OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 206966	Submission Date(s): 9/14/2015, 10/26/2015, 12/16/2015
Brand Name	Xeglyze
Generic Name	Abametapir lotion, 0.74% w/w
Primary Reviewer	Doanh Tran, Ph.D.
Secondary Reviewer	Capt. E. Dennis Bashaw, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Dermatology and Dental Products
Applicant	Dr. Reddy's Laboratories
Relevant IND(s)	77510
Submission Type	Original NDA
Formulation; Strength(s)	Lotion; 0.74% w/w
Indication	Topical treatment of head lice infestation in patients 6 months and older

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1 Executive Summary

The Applicant has developed Abametapir lotion 0.74% for the treatment of head lice infestation in patients 6 months of age and older. Abametapir (initially referred to as Ha44) is a compound from the class of bipyridinium molecules. Bipyridine molecules can coordinate as chelating ligands to form complexes with transition metal ions. The mechanism of action of abametapir as a pediculicide is believed to be via the chelation of metal cations which results in inhibition of metalloproteinases critical to louse egg development and survival.

The abametapir lotion formulation has been evaluated in a Phase 2a study (Ha02-002) and a Phase 2b study (Ha02-003) in both a 0.37% and 0.74% strength. Based on superior efficacy and equivalent safety, the higher concentration (0.74%) was chosen for commercial development. The NDA also includes 2 Phase 3 studies (Ha03-001 and Ha03-002), a Phase 2 study investigating ovicidal activity (Ha03-008), 2 pediatric pharmacokinetic (PK) studies (Ha03-003 and Ha03-004), a cardiac safety (TQT) study (Ha02-005), and 2 dermal safety studies (Ha03-006 and Ha03-007). A prototype formulation, referred to as "Ha44 Lotion," was also evaluated in a Phase 1 study (Ha01-001) but it is not considered in support of the NDA.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds NDA 206966 acceptable pending agreement on recommended labeling changes and post marketing requirements and commitments.

1.2 Phase IV Requirements and Commitments

Requirements:

Conduct a maximal use pharmacokinetic trial of Xeglyze lotion, 0.74% in 16 pediatric subjects 6 months to 3 years 11 months of age to fully characterize the concentration time profile of abametapir and metabolite abametapir carboxyl.

Conduct a clinical trial to evaluate the potential for Xeglyze lotion, 0.74% to inhibit the activity of cytochrome P450 3A4 at several time points post dosing. The systemic exposure of abametapir and abametapir carboxyl should be similar to those observed under maximal use conditions in pediatrics. Additional drug interaction trials may be needed depending on the results of this trial.

Commitments:

Conduct a study to evaluate the long-term storage stability of abametapir carboxyl in plasma stored at -80 ºC for duration of at least 1251 days.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Bioavailability:
The pharmacokinetics of Abametapir lotion, 0.74% were evaluated in 3 trials, namely Trials Ha02-003, Ha03-003 and Ha03-004. Each trial enrolled lice infested subjects who received a single 10 minute application of Abametapir lotion, 0.74%. Pharmacokinetic samplings were carried out to 72 hours post dose in adults and 8 hours post dose in pediatrics for all trials.

Trial Ha02-003 evaluated pharmacokinetics in 6 adult and 12 pediatric subjects aged 3 to 12 years of age. The mean (%CV) abametapir plasma maximum concentration (Cmax) and area under the concentration time curve from 0 to 8 hours post dose (AUC0-8h) in the adult group were 41 (66%) ng/mL and 121 (50%) ng*h/mL, respectively. The mean (%CV) Cmax and AUC0-8h in the pediatric group were 73 (57%) ng/mL and 264 (67%) ng*h/mL, respectively, and were higher compared to the values for adults. The mean (%CV) terminal half-life in adults was 21 (11%) hours.

Trials Ha03-003 and Ha03-004 evaluated pharmacokinetics in pediatric subjects aged 6 months to 17 years of age. The pharmacokinetic results for plasma abametapir are shown in table below. As expected, even though the values varied between the 2 trials, abametapir exposure increased as the age of the subject decreased. Abametapir absorption was rapid with a median Tmax of 0.57 to 1.54 hours.

Table 1: Abametapir pharmacokinetic parameters in subjects with head lice infestation

Study	Age Group	n	C_{max} (ng/mL) Mean (%CV)	AUC_{0-8} (ng*h/mL) Mean (%CV)
HA03-003	6 months to <1 year	1	418	1057
HA03-004		5	228 (50%)	688 (43%)
HA03-003	1 year to <2 years	3	209 (62%)	446 (65%)
HA03-004		8	147 (49%)	406 (37%)
HA03-003	2 years to <3 years	6	206 (66%)	633 (57%)
HA03-004		8	160 (48%)	602 (51%)
HA03-003	3 years to 17 years	12	121 (60%)	330 (49%)
HA03-004		7	52 (45%)	254 (67%)

Serum concentration of benzyl alcohol, an excipient in the formulation of Abametapir lotion, 0.74%, was assessed in Trials Ha03-003 and Ha03-004. Benzyl alcohol in serum was measurable (limit of quantitation = 0.5 µg/mL) in 7 subjects out of 39 evaluable subjects. The Cmax of benzyl alcohol in these 7 subjects ranged from 0.52 to 3.57 µg/mL.

Distribution:
Abametapir plasm protein binding ranged from 91.3 – 92.3% and was concentration independent within the tested concentration range of 50 – 800 ng/mL. Metabolite abametapir carboxyl plasm protein binding ranged from 96.0 – 97.5% and was concentration independent within the tested concentration range of 1000 – 13000 ng/mL.

Metabolism:
The metabolic pathway of abametapir involves the sequential formation of abametapir hydoxyl followed by abametapir carboxyl catalyzed by phase I oxidative metabolism enzymes with glucuronidation of both metabolites mediated by Phase II metabolism catalyzed by UDP-Glucuronosyltransferases (UGTs). In vitro studies using liver microsomes showed that abametapir is extensively metabolized, primarily by CYP1A2 and to a lesser extent CYP2B6. In vivo data suggests glucuronidated metabolites contribute only a small proportion of total drug related exposure and their overall levels are low. The unconjugated abametapir carboxyl accounts for the vast majority of drug related plasma exposure in humans.

Abametapir carboxyl is cleared slowly from the systemic circulation and results in plasma concentration significantly higher than that of abametapir. Based on data in adults in Trial Ha02-003, where samplings was carried out to 72 hours, the ratios of Cmax and AUC0-72h between abametapir carboxyl and abametapir were about 30 and 250, respectively. The elimination half-life of abametapir carboxyl has not been well characterized but is estimated to be approximately (mean ± SD) 71 ± 40 hours or longer. In vitro data suggest that abametapir carboxyl is not further metabolized by CYP450s or other NADPH-dependent microsomal enzymes.

Drug-drug interactions:
In vitro studies suggest there is low risk of in vivo cytochrome P450 (CYP) inhibition for abametapir and low risk of CYP induction for both abametapir and abametapir carboxyl. However, there is a potential risk of CYP 3A4 inhibition due to high and sustained concentration of abametapir carboxyl following application of Abametapir lotion, 0.74%. Results of microsomes studies suggests that abametapir carboxyl at concentrations observed in clinical trials would not inhibit CYP enzymes. However, studies using hepatocytes showed concentration dependent inhibition of CYP3A4 and to a lesser extent CYP2B6 and CYP1A2. The potential of Abametapir lotion, 0.74% to inhibit CYP3A4 should be further evaluated in vivo.

Abametapir and abametapir carboxyl are not substrates for ABC (ATP binding cassette) efflux transporters MDