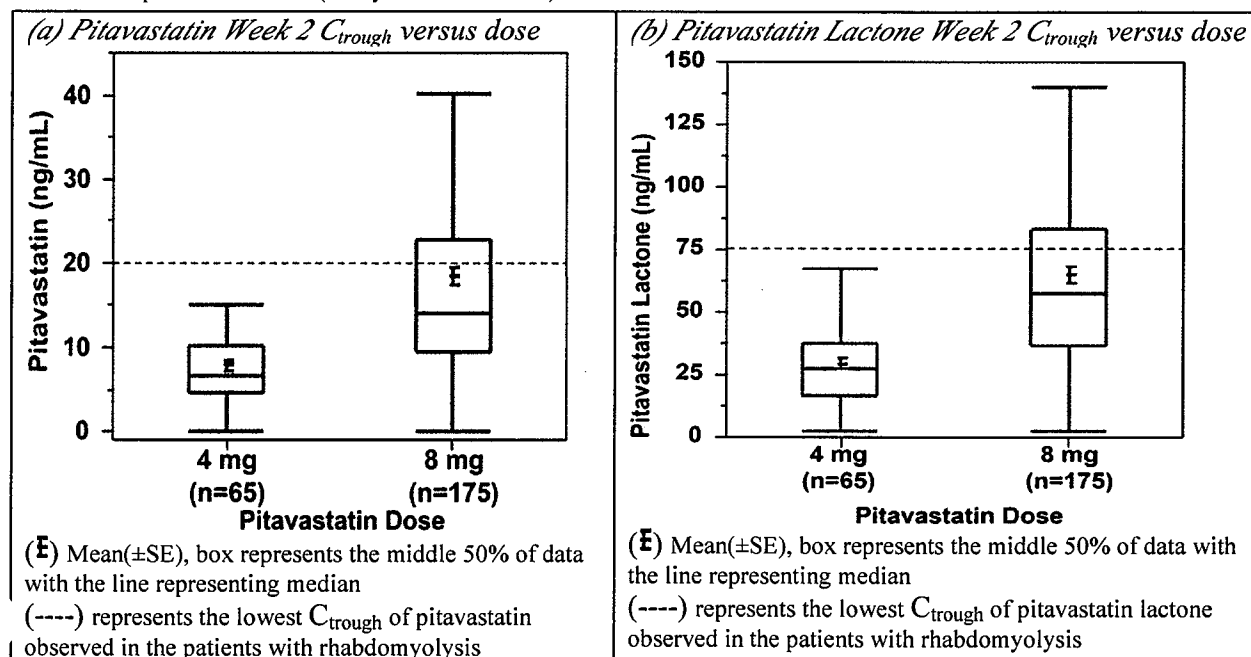


Question 3: Is there a significant overlap in the exposures achieved with 4 and 8 mg?

Since rhabdomyolysis occurred above 4 mg dose, the steady-state drug concentrations at Week 2 were compared among the 4 and 8 mg dose groups to assess if the concentrations overlapped among the two

groups. The data showed that the two doses do not overlap significantly for the majority of patients (i.e. 25th – 75th percentile) with respect to pitavastatin and pitavastatin lactone steady-state exposures (C_{trough}) (see 17 below). The maximal pitavastatin and pitavastatin lactone trough concentrations observed with 4 mg dose groups were below the lowest levels (----) observed in the patients with AE of rhabdomyolysis.

Figure 17. Mean (\pm SE) (blue) and box plots (red) of Week 2 C_{trough} for (Left) pitavastatin and (Right) pitavastatin lactone versus pitavastatin dose (Study NKS104A2204)



Pitavastatin demonstrated dose-response with regards to myalgia and rhabdomyolysis rate over the 1-64 mg dose range. A concentration-AE relationship for muscle related AEs, blood CPK elevation, and myalgia was not apparent in the 4 and 8 mg dose groups as there were comparable pitavastatin and lactone exposures among the patients with muscle related AEs, blood CPK elevation, and myalgia compared to patients with no AEs. For rhabdomyolysis, the pitavastatin and lactone average C_{trough} appeared to be higher compared to all other groups suggesting an exposure-response relationship. However, the data was limited to draw a definite conclusion (only 2 cases in the 8 mg dose group).

2.2.7 What would be the recommended optimal daily oral pitavastatin calcium dose as an adjunct therapy to diet to reduce elevated lipid concentrations?

Per the pitavastatin dose and efficacy relationship plus the plasma pitavastatin concentration and muscle related adverse events relationship, the proposed usual starting 2 mg pitavastatin once daily oral dose and the maximum 4 mg pitavastatin once daily oral dose are acceptable.

2.2.8 How did the sponsor address pitavastatin calcium's potential to prolong QT interval?

Study 1.34US examined pitavastatin's QT prolongation potential in 174 healthy participants. In the mornings of Days 1 – 4, each randomized overnight-fasted participant orally received either 1 of the following treatments daily:

- placebo (4 placebo tablets and 1 placebo capsule)
- 4 mg pitavastatin (a 4 mg pitavastatin tablet, 3 placebo tablets, and 1 placebo capsule)
- 16 mg pitavastatin (four 4 mg pitavastatin tablets 1 placebo capsule)

- 400 mg moxifloxacin (4 placebo tablets and 1 placebo capsule on Days 1 – 3. On day 4, participants received 4 placebo tablets and 1 overencapsulated 400 mg moxifloxacin tablet) The placebo and pitavastatin tablets were identical in appearance and so were the placebo and moxifloxacin containing capsules.

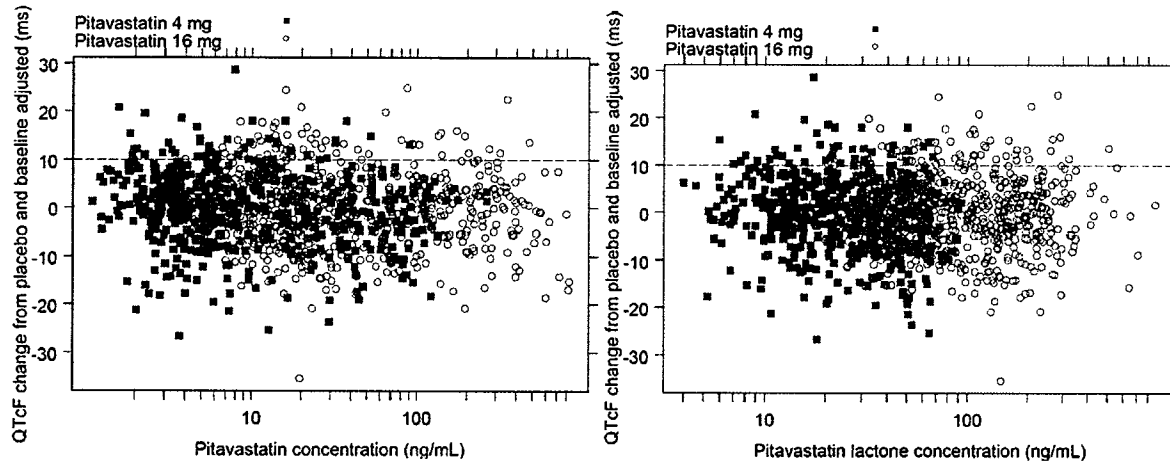
Serial pharmacodynamic (PD) 12-lead ECGs were collected at baseline on Day –1 and on Day 4. The collection of PD ECGs on Day 4 was timed to start 10 minutes before the PK blood collection time points. The timing of the PD ECGs collected at Baseline matched the collection times of Day 4. After each 5-minute collection period, there was a 5-minute rest period before PK sample collection. The ECG data were interpreted at a central cardiac laboratory.

See the Interdisciplinary Review Team’s review dated May 15, 2009 in DFS. Briefly, Study 1.34US does not detect the 4 and 16 mg pitavastatin oral doses have QT prolongation effect in this thorough QT study.

Table 11. Results of statistical analysis for the effect of pitavastatin on QT prolongation

Treatment	Time (hour)	$\Delta\Delta\text{QTcI}$ (ms)	90% CI (ms)
Pitavastatin 4 mg qd	16	2.6	(-0.4, 5.5)
Pitavastatin 16 mg qd	16	2.9	(-0.0, 5.9)
Moxifloxacin 400 mg*	3	11.3	(8.6, 14.1)

Figure 18 (left). $\Delta\Delta\text{QTcF}$ versus plasma pitavastatin concentration. Figure 19 (right). $\Delta\Delta\text{QTcF}$ versus plasma pitavastatin lactone concentration.



2.3 Intrinsic Factors

2.3.1 How does hepatic impairment affect pitavastatin PK?

Study -HK examined the effect of liver impairment on pitavastatin PK in 18 Chinese men (6 healthy, 6 Child-Pugh grade A, and 6 Child-Pugh grade B). Each overnight-fasted participant orally received a 2 mg pitavastatin tablet. Serial plasma samples were collected predose and 72 hours postdose to determine pitavastatin and its lactone via validated HPLC-UV bioanalytical assay.

Figure 20 (left). Mean plasma pitavastatin concentrations vs. time plots. Figure 21(right). Mean plasma pitavastatin lactone concentrations vs. time plots.

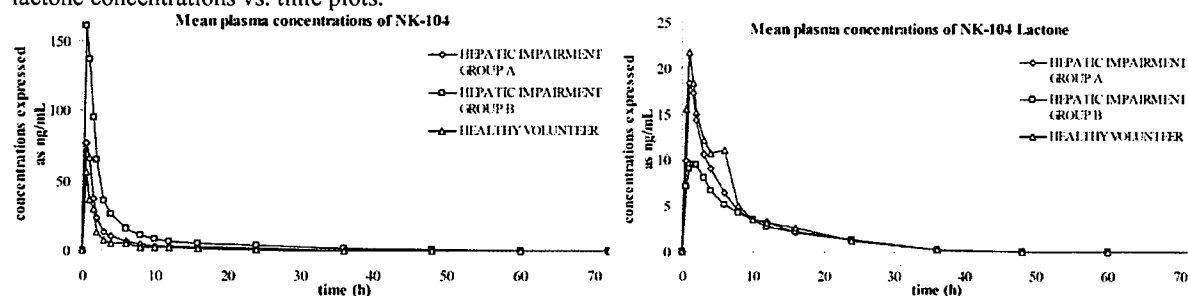


Table 12. Pitavastatin PK parameters for groups of varying liver function

PK Parameter (unit)	Hepatic Function Group		
	Child-Pugh A (N= 6)	Child-Pugh B (N= 6)	Healthy (N= 6)
Mean \pm SD	Mean \pm SD	Mean \pm SD	Mean \pm SD
AUC _t (ng.h.mL ⁻¹)	201.74 \pm 187.12	495.45 \pm 230.10	125.94 \pm 41.73
AUC _{inf} (ng.h.mL ⁻¹)	221.35 \pm 191.81	528.92 \pm 223.41	141.02 \pm 44.29
C _{max} (ng.mL ⁻¹)	81.06 \pm 53.99	162.60 \pm 59.64	60.49 \pm 11.52
T _{max} (h)	0.58 \pm 0.20	0.58 \pm 0.20	0.75 \pm 0.42
T _{1/2} (h)	9.53 \pm 5.49	14.59 \pm 2.37	7.99 \pm 3.71
Cl/F (L.h ⁻¹)	13.93 \pm 9.08	4.73 \pm 3.05	15.21 \pm 4.04
Vd/F (L)	171.64 \pm 116.77	107.12 \pm 92.15	159.37 \pm 59.85

Table 13. Analyses of hepatic impairment's effect on pitavastatin PK

Parameter	Cmax	AUCt	AUCinf
Statistic	p = 0.010 (S)	p = 0.003 (S)	p = 0.002 (S)
90% CI A/HV	0.74 – 1.90	0.71 – 2.28	0.74 – 2.21
90% CI B/HV	1.54 – 3.96	2.04 – 6.52	2.05 – 6.11
90% CI A/B	1.30 – 3.33	1.60 – 5.12	1.60 – 5.12
Ratio A/HV	1.34	1.60	1.57
Ratio B/HV	2.69	3.93	3.75
Ratio A/B	0.50	0.41	0.42

Table 14. Pitavastatin lactone PK parameters for groups of varying liver function

PK Parameter (unit)	Hepatic Function Group		
	Child-Pugh A (N= 6)	Child-Pugh B (N= 6)	Healthy (N= 6)
Mean \pm SD	Mean \pm SD	Mean \pm SD	Mean \pm SD
AUC _t (ng.h.mL ⁻¹)	116.25 \pm 41.84	92.99 \pm 33.26	139.10 \pm 97.23
AUC _{inf} (ng.h.mL ⁻¹)	136.95 \pm 43.58	120.41 \pm 33.16	171.69 \pm 100.98
C _{max} (ng.mL ⁻¹)	19.84 \pm 6.11	10.59 \pm 4.41	22.09 \pm 10.82
T _{max} (h)	1.08 \pm 0.58	1.33 \pm 0.61	1.08 \pm 0.20
T _{1/2} (h)	10.96 \pm 3.76	13.37 \pm 3.15	15.74 \pm 14.76

Table 15. Analyses of hepatic impairment's effect on pitavastatin lactone PK

Parameter	Cmax	AUCt	AUCinf
Statistic	p = 0.008 (S)	p = 0.488 (NS)	p = 0.510 (NS)
90% CI A/HV	0.64 – 1.37	0.57 – 1.44	0.57 – 1.28
90% CI B/HV	0.33 – 0.71	0.46 – 1.16	0.51 – 1.14
90% CI A/B	0.35 – 0.75	0.51 – 1.28	0.60 – 1.33
Ratio A/HV	0.90	0.84	0.80
Ratio B/HV	0.48	0.67	0.70
Ratio A/B	1.87	1.25	1.14

The ratio of pitavastatin C_{max} between patients with moderate hepatic impairment (Child-Pugh grade B) and healthy volunteers is 2.69. The ratio of pitavastatin AUC_{inf} between patients with moderate hepatic impairment and healthy volunteers is 3.75. The ratio of pitavastatin C_{max} between patients with mild hepatic impairment (Child-Pugh grade A) and healthy volunteers is 1.34. The ratio of pitavastatin AUC_{inf} between patients with mild hepatic impairment and healthy volunteers is 1.57. Mean pitavastatin $t_{1/2}$ for moderate hepatic impairment, mild hepatic impairment, and healthy is 14.59, 9.53, and 7.99 hours, respectively. Hui et al. published Study –HK’s results [*Br J Clin Pharmacol* 59:291-7 (2004)].

The pitavastatin C_{max} and AUC_t and pitavastatin lactone C_{max} and AUC_t ’s 90% CIs (A/HV and B/HV) were mislabeled in the sponsor’s Table 7.3 of page 69/920 and Table 7.6 of page 72/920 as 90% CI HV/A and 90% CI HV/B.

This reviewer did not review Study -16 since it concerns the effect of fatty liver on pitavastatin PK. Fatty liver is a milder form of liver disorder than mild hepatic impairment and is not recommended to be studied per the Hepatic Guidance

[<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf>].

2.3.2 Does renal impairment affect pitavastatin PK?

Study 1.24 examined the PK upon receiving an oral 4 mg pitavastatin tablet after a 4-hour fast in:

- 10 healthy participants (glomerular filtration rate [GFR] > 80 mL/min)
- 10 moderately impaired renal patients (GFR 30 – < 50 mL/min)
- 11 patients on maintenance hemodialysis.

Participants were Caucasian men and women. Classification of renal function groups was per the EMEA Renal Guidance. Serial plasma and urine samples were collected predose and for 48 hours postdose to assess pitavastatin and its lactone PK. Plasma and urine concentrations of pitavastatin and its lactone were determined via LC/MS/MS assays. Pitavastatin plasma protein binding was assessed predose and 48 hours postdose for all participants via equilibrium dialysis. The end stage renal disease patients received a predose hemodialysis in the morning and then at 48 – 72 hours postdose; they received the dose at about 13:00.

Figure 22 (left). Mean plasma pitavastatin concentrations vs. time plots. Figure 23 (right). Mean plasma pitavastatin lactone concentrations vs. time plots.

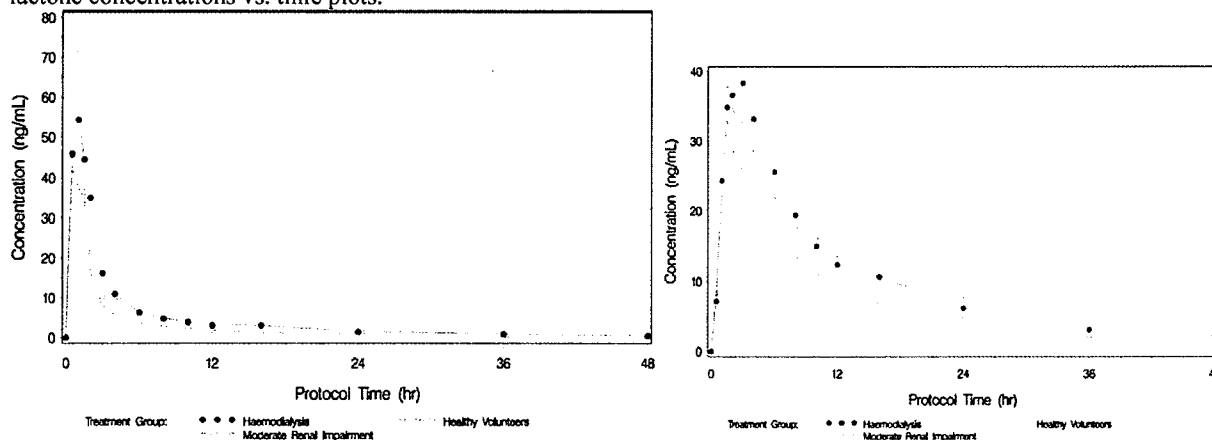


Table 16. Pitavastatin PK analyses.

	N	Haemodialysis Group			Moderate Renal Impairment Group			Healthy Volunteer Group
		LS Geometric Mean	Ratio versus control	90% CI	LS Geometric Mean	Ratio versus control	90% CI	LS Geometric Mean
C_{max} (ng/mL)	30	73.5758	1.4048	0.9464, 2.0852	83.6410	1.5969	1.0758, 2.3705	52.3760
AUC_{0-t} (ngh/mL)	30	190.2320	1.7337	1.2233, 2.4573	196.5627	1.7914	1.2640, 2.5391	109.7229
AUC_{0-inf} (ngh/mL)	24	232.7430	1.8625	1.1987, 2.8940	224.2897	1.7949	1.1867, 2.7148	124.9619
CL/F (mL/min)	24	286.4390	0.5369	0.3455, 0.8343	297.2346	0.5571	0.3684, 0.8427	533.4959

Pitavastatin C_{max} is 40 and 60% higher for the hemodialysis patients vs. healthy participants and moderately impaired renal patients vs. healthy participants, respectively. Pitavastatin AUC_{0-t} is 73 and 79% higher for the hemodialysis patients vs. healthy participants and moderately impaired renal patients vs. healthy participants, respectively. Pitavastatin AUC_{0-inf} is 86 and 79% higher for the hemodialysis patients vs. healthy participants and moderately impaired renal patients vs. healthy participants, respectively.

Table 17. Pitavastatin lactone PK analyses.

	N	Haemodialysis Group			Moderate Renal Impairment Group			Healthy Volunteer Group
		LS Geometric Mean	Ratio versus control	90% CI	LS Geometric Mean	Ratio versus control	90% CI	LS Geometric Mean
C_{max} (ng/mL)	30	42.7003	1.2848	1.0030, 1.6456	41.2611	1.2414	0.9692, 1.5902	33.2362
AUC_{0-t} (ngh/mL)	30	413.6865	1.3047	0.9803, 1.7365	477.2115	1.5051	1.1309, 2.0032	317.0625
AUC_{0-inf} (ngh/mL)	29	417.8627	1.2119	0.9282, 1.5824	537.3014	1.5583	1.2020, 2.0203	344.7898

Pitavastatin lactone C_{max} is 28 and 24% higher for the hemodialysis patients vs. healthy participants and moderately impaired renal patients vs. healthy participants, respectively. Pitavastatin lactone AUC_{0-t} is 30 and 51% higher for the hemodialysis patients vs. healthy participants and moderately impaired renal patients vs. healthy participants, respectively. Pitavastatin lactone AUC_{0-inf} is 21 and 56% higher for the hemodialysis patients vs. healthy participants and moderately impaired renal patients vs. healthy participants, respectively.

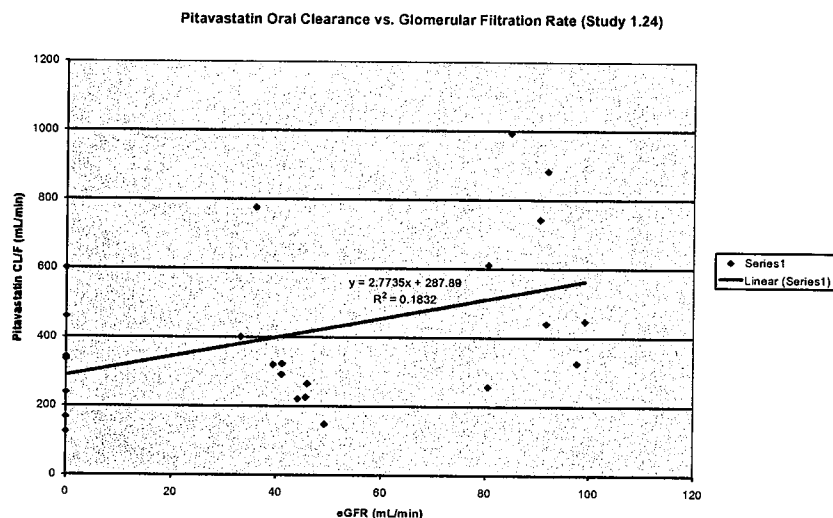
Table 18. Mean (SD) Unbound fraction of pitavastatin in plasma.

	Hemodialysis Patients	Moderately Impaired Renal Patients	Healthy Participants
% unbound, fu	0.55 (0.158)	0.405 (0.087)	0.414 (0.087)

Hemodialysis patients show 33 and 36% increase in mean unbound fraction of pitavastatin as compared to healthy participants and moderately impaired renal patients, respectively.

The sponsor claimed that Study 1.24 is of the reduced or staged design per the EMEA's and FDA's renal Guidances. However, these Guidances recommend studying participants of extreme renal functions (healthy vs. severely impaired). If these results confirm that renal impairment does not alter the drug's PK to a clinically relevant extent, no further study is warranted. Otherwise, patients with mild and moderate renal impairment should also be studied.

Figure 24. Pitavastatin oral clearance vs. renal function status



Only 0.42% of the dose is excreted in healthy volunteers' urine as unchanged pitavastatin. Thus, the pitavastatin urine PK data have limited utility in understanding the overall pitavastatin exposure and will not be further discussed.

The end stage renal disease patients' CL/F values are higher than that of linear decline from the moderate renally impaired patients' CL/F values (intact nephron theory), which may be due to:

- A study design artifact since the predose hemodialysis might remove uremic mediators (which inhibit metabolism and transporters) with subsequent increase in pitavastatin glucuronidation and transport. Chronic renal failure patients' zidovudine (primarily metabolized via UGT2B7) AUC doubled vs. healthy (Driesbach and Lertora. *Expert Opin Drug Metab Toxicol* 4:1065-74 [2008]). Uremic mediators in chronic renal failure rats inhibit liver OATP1B1 activity (Sun et al. *Pharmacol Ther* 109:1-11 [2006]; Naud et al. *Drug Metab Dispos* 36:124-28 [2008]).
- A decrease in oral bioavailability, F. Furosemide F is reduced to 43 – 46% from 47 – 70% in end-stage renal disease patients (DRUGDEX Evaluations®, Furosemide, May 04, 2009 ed). The furosemide F reduction may be due to a decrease in reserve length for absorption (A.J. Atkinson *Principles of Clinical Pharmacology*, Chapter 4, 2nd ed. 2007, Academic Press). Hypertensive patients with normal renal function absorbed 87% of an oral pindolol dose but chronic renal failure patients absorbed 52% of an oral pindolol dose. (DRUGDEX Evaluations®, Pindolol, May 18, 2009 ed).

The sponsor used the MDRD equation [Levey et al. *Ann Intern Med* 130:461-70 (1999)], that may be outdated, to estimate participants' renal function (GFR) status. This reviewer used the MDRD equation per the National Kidney Foundation [<http://www.kidney.org/professionals/KLS/gfr.cfm>] to estimate participants' GFR and found that patients with moderate renal impairment had GFR between 30 – 50 mL/min/1.732 m² and healthy participants had GFR > 80 mL/min/1.732 m², which are consistent with Study 1.24's inclusion criteria.

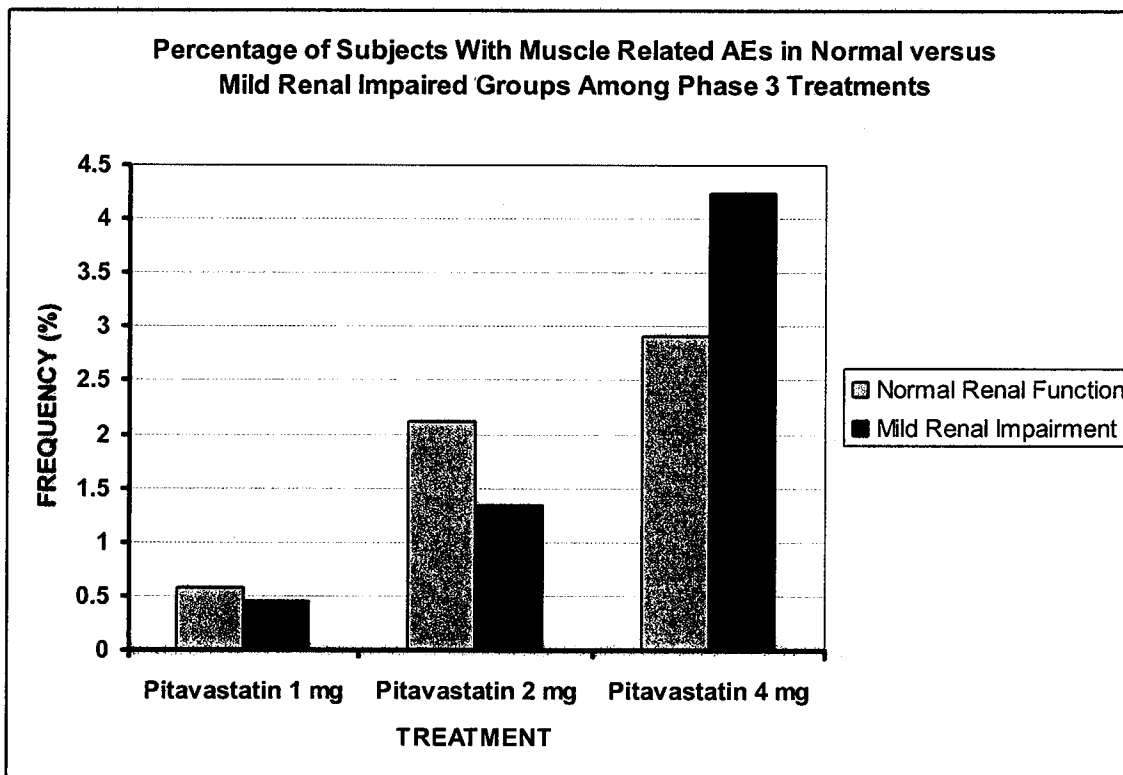
In general, renal impairment leads to increase in statin exposure which may lead to increased safety concern. In the absence of pitavastatin exposure under mild renal impairment, we focused on analyzing the effect of mild renal impairment on the safety of pitavastatin particularly muscle adverse events as compared to those of normal renal function. Drs. Manoj Khurana and Justin Earp performed the evaluation of effect of renal impairment on muscle related adverse events in pitavastatin treated subjects per the data from Phase 3 clinical studies.

The existing Phase 3 studies' data were evaluated to assess the following:

- What is the distribution of subjects with different degrees of renal function in the pooled data?
- What is the distribution of subjects who experienced any muscle related adverse effects (AEs: blood creatine phosphokinase elevation, myalgia and rhabdomyolysis) among Phase 3 pitavastatin treatments and among groups with different degrees of renal function?

There were in total 3577 subjects for whom renal function category was determined based on the MDRD equation. There were 449 subjects with mild renal impairment and 2 subjects with moderate renal impairment. In light of the observed relationship between pitavastatin dose and muscle related AEs, the data was analyzed to determine the frequencies of subjects with and without muscle AEs by renal function and treatment groups. Figure 25 below presents the percentage of subjects with muscle related AEs in Normal versus Mild Renal Impaired groups among the various Phase 3 treatments. The two subjects (one each in 2 and 4 mg Pitavastatin groups) with moderate renal impairment did not have any muscle related AEs.

Figure 25. Percentage of Subjects With Muscle Related AEs in Normal versus Mild Renal Impaired Groups Among Phase 3 Treatments



Renal Function (N)	Frequency of Muscle Related AEs n (%)		
	Pitavastatin 1 mg	Pitavastatin 2 mg	Pitavastatin 4 mg
Mild Impairment (N=449)	2 (0.45)	6 (1.34)	19 (4.23)
Normal (N=3126)	18 (0.58)	66 (2.11)	91 (2.91)

Conclusions:

1. Dose dependent increase in frequency of subjects with muscle related AEs is evident in normal as well as mild renal impairment groups.

2. Within each treatment, mild renal impairment group showed similar percentage of subjects with muscle related AEs in comparison to that of the normal renal function group.

Per the analysis above, clinical pharmacology recommends that the sponsor does not need to further study the effect of mild renal impairment on pitavastatin pharmacokinetics.

Steady-state plasma rosuvastatin concentration in patients receiving chronic hemodialysis were about 50% higher than that of healthy volunteers (despite mild and moderate renal impairment have no influence on rosuvastatin as well as severe renal impairment shows up to a 3 fold increase in rosuvastatin AUC as compared to that of healthy volunteers). See rosuvastatin Clinical Pharmacology review [http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-366_Crestor_BioPharmr.pdf].

Pitavastatin shares many metabolic, excretory, and transporter properties that rosuvastatin has. Pitavastatin shows an 86% increase in exposure (AUC) in patients requiring hemodialysis (despite timing/design may not be optimal) as compared with that of the healthy volunteers. Knowing rosuvastatin's renal impairment data, we may not learn more information if the sponsor were to conduct another pitavastatin hemodialysis study that has a "better" timing/design (rosuvastatin was dosed 24 hours before hemodialysis). Thus, Clinical Pharmacology does not recommend further study for the effect of "end stage renal disease receiving hemodialysis" on pitavastatin pharmacokinetics.

Clinical Pharmacology does not recommend the sponsor to conduct a study for the effect of severe renal impairment ($\text{GFR} < 30 \text{ mL/min/1.732 m}^2$) on pitavastatin pharmacokinetics as Post Marketing Requirement because:

- It may be difficult to recruit patients with severe renal impairments, especially those who have $\text{GFR} < 15 \text{ mL/min/1.732 m}^2$ and not yet on hemodialysis whom will soon require hemodialysis. The current thinking is that such patients may not be recommended to study.
- The labeling will recommend contraindication to the use of pitavastatin in patients with severe renal impairment.

2.3.3 Do gender, age, and race affect pitavastatin PK?

Study -1.22US examined the effect of gender, age, and race on pitavastatin and its lactone's PK in 48 healthy participants. This is a single-dose, parallel, and open-label study with the following 4 treatment cohorts:

- 12 elderly men (≥ 65 years of age)
- 12 elderly women (≥ 65 years of age)
- 12 nonelderly men (18 – 45 years of age)
- 12 nonelderly women (18 – 45 years of age)

Each cohort has 6 Caucasian and 6 African Americans to balance race. Each participant fasted for 10 hours before they orally received a 4 mg pitavastatin tablet. Serial plasma samples were collected predose and 72 hours postdose to determine pitavastatin and its lactone via a validated LC/MS/MS bioanalytical assay.

Figure 26 (left). Mean plasma pitavastatin concentrations vs. time plots with respect to gender. Figure 27 (right). Mean plasma pitavastatin lactone concentrations vs. time plots with respect to gender.

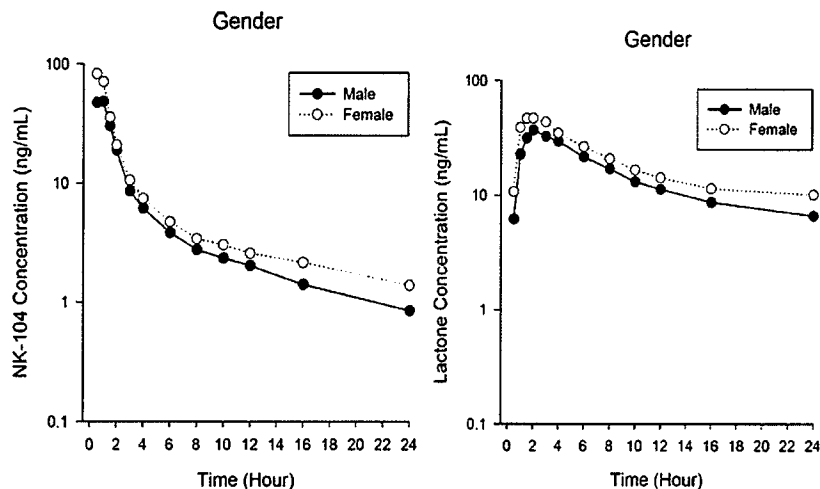


Figure 28 (left). Mean plasma pitavastatin concentrations vs. time plots with respect to age. Figure 29 (right). Mean plasma pitavastatin lactone concentrations vs. time plots with respect to age.

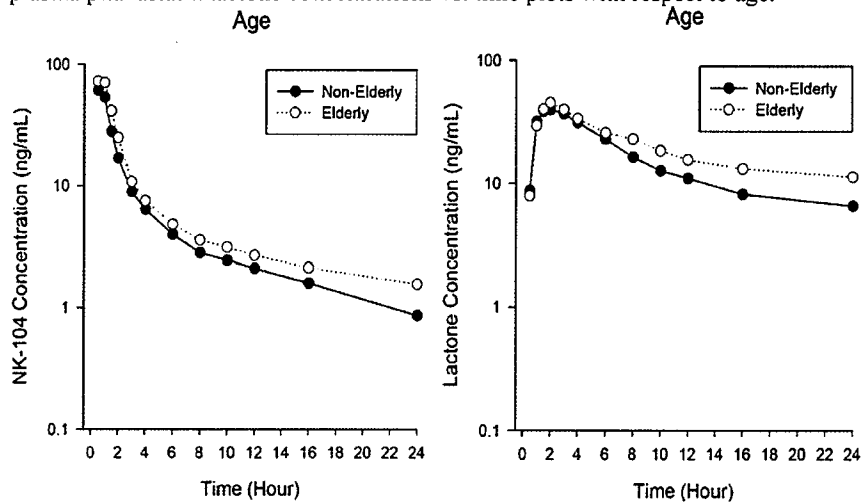


Figure 30 (left). Mean plasma pitavastatin concentrations vs. time plots with respect to race. Figure 31 (right). Mean plasma pitavastatin lactone concentrations vs. time plots with respect to race.

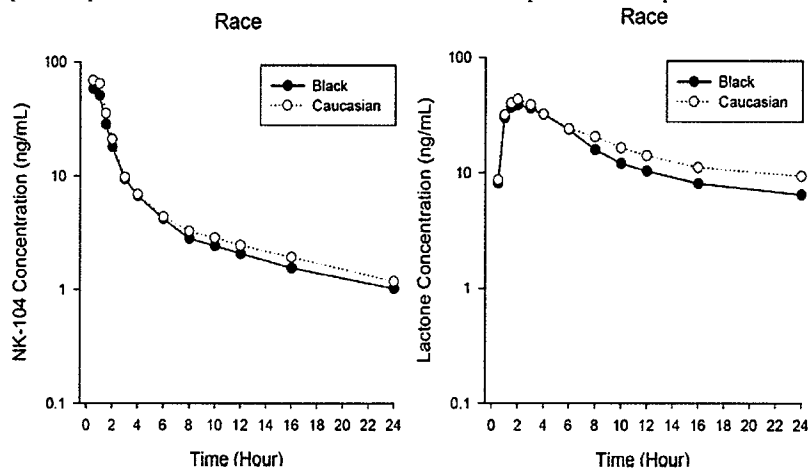


Table 19. Pitavastatin and its lactone PK parameters by gender.

Parameter	Geometric Mean (CV%)			
	NK-104		NK-104 Lactone	
	Male N=19	Female N=19	Male N=19	Female N=19
C_{max} (ng/mL)	54.56 (54.81)	87.50 (37.93)	37.19 (24.01)	49.15 (31.39)
T_{max} (hour)	0.75 (41.9)	0.67 (35.7)	2.29 (28.0)	1.88 (28.2)
T_{max} (hour) ^a	1.00 (0.50-1.50)	0.50 (0.50-1.00)	2.00 (1.50-4.00)	2.00 (1.00-3.00)
AUC_{0-1} (ng•hr/mL)	117.07 (62.24)	175.61 (42.72)	424.76 (35.58)	581.46 (43.87)
AUC_{0-72} (ng•hr/mL)	132.74 (57.04)	200.21 (37.79)	441.29 (33.21)	598.31 (41.92)
AUC_{0-inf} (ng•hr/mL)	134.22 (57.66)	207.28 (38.36)	455.02 (34.56)	624.91 (44.63)
AUC%	11.75 (41.44)	13.14 (56.88)	6.42 (27.87)	6.39 (40.72)
K_{el} (hr ⁻¹)	0.0796 (51.57)	0.0489 (54.51)	0.0500 (23.07)	0.0454 (21.20)
$t_{1/2}$ (hour)	8.71 (48.79)	14.18 (50.29)	13.87 (22.94)	15.27 (20.97)
CL/F (L/hr)	29.80 (39.98)	19.30 (39.79)	—	—
V_d/F (L)	374.6 (45.63)	394.9 (45.52)	—	—
MRT_{0-1} (hour)	7.67 (46.09)	10.88 (56.25)	17.35 (19.73)	19.42 (24.81)

Table 20. Pitavastatin and its lactone PK parameters by age.

Parameter	Geometric Mean (CV%)			
	NK-104		NK-104 Lactone	
	Non-Elderly N=24	Elderly N=14	Non-Elderly N=24	Elderly N=14
C_{max} (ng/mL)	64.63 (43.17)	77.48 (51.86)	41.69 (30.56)	44.65 (35.19)
T_{max} (hour)	0.67 (35.5)	0.79 (42.4)	2.03 (28.0)	2.16 (32.3)
T_{max} (hour) ^a	0.50 (0.50-1.00)	1.00 (0.50-1.50)	2.00 (1.00-3.00)	2.00 (1.50-4.00)
AUC_{0-1} (ng•hr/mL)	129.48 (46.17)	170.78 (54.43)	439.33 (34.01)	613.93 (44.62)
AUC_{0-72} (ng•hr/mL)	148.39 (42.70)	191.55 (50.04)	457.01 (32.22)	628.18 (42.93)
AUC_{0-inf} (ng•hr/mL)	151.70 (43.92)	196.25 (50.77)	470.53 (32.71)	660.79 (45.64)
AUC%	12.76 (54.90)	11.87 (42.89)	6.29 (32.28)	6.62 (39.00)
K_{el} (hr ⁻¹)	0.0671 (56.92)	0.0550 (59.28)	0.0502 (19.32)	0.0435 (26.71)
$t_{1/2}$ (hour)	10.33 (65.40)	12.60 (41.92)	13.80 (21.32)	15.94 (20.86)
CL/F (L/hr)	26.37 (41.70)	20.38 (53.89)	—	—
V_d/F (L)	393.1 (43.19)	370.5 (50.00)	—	—
MRT_{0-1} (hour)	8.45 (67.30)	10.43 (40.71)	16.87 (18.55)	21.21 (21.87)

Table 21. Pitavastatin and its lactone PK parameters by race.

Parameter	Geometric Mean (CV%)			
	NK-104		NK-104 Lactone	
	Black N=14	Caucasian N=24	Black N=14	Caucasian N=24
C_{max} (ng/mL)	58.38 (45.12)	76.23 (47.93)	38.97 (42.10)	45.13 (26.76)
T_{max} (hour)	0.69 (43.4)	0.72 (38.2)	2.11 (26.4)	2.05 (31.8)
T_{max} (hour) ^a	0.50 (0.50-1.50)	0.75 (0.50-1.50)	2.00 (1.50-3.00)	2.00 (1.00-4.00)
AUC_{0-1} (ng•hr/mL)	130.66 (48.89)	151.37 (54.73)	427.29 (42.43)	542.76 (43.61)
AUC_{0-72} (ng•hr/mL)	152.96 (44.50)	169.20 (50.75)	444.78 (39.66)	558.97 (41.74)
AUC_{0-inf} (ng•hr/mL)	158.99 (45.67)	171.52 (51.95)	458.67 (39.96)	582.21 (44.82)
$AUC\%$	15.01 (56.64)	11.12 (31.23)	6.39 (35.33)	6.42 (35.15)
K_{el} (hr ⁻¹)	0.0547 (79.04)	0.0673 (45.18)	0.0491 (15.82)	0.0468 (26.12)
$t_{1/2}$ (hour)	12.68 (61.65)	10.29 (44.31)	14.11 (16.52)	14.82 (24.46)
CL/F (L/hr)	25.16 (50.02)	23.32 (44.09)	-	-
V_d/F (L)	460.2 (51.21)	346.4 (24.68)	-	-
MRT_{0-1} (hour)	10.62 (62.58)	8.36 (42.59)	17.20 (16.95)	19.07 (24.96)

Table 22. Pitavastatin PK parameters analyses.

Parameter	Test	Reference	LS Mean		Ratio ^a	90% CI
			Test	Reference		Lower-Upper
C_{max}	Female	Male	85.98	53.62	1.60	1.28-2.01
AUC_{0-1}	(n=19)	(n=19)	180.33	120.22	1.50	1.19-1.89
AUC_{0-72}			206.63	137.01	1.51	1.21-1.88
AUC_{0-inf}			215.13	139.30	1.54	1.23-1.94
C_{max}	Elderly	Non-elderly	71.33	64.63	1.10	0.86-1.42
AUC_{0-1}	(n=14)	(n=24)	167.43	129.48	1.29	1.00-1.68
AUC_{0-72}			190.79	148.39	1.29	1.01-1.64
AUC_{0-inf}			197.55	151.70	1.30	1.01-1.67
C_{max}	Black	Caucasian	60.48	76.23	0.79	0.62-1.02
AUC_{0-1}	(n=14)	(n=24)	143.22	151.37	0.95	0.73-1.23
AUC_{0-72}			167.32	169.20	0.99	0.77-1.27
AUC_{0-inf}			174.72	171.52	1.02	0.79-1.31

Table 23. Pitavastatin lactone PK parameters analyses.

Parameter	Test	Reference	LS Mean		Ratio ^a	90% CI
			Test	Reference		Lower-Upper
C_{max}	Female	Male	48.37	36.60	1.32	1.15-1.52
AUC_{0-1}	(n=19)	(n=19)	592.93	433.13	1.37	1.15-1.63
AUC_{0-72}			609.38	449.46	1.36	1.15-1.60
AUC_{0-inf}			637.97	464.53	1.37	1.15-1.64
C_{max}	Elderly	Non-elderly	42.47	41.69	1.02	0.87-1.19
AUC_{0-1}	(n=14)	(n=24)	584.58	439.33	1.33	1.09-1.62
AUC_{0-72}			599.31	457.01	1.31	1.09-1.58
AUC_{0-inf}			629.83	470.53	1.34	1.10-1.63
C_{max}	Black	Caucasian	39.23	45.13	0.87	0.75-1.01
AUC_{0-1}	(n=14)	(n=24)	473.18	542.76	0.87	0.72-1.06
AUC_{0-72}			489.99	558.97	0.88	0.73-1.06
AUC_{0-inf}			509.02	582.21	0.87	0.72-1.06

The pitavastatin C_{max} geometric mean ratio of women to men as well as that of AUC_{0-inf} is 1.60 and 1.54, respectively. The pitavastatin C_{max} geometric mean ratio of elderly to nonelderly as well as that

of AUC_{0-inf} is 1.10 and 1.30, respectively. The pitavastatin C_{max} geometric mean ratio of African American to Caucasian American as well as that of AUC_{0-inf} is 0.79 and 1.02, respectively.

The pitavastatin lactone C_{max} geometric mean ratio of women to men as well as that of AUC_{0-inf} is 1.32 and 1.37, respectively. The pitavastatin lactone C_{max} geometric mean ratio of elderly to nonelderly as well as that of AUC_{0-inf} is 1.02 and 1.34, respectively. The pitavastatin lactone C_{max} geometric mean ratio of African American to Caucasian American as well as that of AUC_{0-inf} is 0.87 and 0.87, respectively.

Nakaya et al. examined a 2 mg pitavastatin once daily dose for 5 days in 11 healthy Japanese men (6 of 65 – 71 years old and 5 of 22 – 24 years old) and claimed that pitavastatin and its lactone PK do not significantly differ between the elderly and nonelderly groups [*Rinsho Iyaku* 17:957-70 (2001)].

Study 1.35 examined the pitavastatin PK between Japanese and Euroid men as well as the relative bioavailability between the Japanese formulation (JP) and the European formulation (EU) of the 2 mg pitavastatin tablets. This was a single-dose, randomized, 2-period, 2-sequence balanced crossover study in 60 healthy men (48 Euroid of 18 – 41 years old and 12 Japanese of 22 – 30 years old). Twenty four Euroid and 6 Japanese orally received a 2 mg pitavastatin JP and then 2 mg pitavastatin EU as 1 sequence and another 24 Euroid and 6 Japanese received 2 mg pitavastatin EU and 2 mg pitavastatin JP tablets in another sequence. All drug administration was under fasted state. A ≥ 7 days washout separated the 2 pitavastatin doses. Serial plasma samples were collected predose and 48 hours postdose to determine pitavastatin and its lactone via a validated LC/MS/MS bioanalytical assay.

Since JP is the marketed Japanese formulation and EU is the European Clinical Investigation formulation, their pitavastatin relative bioavailability may not be relevant to this NDA. Thus their results are not discussed here.

Table 24. Pitavastatin PK parameters analyses of Euroid vs. Japanese (including all formulations).

Parameter	LS geo mean (Test)	LS geo mean (Reference)	Ratio of LS geo means	LCL	UCL
C _{max} (ng/mL)	22.11	24.60	89.86	83.76	96.41
N	48	12			
AUC _{0-t} (ng*h/mL)	43.71	49.90	87.61	83.91	91.47
N	48	12			
	51.93	62.78	82.71	78.11	87.59
AUC _{0-∞} (ng*h/mL) N	29	8			

Table 25. Pitavastatin lactone PK parameters analyses of Euroid vs. Japanese (including all formulations).

Parameter	LS geo mean (Test)	LS geo mean (Reference)	Ratio of LS geo means	LCL	UCL
C _{max} (ng/mL)	17.07	17.82 1	95.78	92.72	98.94
N	48	2			
AUC _{0-t} (ng*h/mL)	150.57	152.87	98.50	95.35	101.75
N	48	12			
	164.43	167.64	98.09	94.57	101.73
AUC _{0-∞} (ng*h/mL) N	40	10			

The pitavastatin C_{max} geometric mean ratio of the Euroid to Japanese is 89.86 as well as those of AUC_{0-t} and AUC_{0-∞} are 87.61 and 82.71, respectively. Per the 90% CL of the geometric mean ratios, Euroid's pitavastatin C_{max} and AUC_{0-t} are not significantly different from those of Japanese, whereas Euroid's pitavastatin AUC_{0-∞} is significantly different from that of Japanese.

The pitavastatin C_{max} geometric mean ratio of the Euroid to Japanese is 95.78 as well as those of AUC_{0-t} and $AUC_{0-\infty}$ are 98.50 and 98.09, respectively. Per the 90% CL of the geometric mean ratios, Euroid's pitavastatin C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ are not significantly different from those of Japanese.

The sponsor defined a Euroid volunteer as a person having origins in any of the original peoples of Europe, the Middle East, or North Africa, whereas a Japanese volunteer as a person who was born in Japan; has 4 ethnic Japanese grandparents; has not lived outside Japan for > 5 years; has a Japanese passport; and speaks Japanese.

2.3.4 What population PK and PD information is in the application?

Population or model-based PK and PD data are not available in this submission.

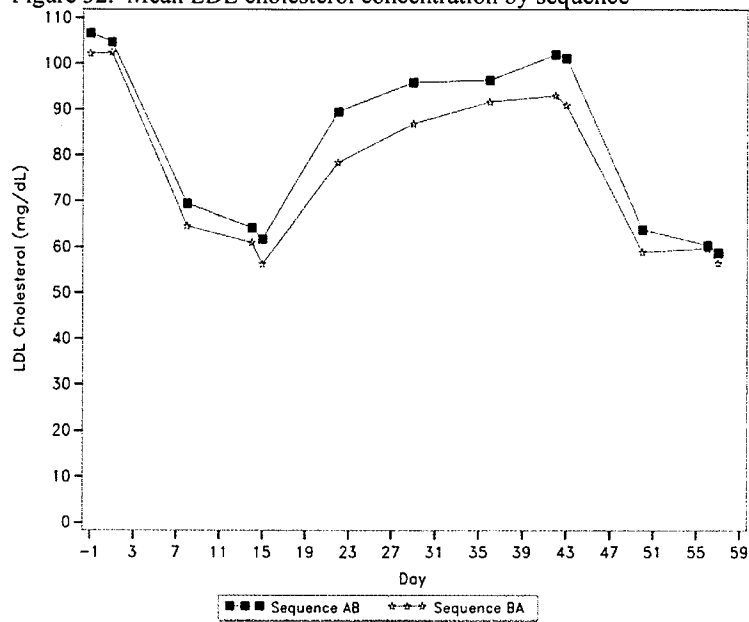
2.3.5 What pharmacogenomic information is in the application?

Pharmacogenomic information is not available in this submission.

2.3.6 Does dose timing affect pitavastatin PK and PD?

Study 1.23US examined the LDL-C lowering and pitavastatin PK dosing in the morning vs. that in the evening in 35 healthy volunteers (20 women and 15 men; 24 white, 8 African American, 2 Asian, and 1 other). This is a randomized, 3-period, crossover study. Each participant orally received a 4 mg pitavastatin tablet under fasting (10 hour predose and 2 hour postdose or 2 hour predose and 2 hour postdose) in Period -1, which was for safety assessment. In Period 1, each participant orally received a 4 mg pitavastatin tablet under fasting in the timing as they did in Period -1. In Period 2, each participant orally received a 4 mg pitavastatin tablet under fasting in the timing as they did not receive in Period 1. A 30-day washout separated each period. Blood samples were collected on Days -1, 1, 8, 14, and 15 of Period 1 and then Days 22, 29, and 36 in washout as well as Days 42, 43, 50, 56, and 57 of Period 2 to measure lipid profile. Serial plasma samples were collected predose and for 24 hours postdose on Days 14 and 56 to determine pitavastatin and its lactone via an LC/MS/MS bioanalytical assay.

Figure 32. Mean LDL cholesterol concentration by sequence



Treatment A = 4 mg pitavastatin x 14 days of am dosing

Treatment B = 4 mg pitavastatin x 14 days of pm dosing

Table 26. Pitavastatin PD parameters

Parameter (% change)	Number participants	Test (Treatment A: LSM)	Reference (Treatment B: LSM)	Difference	90% CI of the Difference (lower, upper)
LDL-C	27	-37.23	-39.96	2.728	(-1.503, 6.960)
HDL-C	27	-17.35	-17.10	-0.253	(-4.948, 4.442)
Cholesterol	27	-28.77	-31.27	2.498	(-0.320, 5.316)
Triglyceride	27	2.22	-4.58	6.798	(-5.282, 18.878)
ApoB	27	-29.69	-31.38	1.692	(-1.393, 4.777)
ApoA1	27	-9.95	-11.00	1.048	(-2.181, 4.277)

The 90% CI of the difference between am and pm pitavastatin dosing in lowering the lipids from baseline contains zero. Thus, the differences in lipid lowering are not statistically significant between am and pm pitavastatin dosing

Figure 33 (left). Mean plasma pitavastatin concentrations vs. time plots. Figure 34 (right). Mean plasma pitavastatin lactone concentrations vs. time plots.

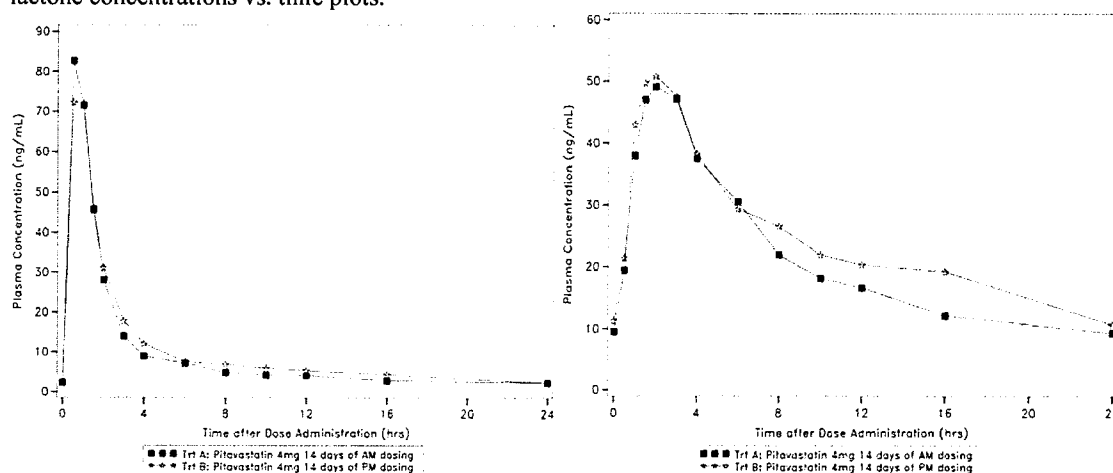


Table 27. Pitavastatin and its lactone's PK parameters.

Parameter	Treatment							
	Pitavastatin AM Dosing Geometric Mean (CV%)				Pitavastatin PM Dosing Geometric Mean (CV%)			
	n	Pitavastatin	n	Pitavastatin Lactone	n	Pitavastatin	n	Pitavastatin Lactone
AUC ₀₋₂₄ (ng·h/mL)	31	198.705 (48.3509)	31	468.801 (36.1582)	29	222.459 (47.2963)	29	539.143 (37.6835)
C _{max} (ng/mL)	31	82.307 (49.4992)	31	49.692 (33.7341)	29	84.368 (52.2558)	29	54.980 (34.5652)
T _{max} (h)	31	0.627 (0.50, 1.50)	31	2.162 (1.03, 6.00)	29	0.752 (0.50, 4.00)	29	1.750 (1.00, 4.00)
t _{1/2b,c} (h)	16	12.426 (3.7174)	26	12.920 (3.3743)	26	10.793 (1.5773)	21	11.122 (2.0206)
CL/F (L/h)	31	20.130 (41.2185)		ND	29	17.985 (47.8870)		ND
V _d /F (L)	16	320.695 (37.1384)		ND	26	271.128 (47.9024)		ND

Table 28. Pitavastatin and its lactone's PK parameters.

	Parameter	Number of subjects	Test (Treatment A)	Reference (Treatment B)	Ratio	90% CI of the Ratio (lower, upper)
Pitavastatin	AUC ₀₋₂₄ (ng·h/mL)	27	202.84	228.35	0.888	(0.828, 0.953)
	C _{max} (ng/mL)	27	84.24	89.26	0.944	(0.823, 1.082)
Pitavastatin lactone	AUC ₀₋₂₄ (ng·h/mL)	27	470.59	553.34	0.850	(0.781, 0.926)
	C _{max} (ng/mL)	27	49.43	56.04	0.882	(0.801, 0.971)

The pitavastatin C_{max} ratio in the morning vs. evening dosing as well as that of AUC₀₋₂₄ is 0.94 and 0.89, respectively. Morning vs. evening pitavastatin dosing does not significantly affect pitavastatin exposure since the 90% CI for the ratios of pitavastatin C_{max} and AUC₀₋₂₄ are within the 0.80 – 1.25 bioequivalence goalpost.

The pitavastatin lactone C_{max} ratio in the morning vs. evening dosing as well as that of AUC₀₋₂₄ is 0.88 and 0.85, respectively. Morning vs. evening pitavastatin dosing did significantly affect pitavastatin lactone AUC₀₋₂₄ since the 90% CI for its ratio of pitavastatin lactone AUC₀₋₂₄ is outside the 0.80 – 1.25 bioequivalence goalpost, whereas morning vs. evening pitavastatin dosing did not significantly affect pitavastatin lactone C_{max} since the 90% CI for its ratio of pitavastatin lactone C_{max} is within the 0.80 – 1.25 bioequivalence goalpost.

2.4 Extrinsic Factors

2.4.1 How does food affect pitavastatin calcium bioavailability (BA)?

Study 1.21US is a single-dose, randomized, 2-period, 2-sequence crossover food effect study in 34 healthy participants who received a 4 mg pitavastatin tablet (Lot number N029; SkyePharma). The high-fat breakfast content was per the Food Effect Guidance. Participants ate the breakfast starting 30 minutes prior dose administration. A washout of 14 days separated each single dose. Serial plasma samples were collected predose and postdose to determine pitavastatin and its lactone PK via LC/MS/MS analyses.

Figure 35 (left). Mean plasma pitavastatin concentrations vs. time plots. Figure 36 (right). Mean plasma pitavastatin lactone concentrations vs. time plots.

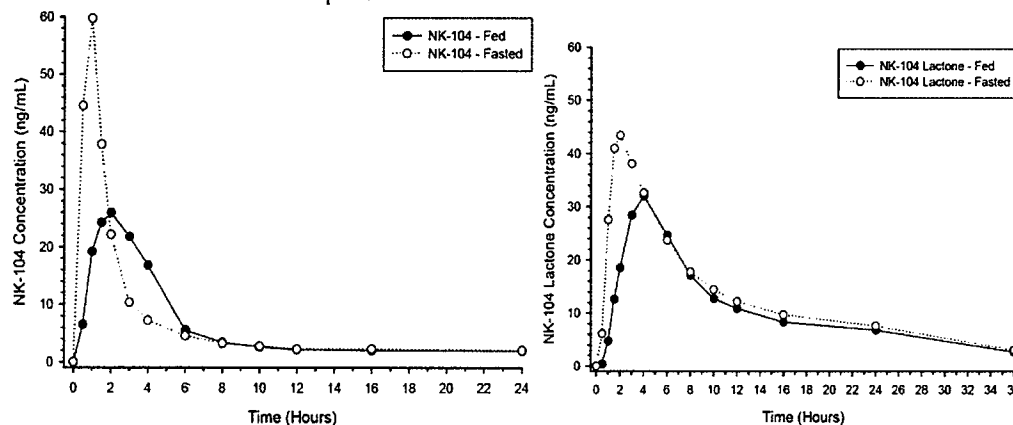


Table 29. Analyses of food effect on pitavastatin PK and its lactone PK

Analyte	Parameter	Test Fed ^a	Reference Fasted ^a	Ratio ^b	90% CI Lower-Upper
NK-104	C _{max}	33.26	58.44	56.91	50.56-64.07
	AUC _{0-t}	112.81	126.76	89.00	83.29-95.09
	AUC ₀₋₇₂	128.18	144.11	88.94	83.15-95.14
	AUC _{0-inf}	130.01	145.52	89.34	83.26-95.86
NK-104 Lactone	C _{max}	32.96	43.78	75.27	70.34-80.55
	AUC _{0-t}	382.20	464.45	82.29	78.47-86.30
	AUC ₀₋₇₂	404.01	485.91	83.15	79.68-86.76
	AUC _{0-inf}	414.81	496.15	83.61	80.02-87.36

Pitavastatin C_{max} and AUC decreased 43.1 and 11%, respectively, in the presence of a high fat meal for the 4 mg pitavastatin tablet. The 90% CI of fed to fast AUC ratios are within the 80 – 125% bioequivalence assessment, whereas that for the Cmax ratio is not.

2.4.2 What are the potential drug-drug interactions for pitavastatin calcium?

Coadministered drugs' effect on pitavastatin PK: (Hirano et al. *Drug Metab Dispos* 34:1229-36 [2006])

2.4.2.1 Cyclosporine

Study -20 examined the effect of single-dose cyclosporine on multiple-dose pitavastatin in 6 healthy Japanese men. Each fasted participant orally received a 2 mg pitavastatin tablet once daily for 6 days. On Day 6, they received an oral single dose of 2 mg cyclosporine/kg capsules an hour before pitavastatin administration under fasting conditions. Serial plasma samples were collected predose and after the daily pitavastatin doses on Day 4 for 24 hours and on Day 6 for 48 hours to determine pitavastatin and its lactone concentrations via a validated HPLC-UV bioanalytical assay.

Figure 37 (left). Mean plasma pitavastatin concentration vs. time profile. Figure 38 (right). Mean plasma pitavastatin lactone concentration vs. time profile.

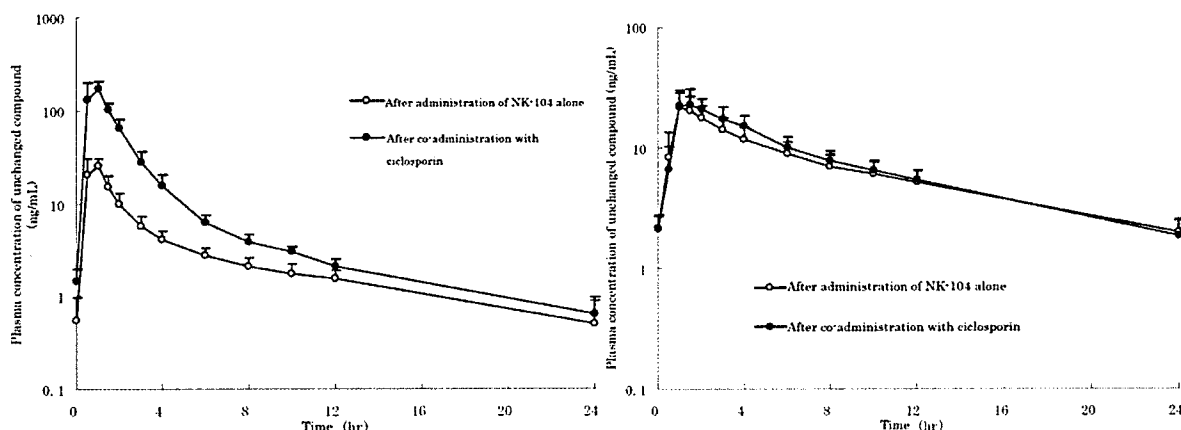


Table 30. PK parameters of pitavastatin and its lactone in plasma.

Pharmacokinetic parameter		After administration of NK-104 alone (Day 4)		After co-administration with ciclosporin (Day 6)		One-sample t-test	
		mean	(SD)	mean	(SD)	t value	P value
Unchanged compound	C _{max}	(ng/mL)	27.62 (7.28)	179.27 (33.23)		14.019	0.000**
	AUC ₀₋₂₄	(ng·hr/mL)	76.87 (17.61)	347.03 (70.20)		25.462	0.000**
	T _{max}	(hr)	0.92 (0.20)	0.75 (0.27)		-1.581	0.175
	T _{1/2}	(hr)	8.50 (2.73)	6.60 (1.55)		-1.869	0.121
	MRT ₀₋₂₄	(hr)	4.598 (1.065)	2.638 (0.297)		—	—
	Clp/F	(L/hr)	27.43 (7.60)	5.93 (1.11)		—	—
	Vd/F	(L)	315.57 (70.91)	56.48 (16.74)		—	—
Lactone	C _{max}	(ng/mL)	22.72 (6.98)	24.22 (8.25)		1.000	0.363
	AUC ₀₋₂₄	(ng·hr/mL)	162.75 (40.09)	179.25 (36.94)		3.482	0.018*
	T _{max}	(hr)	1.17 (0.26)	1.50 (0.45)		1.581	0.175
	T _{1/2}	(hr)	8.97 (1.40)	7.83 (1.79)		-3.083	0.027*
	MRT ₀₋₂₄	(hr)	7.558 (0.343)	7.270 (0.660)		—	—

* : P < 0.05, ** : P < 0.01

Table 31. Pitavastatin PK parameters ratios in the presence and absence of cyclosporine as well as those for its lactone in plasma.

Pharmacokinetic parameter		Ratio	(90% CI)	Min	Max	
Unchanged compound	C _{max}	(ng/mL)	6.581	(5.020~8.628)	4.430	10.357
	AUC ₀₋₂₄	(ng·hr/mL)	4.553	(4.039~5.134)	3.930	5.862
	T _{max}	(hr)	0.833	(0.587~1.050)	0.500	1.000
	T _{1/2}	(hr)	0.865	(0.536~1.018)	0.576	1.775
Lactone	C _{max}	(ng/mL)	1.057	(0.945~1.183)	0.934	1.295
	AUC ₀₋₂₄	(ng·hr/mL)	1.110	(1.045~1.179)	1.005	1.227
	T _{max}	(hr)	1.333	(0.922~1.650)	0.667	2.000
	T _{1/2}	(hr)	0.868	(0.791~0.956)	0.783	1.061

The pitavastatin C_{max} ratio in the presence and absence of cyclosporine as well as that of AUC_{0-24h} is 6.6 and 4.6, respectively. The pitavastatin lactone C_{max} ratio in the presence and absence of cyclosporine as well as that of AUC_{0-24h} is 1.1 and 1.1, respectively. Hasunuma et al. published Study -20's results [*J Clin Ther Med*19:381-89 (2003)].

Fujino et al. showed that cyclosporine inhibits OATP1B1-mediated pitavastatin uptake in *Xenopus laevis* oocytes [*Arzneim Forsch Drug Res* 54:382-8 (2004)]. Hirano et al. showed that human BCRP, MDR1, and MRP2 involve in the biliary excretion of pitavastatin via Madin-Darby canine kidney 2 cells [*Mol Pharmacol*68:800-7 (2005)]. Hirano et al. further showed that cyclosporine inhibits the OATP1B1-mediated uptake and also inhibits the MRP2, MDR1, and BCRP efflux transporters [*Drug Metab Dispos* 34:1229-36 (2006)].

	Study -20	Reviewer's Comments
Population	Healthy men	OK
Choice of substrate/interacting drugs	Cyclosporine	Per Draft Drug Interaction Guidance, cyclosporine is a recommended OATP1B1 inhibitor.
Route of administration	Oral	Relevant to pitavastatin tablet
Number of participants	6	Relative bioavailability, OK, recruitment issue for healthy volunteers to receive cyclosporine.
Dose selection	Single 2 mg cyclosporine (CyA)/kg dose on Day 6 an hour before pitavastatin dose 2 mg pitavastatin QD x 6 days	Study of colestimide and CyA [<i>Transplantation</i> 37:12-7 (2002)]; minimum maintenance dose after kidney transplantation. Single dose to protect healthy participants. Dosing CyA 1 hour before pitavastatin may prime the transporters for interaction. Usual oral pitavastatin dose.

2.4.2.2 Erythromycin

Study -1.31 examined the effect of multiple-dose erythromycin on single-dose pitavastatin in 18 healthy men (17 Caucasian and 1 Asian). This was a 2-way crossover randomized study. Each participant orally received a 500 mg erythromycin tablet 4 times daily from Days 1 to 6 and a 4 mg pitavastatin tablet on Day 4 in Treatment A. In Treatment B, each participant orally received a 4 mg pitavastatin tablet on Day 1. At least 2 days separated the 2 treatments. There were 2 treatment sequences (AB and BA). Participants received all drugs 3 hours after breakfast to minimize erythromycin's gastric irritation. Serial plasma samples were collected predose and 72 hours post the pitavastatin dose for determination of pitavastatin and its lactone via validated HPLC/MS/MS.

Figure 39. Mean plasma pitavastatin concentration-time profiles. Figure 40. Mean plasma pitavastatin lactone concentration-time profiles.

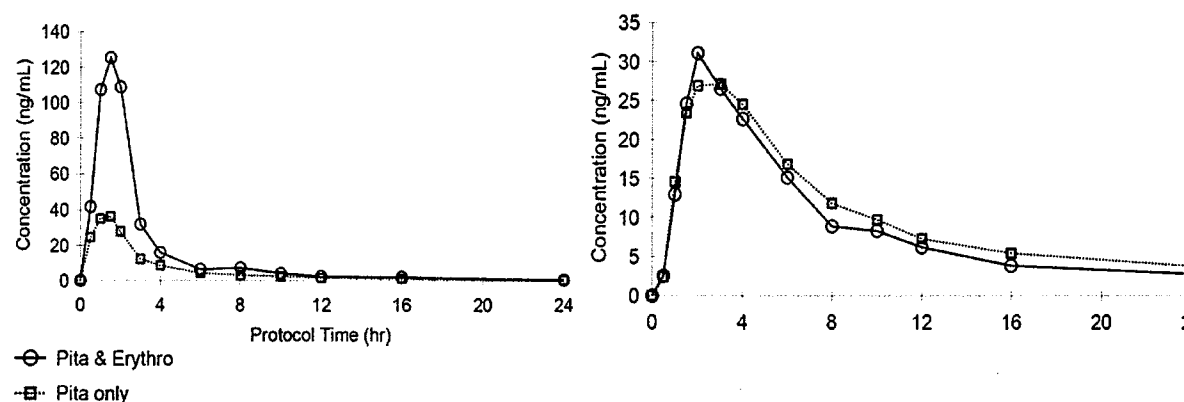


Table 32. Pitavastatin PK parameters.

Treatment Variable	Pitavastatin and erythromycin			Pitavastatin		
	Number of subjects used in analysis	Geometric Mean	CV% ¹	Number of subjects used in analysis	Geometric Mean	CV% ¹
Tmax (h)	18	1.50 ²	0.50-2.00 ³	18	1.00 ²	0.50-2.00 ³
Cmax (ng/mL)	18	181.46	29.92	18	50.11	66.62
AUC0-t (ng*h/mL)	18	310.80	31.74	18	110.34	54.26
kel (L/h)	9 ⁴	0.1327	60.07	17 ⁵	0.1055	54.68
t1/2 (h)	9 ⁴	5.22	40.09	17 ⁵	6.57	84.86
AUC0-inf (ng*h/mL)	9 ⁴	347.33	32.51	17 ⁵	124.30	53.50
Vd/F (L)	9 ⁴	86.76	36.50	17 ⁵	305.11	49.83
MRT0-t (h)	18	3.04	21.47	18	3.91	24.97
CL/F (L/h)	9 ⁴	11.52	55.90	17 ⁵	32.18	54.74

¹CV% calculated from arithmetic mean, ²Median, ³Range, ⁴9 subjects excluded due to regression coefficient of determination outside predetermined range, ⁵1 subject excluded due to regression coefficient of determination outside predetermined range.

Table 33. Pitavastatin lactone PK parameters.

Treatment Variable	Pitavastatin and erythromycin			Pitavastatin		
	Number of subjects used in analysis	Geometric Mean	CV% ¹	Number of subjects used in analysis	Geometric Mean	CV% ¹
Tmax (h)	18	2.00 ²	1.00-4.00 ³	18	2.00 ²	1.50-4.00 ³
Cmax (ng/mL)	18	32.64	26.30	18	30.33	27.59
AUC0-t (ng*h/mL)	18	239.16	29.85	18	276.38	42.05
kel (L/h)	16 ⁴	0.0615	43.51	17 ⁵	0.0567	31.76
t1/2 (h)	16 ⁴	11.28	38.44	17 ⁵	12.23	25.20
AUC0-inf (ng*h/mL)	16 ⁵	262.56	32.06	17 ⁵	305.98	40.18
MRT0-t (h)	18	9.45	22.87	18	10.81	23.12

¹CV% calculated from arithmetic mean, ²Median, ³Range, ⁴9 subjects excluded due to regression coefficient of determination outside predetermined range, ⁵1 subject excluded due to regression coefficient of determination outside predetermined range.

Table 34. Comparison of pitavastatin PK parameters

Treatment Variable	Pitavastatin	Pitavastatin and erythromycin		
	Geometric mean		Ratio of geometric means	90% CI
C _{max} (ng/mL)	50.11	181.46	3.62	2.96-4.42
AUC _{0-t} (ng*h/mL)	110.34	310.80	2.82	2.47-3.22

Table 35. Comparison of pitavastatin lactone PK parameters

Treatment	Pitavastatin	Pitavastatin and erythromycin		
Variable	Geometric mean		Ratio of geometric means	90% CI
C _{max} (ng/mL)	30.33	32.64	1.08	0.97–1.19
AUC _{0-t} (ng*h/mL)	276.38	239.16	0.87	0.79–0.95

The pitavastatin C_{max} geometric mean ratio in the presence and absence of erythromycin as well as that of AUC_{0-t} is 3.6 and 2.8, respectively. The pitavastatin lactone C_{max} geometric mean ratio in the presence and absence of erythromycin as well as that of AUC_{0-t} is 1.1 and 0.9, respectively. Seithel et al. showed that the OATP1B1- and OATP1B3- mediated uptake of pravastatin can be inhibited via increasing erythromycin concentrations [*Drug Metab Dispos* 35:779-86 (2007)].

	Study -1.31	Reviewer's Comments
Population	Healthy men	OK
Choice of substrate/interacting drugs	Erythromycin	Erythromycin is a known inhibitor for both CYP3A4 and OATP1B1.
Route of administration	Oral	Relevant to pitavastatin tablet
Number of participants	18	Relative bioavailability, OK.
Washout	≥ 2 days	Minimal. Pitavastatin t _{1/2} is ~10 hours and erythromycin t _{1/2} is 1.5 – 2 hours.
Dose selection	4 mg pitavastatin on Day 4 500 mg erythromycin QID x 6 days	Usual oral pitavastatin dose. Adult dose is 250 – 500 mg erythromycin QID for moderately to severe respiratory infection
Dose administration	Erythromycin administration 3 hours after breakfast	Per Clinical Pharmacology Online, erythromycin should be administered 1 hour or 2 hours after meals.

2.4.2.3 Gemfibrozil

Study -109 examined the effect of multiple-dose gemfibrozil and fenofibrate on multiple-dose of pitavastatin in 21 healthy participants (21 male and 3 female). Participants orally received two 2 mg pitavastatin tablets every morning from Days 1 – 6 in Period 1 and then from Days 8 – 14 in Period 2. No dosing occurred in Day 7. On Days 8 – 14, participants orally received a 600 mg gemfibrozil tablet twice daily (30 minutes before breakfast and dinner) or 160 mg fenofibrate tablet daily with breakfast. Food was restricted for 12 hours predose on Days 6, 14, and 15. Serial plasma samples were collected predose and 48 hours postdose on Days 6 and 14 as well as predose on Days 5 and 13 to determine pitavastatin and its lactone concentrations via a validated LC/MS/MS bioanalytical assay. Serial urine samples were also collected 48 hours postdose on Days 6 and 14 to determine pitavastatin lactone concentrations via a validated LC/MS/MS bioanalytical assay.

Figure 41. Pitavastatin concentration – time profile.

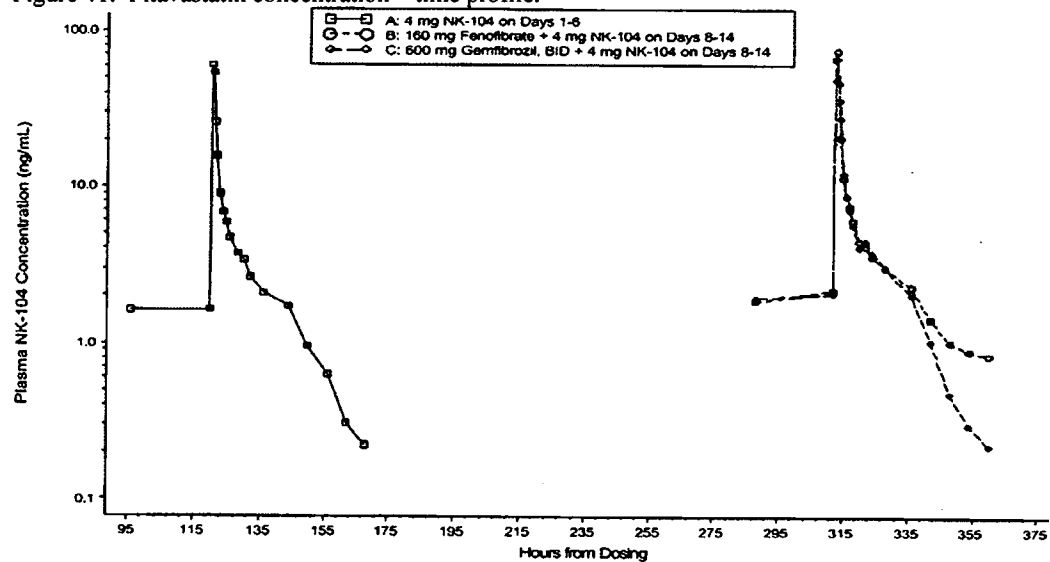


Figure 42. Pitavastatin lactone concentration – time profile.

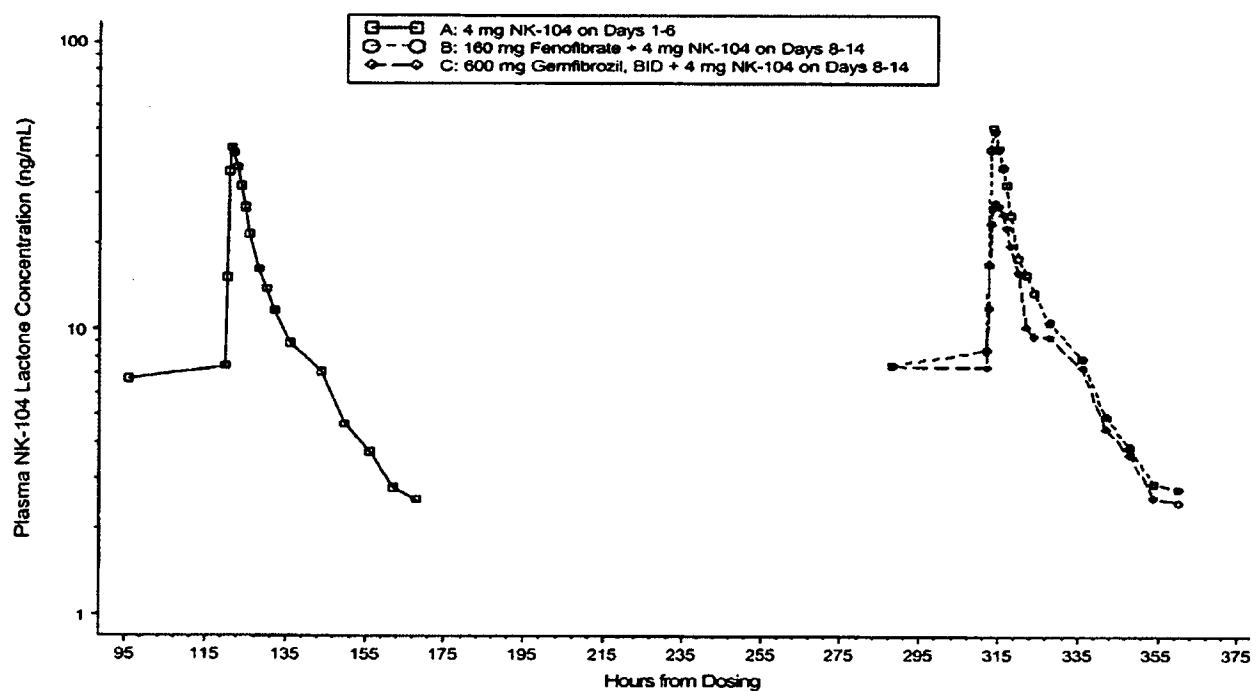


Table 36. Pitavastatin PK parameters in the presence and absence of gemfibrozil.

Plasma NK-104						
	Treatment C		Treatment A			
Pharmacokinetic	Arithmetic		Arithmetic			
Mean						
Parameters	Mean	SD	Mean	SD	90% CI*	
Ratio*						
Cmax (ng/mL)	75.00	11.67	67.70	25.52	. - .	
Cmin (ng/mL)	2.08	0.55	1.60	0.79	. - .	
Tmax (hr)	0.960	0.348	0.707	0.238	. - .	
AUC (0-24) (ng*hr/mL)	193.45	37.184	151.98	48.211	. - .	
AUC (0-48) (ng*hr/mL)	208.10	50.327	166.47	57.298	. - .	
T1/2 (hr)	14.05	4.525	18.77	8.921	. - .	
Kel (1/hr)	0.0535	0.0148	0.0447	0.0211	. - .	
ln (Cmax)	4.31	0.161	4.15	0.365	115.7-147.9	
ln (Cmin)	0.705	0.248	0.567	0.279	105.0-130.5	
ln [AUC (0-24)]	5.25	0.189	4.98	0.322	134.4-156.1	
ln [AUC (0-48)]	5.31	0.236	5.05	0.362	129.9-154.0	
Treatment C = gemfibrozil and Treatment A = pitavastatin						

Table 37. Pitavastatin lactone PK parameters in the presence and absence of gemfibrozil.

	----- Plasma NK-104 Lactone -----					
	Treatment C		Treatment A			
	Arithmetic		Arithmetic			
Pharmacokinetic					%	
Mean						
Parameters	Mean	SD	Mean	SD	90% CI*	
Ratio*						
Cmax (ng/mL)	30.43	6.64	44.74	12.13	. - .	
Cmin (ng/mL)	7.38	2.26	7.40	3.01	. - .	
Tmax (hr)	2.37	1.10	1.71	0.448	. - .	
AUC (0-24) (ng*hr/mL)	323.97	68.445	383.22	105.06	. - .	
AUC (0-48) (ng*hr/mL)	418.01	103.63	478.86	138.13	. - .	
T1/2 (hr)	18.24	4.811	18.50	6.317	. - .	
Kel (1/hr)	0.0416	0.0160	0.0413	0.0123	. - .	
ln (Cmax)	3.40	0.188	3.76	0.278	63.1- 81.7	
ln (Cmin)	1.95	0.337	1.91	0.468	82.4-107.8	
ln [AUC (0-24)]	5.76	0.234	5.91	0.293	78.3- 91.2	
ln [AUC (0-48)]	6.01	0.267	6.13	0.305	79.0- 92.1	

Treatment C = gemfibrozil and Treatment A = pitavastatin

See this review's Section 2, Question 2.6 for the ^{(b) (4)} bioanalytical issue for gemfibrozil and fenofibrate.

The pitavastatin C_{max} LS mean ratio in the presence and absence of gemfibrozil as well as that of AUC₀₋₂₄ is 1.31 and 1.45, respectively. The pitavastatin lactone C_{max} LS mean ratio in the presence and absence of gemfibrozil as well as that of AUC₀₋₂₄ is 0.72 and 0.85, respectively. Matthew et al published Study -109's abstract in [*Clin Pharmacol Ther*75:33 (2004)].

	Study -109	Reviewer's Comments
Population	Healthy men and women	OK
Choice of substrate/interacting drugs	Gemfibrozil	Gemfibrozil is a recommended in vivo CYP2C8 inhibitor per the draft Drug Interaction Guidance.
Route of administration	Oral	Relevant to pitavastatin tablet
Number of participants	21	Relative bioavailability, OK.
Washout	Day 7	Not long enough, pitavastatin $t_{1/2}$ is ~10 hours. Washout is unnecessary for a continuous sequence.
Dose selection	4 mg pitavastatin on Day 4 600 mg gemfibrozil BID x 7 days	Usual oral pitavastatin dose. Adult dose is 600 mg gemfibrozil BID to treat dyslipidemia
Dose administration	Gemfibrozil administration 30 minutes before breakfast	Per Clinical Pharmacology Online, gemfibrozil should be administered 30 minutes before meals.

2.4.2.4 Fenofibrate

Part of Study -109, thus see 2.4.2.3 above for details.

Table 38. Pitavastatin PK parameters in the presence and absence of fenofibrate.

----- Plasma NK-104 -----						
		Treatment B		Treatment A		
		Arithmetic		Arithmetic		%
Pharmacokinetic						
Mean						
Parameters		Mean	SD	Mean	SD	
Ratio*					90% CI*	

C _{max} (ng/mL)		84.33	28.63	67.70	25.52	. . .
C _{min} (ng/mL)		2.18	0.80	1.60	0.79	. . .
T _{max} (hr)		0.754	0.263	0.707	0.238	. . .
AUC (0-24) (ng*hr/mL)		197.51	55.782	151.98	48.211	. . .
AUC (0-48) (ng*hr/mL)		225.97	67.267	166.47	57.298	. . .
T _{1/2} (hr)		19.52	4.200	18.77	8.921	. . .
K _{el} (1/hr)		0.0367	0.00639	0.0447	0.0211	. . .
ln(C _{max})		4.37	0.388	4.15	0.365	98.8-125.0 111.1
ln(C _{min})		0.852	0.181	0.567	0.279	118.8-144.6 131.0
ln[AUC (0-24)]		5.24	0.315	4.98	0.322	110.1-127.0 118.2
ln[AUC (0-48)]		5.37	0.345	5.05	0.362	114.5-134.8 124.2

Treatment B = fenofibrate and Treatment A = pitavastatin

Table 39. Pitavastatin lactone PK parameters in the presence and absence of fenofibrate.

	----- Plasma NK-104 Lactone -----					
	Treatment B		Treatment A			
Pharmacokinetic	Arithmetic		Arithmetic			%
Mean						
Parameters	Mean	SD	Mean	SD	90% CI*	
Ratio*						
Cmax (ng/mL)	51.65	11.94	44.74	12.13	. - .	
Cmin (ng/mL)	8.44	2.40	7.40	3.01	. - .	
Tmax (hr)	1.63	0.231	1.71	0.448	. - .	
AUC (0-24) (ng*hr/mL)	444.15	98.681	383.22	105.06	. - .	
AUC (0-48) (ng*hr/mL)	546.74	127.40	478.86	138.13	. - .	
T1/2 (hr)	18.85	6.655	18.50	6.317	. - .	
Kel (1/hr)	0.0417	0.0169	0.0413	0.0123	. - .	
ln (Cmax)	3.92	0.231	3.76	0.278	96.0-123.0	
108.6						
ln (Cmin)	2.10	0.286	1.91	0.468	111.2-143.8	
126.4						
ln [AUC (0-24)]	6.07	0.226	5.91	0.293	106.3-123.1	
114.4						
ln [AUC (0-48)]	6.28	0.238	6.13	0.305	106.6-123.5	
114.7						

Treatment B = fenofibrate and Treatment A = pitavastatin						

The pitavastatin C_{max} LS mean ratio in the presence and absence of fenofibrate is 1.11 as well as that of AUC₀₋₂₄ is 1.18, respectively. The pitavastatin lactone C_{max} LS mean ratio in the presence and absence of fenofibrate is 1.09 as well as that of AUC₀₋₂₄ is 1.14, respectively.

The reason for gemfibrozil decreases the pitavastatin lactone exposure, whereas fenofibrate increases the pitavastatin lactone exposure is unknown.

	Study -109	Reviewer's Comments
Population	Healthy men and women	OK
Choice of substrate/interacting drugs	Fenofibrate	Fenofibrate is used to treat dyslipidemia.
Route of administration	Oral	Relevant to pitavastatin tablet
Number of participants	21	Relative bioavailability, OK.
Washout	Day 7	Not long enough, pitavastatin $t_{1/2}$ is ~10 hours. Washout is unnecessary for a continuous sequence.
Dose selection	4 mg pitavastatin on Day 4 160 mg fenofibrate QD x 7 days	Usual oral pitavastatin dose. Adult maximum dose is 160 mg fenofibrate QD to treat dyslipidemia
Dose administration	Fenofibrate administration with breakfast	Per Clinical Pharmacology Online, fenofibrate should be administered with meals to optimize bioavailability.

(b) (4)

2.4.2.6 Grapefruit Juice

Study –GJ examined the effect of multiple-dose grapefruit juice on single-dose pitavastatin in 12 healthy Chinese men. In the 1st period, each randomized participant received 200 mL of double-strength grapefruit juice or water 3 times daily for 4 days. On Day 3, each fasted participant orally received a 2 mg pitavastatin tablet in the morning. In the 2nd period, each participant repeated Period 1's procedure except they drank the test liquid that they did not drink in the 1st period and received the pitavastatin on Day 28. A 3-week washout separated the 2 periods. Serial plasma samples were collected on Days 3 and 28 at predose and 48 hours after the pitavastatin dose to determine pitavastatin and its lactone via validated HPLC/UV method.

Table 40. Pitavastatin PK parameters and pitavastatin lactone PK parameters.

NK-104			
Parameters	Water (W)	Grapefruit juice (GFJ)	Students' t-test for paired data
t_{max} (h)	0.75 (0.5-1) ^a	1 (1-2) ^a	P=0.007 ^b (S)
C_{max} (ng/ml)	38.5 ± 14.0	33.2 ± 10.1	P=0.117 (NS)
AUC ₀₋₂₄ (ng·h/ml)	84.94 ± 22.53	95.55 ± 29.45	P=0.022 (S)
AUC ₀₋₄₈ (ng·h/ml)	87.20 ± 23.47	100.78 ± 33.36	P=0.023 (S)
AUC _{0-t} (ng·h/ml)	83.04 ± 24.01	96.20 ± 33.38	P=0.025 (S)
AUC _{0-∞} (ng·h/ml)	93.71 ± 24.36	105.49 ± 34.29	P=0.037 (S)
$t_{1/2}$ (h)	9.10 ± 3.44	9.19 ± 3.37	P=0.930 (NS)
NK-104 lactone			
Parameters	Water (W)	Grapefruit juice (GFJ)	Students' t-test for paired data
t_{max} (h)	1 (1-1.5) ^a	2 (1.5-3) ^a	P=0.002 ^b (S)
C_{max} (ng/ml)	24.7 ± 7.7	21.2 ± 5.4	P=0.021 (S)
AUC ₀₋₂₄ (ng·h/ml)	155.04 ± 37.57	172.48 ± 44.75	P=0.041 (S)
AUC ₀₋₄₈ (ng·h/ml)	176.77 ± 41.82	202.51 ± 53.06	P=0.024 (S)
AUC _{0-t} (ng·h/ml)	174.10 ± 43.66	201.02 ± 54.03	P=0.025 (S)
AUC _{0-∞} (ng·h/ml)	186.16 ± 43.37	217.65 ± 54.11	P=0.016 (S)
$t_{1/2}$ (h)	12.35 ± 3.97	15.22 ± 4.57	P=0.071 (NS)

^a Median and range^b Wilcoxon signed-rank test

Table 41. Ratio and 90% confidence interval between the grapefruit juice and water treatments

Pitavastatin					
	Cmax	AUC0-24	AUC0-48	AUC0-t	AUC0-∞
	(ng/ml)	(ng·h/ml)	(ng·h/ml)	(ng·h/ml)	(ng·h/ml)
GFJ/W ratio	0.88	1.12	1.14	1.15	1.11
90%CI	0.76-1.02	1.05-1.19	1.06-1.23	1.06-1.24	1.04-1.19
Pitavastatin Lactone					
	Cmax	AUC0-24	AUC0-48	AUC0-t	AUC0-∞
	(ng/ml)	(ng·h/ml)	(ng·h/ml)	(ng·h/ml)	(ng·h/ml)
GFJ/W ratio	0.87	1.11	1.14	1.16	1.17
90%CI	0.82-0.93	1.04-1.19	1.06-1.24	1.06-1.26	1.07-1.28

The pitavastatin C_{\max} ratio in the presence and absence of double-strength grapefruit juice is 0.88 as well as that of AUC_{0-24h} is 1.12, respectively. The pitavastatin lactone C_{\max} ratio in the presence and absence of double-strength grapefruit juice is 0.87 as well as that of AUC_{0-24h} is 1.11, respectively.

Grapefruit juice can inhibit OATP1A2 and OATP2B1 in vitro, especially OATP1A2 in vivo [Kirby et al. *Clin Pharmacol Ther* 61:631-3 (2007)] besides inhibiting CYP3A and Pg-p. The minor effect of grapefruit juice on pitavastatin exposure is consistent that pitavastatin's hepatic uptake does not involve OATP1A2 and OATP2B1 but primarily involves OATP1B1 and OATP1B3 transporters. Ando et al. observed similar results as those with Study –GJ with single-strength grapefruit juice and 4 mg pitavastatin in 8 healthy Japanese men [*Br J Clin Pharmacol* 60:494-7 (2005)].

	Study -GJ	Reviewer's Comments
Population	Healthy men	OK
Choice of interacting drug	Grapefruit juice	Per the draft Drug Interaction Guidance, grapefruit juice is a moderate CYP3A inhibitor
Route of administration	Oral	Relevant to pitavastatin tablet
Number of participants	12	Relative bioavailability, OK.
Washout	3 weeks	Long enough for the recovery of CYP enzymes. Pitavastatin $t_{1/2}$ is ~10 hours.
Dose selection	2 mg pitavastatin on Days 3 and 28 200 mL double-strength grapefruit juice	Usual oral pitavastatin dose. Usual strength and volume of grapefruit juice that other researchers used.

2.4.2.7 Atazanavir

Study 1.29 examined the multiple-dose mutual interaction of atazanavir and pitavastatin in 18 healthy men (17 Caucasian and 1 Black). Each participant completed 2 treatments, A and B. A period of 5 – 7 days separated these 2 treatments. In Treatment A, each participant orally received a 4 mg pitavastatin tablet daily on Days 1 – 5. In Treatment B, each participant orally received two 150 mg atazanavir capsules daily on Days 1 – 9 and a 4 mg pitavastatin tablet daily on Days 5 – 9. Participants received all drugs 5 minutes after a light breakfast. Serial plasma samples were collected at predose (Day 4 of Treatment A and Day 8 of Treatment B) and 24 hours postdose (Day 5 of Treatment A and Day 9 of Treatment B) to determine pitavastatin and its lactone via validated HPLC/MS/MS assay. Other serial plasma samples were collected at predose (Day 3 of Treatment B) and 24 hours postdose (Days 4 and 9 of Treatment B) to determine atazanavir via validated LC/MS/MS assay.

Figure 43 (left). Plasma pitavastatin concentration – time profile. Figure 44 (right). Plasma pitavastatin lactone concentration – time profile.

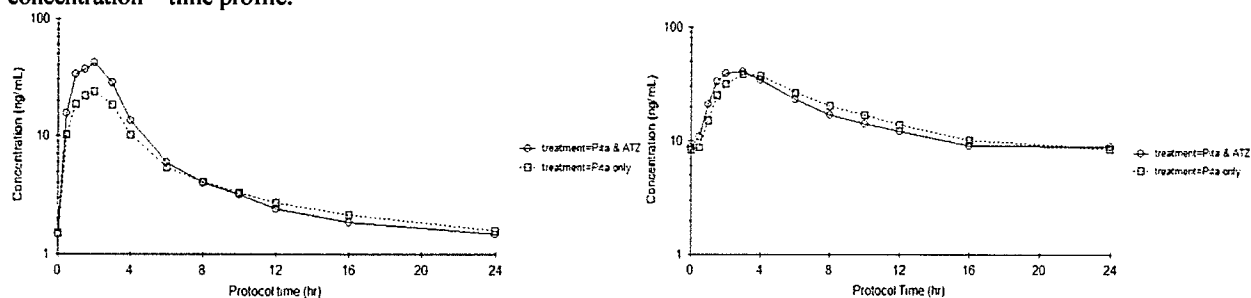


Table 42. Pitavastatin PK parameters.

Parameter	Number of subjects in Day 5 Treatment A	Day 5 Treatment A (pitavastatin) Geometric Mean	Day 5 Treatment A (pitavastatin) CV%	Number of subjects in Day 9 Treatment B	Day 9 Treatment B (pitavastatin + atazanavir) Geometric Mean	Day 9 Treatment B (pitavastatin + atazanavir) CV%
t _{max} (h)	17	1.50 ¹	0.50-3.02 ²	17	1.52 ¹	0.50-3.00 ²
C _{max} (ng/mL)	17	34.78	35.34	17	55.62	47.56
AUC _{0-τ} (ng*h/mL)	17	126.52	25.82	17	165.75	30.99
t _{1/2} (h)	11	11.87	38.21	84	14.91	73.87
V _d /F (L)	11	579.97	52.10	84	511.07	52.15
CL/F (L/h)	17	31.62	25.56	17	24.13	33.91

¹ = Median, ² = Range

Table 43. Pitavastatin lactone PK parameters.

Parameter	Number of subjects in Day 5 Treatment A	Day 5 Treatment A (pitavastatin) Geometric Mean	Day 5 Treatment A (pitavastatin) CV%	Number of subjects in Day 9 Treatment B	Day 9 Treatment B (pitavastatin and atazanavir) Geometric Mean	Day 9 Treatment B (pitavastatin and atazanavir) CV%
t _{max} (h)	17	3.00 ¹	1.50-4.03 ²	17	2.00 ¹	1.50-4.00 ²
C _{max} (ng/mL)	17	41.16	12.99	17	45.28	20.91
AUC _{0-τ} (ng*h/mL)	17	402.94	19.33	17	383.42	20.76
t _{1/2} (h)	9	15.22	51.96	6	17.22	61.13

¹ = Median, ² = Range

Table 44. Pitavastatin PK parameter analyses.

Parameter	Geometric mean Treatment A Day 5 (pitavastatin)	Geometric mean Treatment B Day 9 (pitavastatin and atazanavir)	Ratio of geometric means	90% CI
C _{max} (ng/mL)	34.70	55.67	1.60	1.39-1.85
AUC _{0-τ} (ng*h/mL)	127.07	165.83	1.31	1.23-1.39

Table 45. Pitavastatin lactone PK parameter analyses.

Parameter	Geometric mean Treatment A Day 5 (pitavastatin)	Geometric mean Treatment B Day 9 (pitavastatin and atazanavir)	Ratio of geometric means	90% CI
C _{max} (ng/mL)	41.10	45.17	1.10	1.01-1.20
AUC _{0-τ} (ng*h/mL)	402.89	382.21	0.95	0.87-1.04

The pitavastatin C_{max} geometric mean ratio in the presence and absence of atazanavir as well as that of AUC_{0-τ} is 1.60 and 1.31, respectively. These observations are consistent that atazanavir inhibits the key metabolic enzymes of pitavastatin, which are UGT1A3 and UGT2B7. Zhang et al. showed that atazanavir inhibits UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 [*Drug Metab Dispos* 33:1729-39 (2005)].

The pitavastatin lactone C_{max} geometric mean ratio in the presence and absence of atazanavir is 1.10 and 0.95, respectively. The presence of atazanavir did not significantly affect the pitavastatin lactone exposure since the 90% CI of their geometric mean ratios are within the 0.8 and 1.25 bioequivalence goalpost.

Figure 45. Plasma atazanavir concentration – time profile.

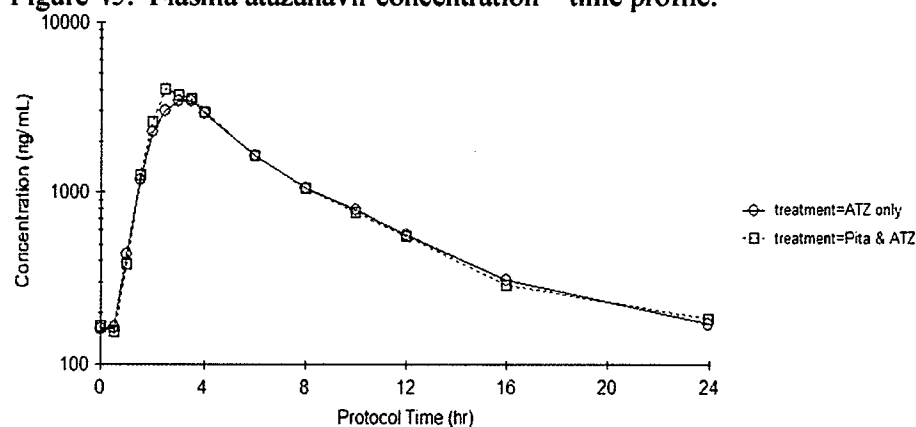


Table 46. Atazanavir PK parameters.

Parameter	Number of subjects in Day 4 Treatment B	Day 4 Treatment B (atazanavir) Geometric Mean	Day 4 Treatment B (atazanavir) CV%	Number of subjects in Day 9 Treatment B	Day 9 Treatment B (atazanavir and pitavastatin) Geometric Mean	Day 9 Treatment B (atazanavir and pitavastatin) CV%
t _{max} (h)	17	2.50 ¹	1.50-4.00 ²	17	2.50 ¹	1.00-3.50 ²
C _{max} (ng/mL)	17	3948.03	30.80	17	4445.35	28.47
AUC _{0-τ} (ng*h/mL)	17	20474.46	29.81	17	21799.26	26.68
t _{1/2} (h)	17	6.47	31.50	17	5.77	33.91
Vd/F (L)	17	136.67	41.97	17	114.64	36.27
CL/F (L/h)	17	14.65	64.68	17	13.76	32.82

¹ = Median, ² = Range

Table 47. Atazanavir PK parameter analyses.

Parameter	Mean Treatment B Day 4 (atazanavir)	Mean Treatment B Day 9 (atazanavir and pitavastatin)	Ratio of geometric means	90% CI
C _{max} (ng/mL)	3930.90	4425.69	1.13	0.96-1.32
AUC _{0-τ} (ng*h/mL)	20427.66	21733.65	1.06	0.90-1.26

The atazanavir C_{max} geometric mean ratio in the presence and absence of pitavastatin as well as that of AUC_{0-τ} is 1.13 and 1.06, respectively. The presence of pitavastatin significantly affected the atazanavir exposure since the 90% CI of their geometric mean ratios are outside the 0.8 and 1.25 bioequivalence goalpost.

	Study 1.29	Reviewer's Comments
Population	Healthy men	OK
Choice of interacting drug	Atazanavir	Per the draft Drug Interaction Guidance, atazanavir is an in vivo strong CYP3A4/5 inhibitor
Route of administration	Oral	Relevant to pitavastatin tablet
Number of participants	18	Relative bioavailability, OK.
Washout	5 – 7 days	Atazanavir t _{1/2} is ~ 7 hours. Pitavastatin t _{1/2} is ~10 hours.
Dose selection	4 mg pitavastatin daily for 5 days Two 150 mg atazanavir	Usual oral pitavastatin dose. Usual dose is 300 mg atazanavir/day PO.
Administration	Atazanavir	With a low- calorie or fat snack to enhance absorption.

The lopinavir and ritonavir combination increases rosuvastatin AUC and C_{max} to 2 and 5 fold, respectively, as compared to those of rosuvastatin alone administration [Kiser et al. *J Acquir Immune Defic Syndr* 47:570-8 (2008)]. This interaction results in the rosuvastatin dose being limited to 10 mg once daily (5 – 40 mg/day) when receiving the combination [rosuvastatin labeling]. Pitavastatin shares many metabolic, excretory, and transporter pathways as those of rosuvastatin. Thus, the sponsor should conduct a drug interaction study with the lopinavir and ritonavir combination to characterize the potential increase in pitavastatin exposure for safety concerns as a post marketing requirement.

2.4.2.10 Itraconazole

Study 1.30 examined the effect of multiple-dose itraconazole on single-dose pitavastatin in 18 healthy men (17 Caucasian and 1 Black). Each participant orally received a 4 mg pitavastatin tablet on Days 1 and 8. Each participant orally received two 100 mg itraconazole tablets daily on Days 5 – 9. There were 4 days separating the dosing of pitavastatin and itraconazole. Participants received all drugs fasted on Days 1 and 8. Serial plasma samples were collected at predose and 72 hours postdose on Days 1 and 8 to determine pitavastatin and its lactone via validated HPLC/MS/MS assay.

Figure 46 (left). Plasma pitavastatin concentration – time profile. Figure 47 (right). Plasma pitavastatin lactone concentration – time profile.

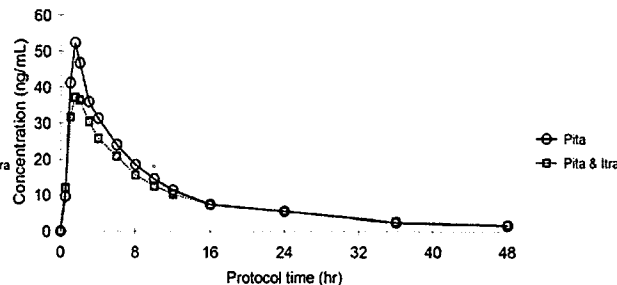
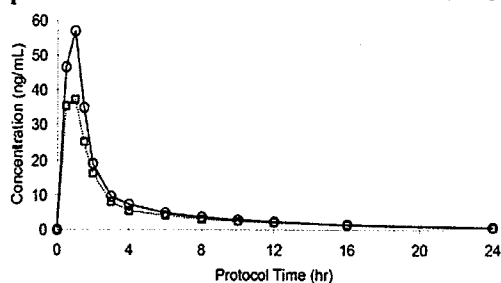


Table 48. Pitavastatin PK parameter

Parameter	Number of subjects in Day 1	Day 1 Geometric Mean	Day 1 CV%	Number of subjects in Day 8	Day 8 Geometric Mean	Day 8 CV%
T _{max} (h)	18	1.00*	0.50-1.50	18	0.75*	0.50-2.00
C _{max} (ng/mL)	18	63.76	38.97	18	49.54	33.01
AUC _{0-t} (ng*h/mL)	18	138.14	30.09	18	106.48	34.77
t _{1/2} (h)	15	7.86	39.02	16	8.31	40.21
AUC _{0-inf} (ng*h/mL)	15	155.90	28.38	16	123.43	31.63
CL/F (L/h)	15	25.66	32.49	16	32.41	30.76

* = median

Table 49. Pitavastatin lactone PK parameter

Parameter	Number of subjects in Day 1	Day 1 Geometric Mean	Day 1 CV%	Number of subjects in Day 8	Day 8 Geometric Mean	Day 8 CV%
T _{max} (h)	18	1.50*	1.00-2.00	18	1.50*	1.00-3.00
C _{max} (ng/mL)	18	50.53	29.03	18	40.80	27.95
AUC _{0-t} (ng*h/mL)	18	439.63	34.49	18	401.25	27.19
t _{1/2} (h)	14	13.96	30.99	18	15.06	26.27
AUC _{0-inf} (ng*h/mL)	14	492.15	33.20	18	435.90	26.19

* = median

Table 50. Pitavastatin PK parameter analyses

Parameter	Geometric mean Day 1	Geometric mean Day 8	Ratio of geometric means	90% CI
C _{max} (ng/mL)	63.76	49.54	0.78	0.69-0.88
AUC _{0-t} (ng*h/mL)	138.14	106.48	0.77	0.71-0.84

Table 51. Pitavastatin lactone PK parameter analyses

Parameter	Geometric mean Day 1	Geometric mean Day 8	Ratio of geometric means	90% CI
C _{max} (ng/mL)	50.53	40.80	0.81	0.76-0.86
AUC _{0-t} (ng*h/mL)	439.63	401.25	0.91	0.86-0.97

The pitavastatin C_{max} geometric mean ratio in the presence and absence of itraconazole as well as that of AUC_{0-t} is 0.78 and 0.77, respectively. The presence of itraconazole significantly affected the pitavastatin exposure since the 90% CI of their geometric mean ratios are outside of the 0.8 and 1.25 bioequivalence goalpost.

The pitavastatin lactone C_{max} geometric mean ratio in the presence and absence of itraconazole as well as that of AUC_{0-t} is 0.81 and 0.91, respectively. The presence of itraconazole significantly affected the pitavastatin lactone exposure since the 90% CI of their geometric mean ratios are outside the 0.8 and 1.25 bioequivalence goalpost.

	Study 1.30	Reviewer's Comments
Population	Healthy men	OK
Choice of interacting drug	Itraconazole	Per the draft Drug Interaction Guidance, itraconazole is an in vivo strong CYP3A4/5 inhibitor and a P-gp inhibitor
Route of administration	Oral	Relevant to pitavastatin tablet
Number of participants	18	Relative bioavailability, OK.
Washout	5 – 7 days	Itraconazole $t_{1/2}$ is ~ hours. Pitavastatin $t_{1/2}$ is ~10 hours.
Dose selection	4 mg pitavastatin daily for 5 days Two 100 mg atazanavir	Usual oral pitavastatin dose. Usual dose is 200 mg itraconazole/day PO.
Administration	Itraconazole	With a low- calorie or fat snack to enhance absorption.

2.4.2.11 Enalapril

Study 1.28 examined the multiple-dose mutual interaction of enalapril and pitavastatin in 18 healthy men (15 Caucasian, 1 Black, 1 Asian, and 1 other). Each participant completed 2 treatments, A and B. A period of 7 days separated these 2 treatments. In Treatment A, each participant orally received a 4 mg pitavastatin tablet daily on Days 1 – 5. In Treatment B, each participant orally received a 20 mg enalapril tablet daily on Days 1 – 11 and a 4 mg pitavastatin tablet daily on Days 7 – 11. Participants received all drugs in the fasted state. Serial plasma samples were collected at predose (Day 4 of Treatment A and Day 10 of Treatment B) and 24 hours postdose (Day 5 of Treatment A and Day 11 of Treatment B) to determine pitavastatin and its lactone via validated HPLC/MS/MS assay. Other serial plasma samples were collected at predose (Day 5 of Treatment B) and 24 hours postdose (Days 6 and 11 of Treatment B) to determine enalapril and enalaprilat via validated LC/MS/MS assay.

Figure 48 (left). Plasma pitavastatin concentration – time profile. Figure 49 (right). Plasma pitavastatin lactone concentration – time profile.

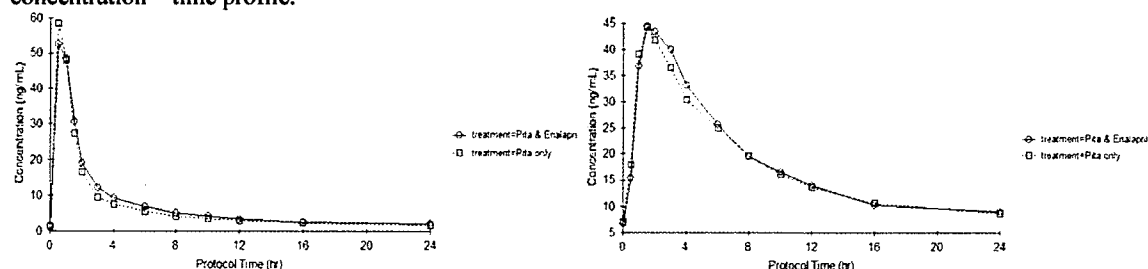


Table 52. Pitavastatin PK parameters.

Treatment	Pitavastatin			Pitavastatin and enalapril		
Parameter	Number of subjects in Day 5	Day 5 Geometric Mean	Day 5 CV%	Number of subjects in Day 11	Day 11 Geometric Mean	Day 11 CV%
Tmax (h)	18	0.50*	0.50-1.00	18	1.002	0.50-1.50
Cmax (ng/mL)	18	62.39	48.74	18	57.80	51.78
AUC0- τ (ng*h/mL)	18	147.33	39.78	18	156.43	48.51
t1/2 (h)	10	14.60	29.63	10	11.62	36.37
CL/F (L/h)	18	27.15	30.81	18	25.57	41.73

* = median

Table 53. Pitavastatin lactone PK parameters.

Treatment	Pitavastatin			Pitavastatin and enalapril		
Parameter	Number of subjects in Day 5	Day 5 Geometric Mean	Day 5 CV%	Number of subjects in Day 11	Day 11 Geometric Mean	Day 11 CV%
T _{max} (h)	18	1.50*	1.00-3.00	18	1.50 ₂	1.00-2.00
C _{max} (ng/mL)	18	44.02	28.20	18	44.67	36.17
AUC _{0-τ} (ng*h/mL)	18	402.77	34.78	18	397.48	47.46
t _{1/2} (h)	10	13.60	14.82	8 ₅	10.33	40.80

* = median

Table 54. Pitavastatin PK parameter analyses.

Treatment Parameter	Pitavastatin Geometric mean	Pitavastatin and enalapril Geometric mean	Ratio of geometric means	90% CI
C _{max} (ng/mL)	62.39	57.80	0.93	0.76-1.13
AUC _{0-τ} (ng*h/mL)	147.33	156.43	1.06	0.99-1.14

Table 55. Pitavastatin lactone PK parameter analyses.

Treatment Parameter	Pitavastatin Geometric mean	Pitavastatin and enalapril Geometric mean	Ratio of geometric means	90% CI
C _{max} (ng/mL)	44.02	44.67	1.02	0.95-1.09
AUC _{0-τ} (ng*h/mL)	402.77	397.48	0.99	0.92-1.06

The pitavastatin C_{max} geometric mean ratio in the presence and absence of enalapril as well as that of AUC_{0-τ} is 0.93 and 1.06, respectively. The presence of enalapril significantly affected the pitavastatin C_{max} since the 90% CI of their geometric mean ratios are outside of the 0.8 and 1.25 bioequivalence goalpost; however, but not pitavastatin AUC_{0-τ}.

The pitavastatin lactone C_{max} geometric mean ratio in the presence and absence of enalapril is 1.02 and 0.99, respectively. The presence of enalapril did not significantly affect the pitavastatin lactone exposure since the 90% CI of their geometric mean ratios are within the 0.8 and 1.25 bioequivalence goalpost.

Figure 50 (left). Plasma enalapril concentration – time profile. Figure 51 (right). Plasma enalaprilat concentration – time profile.

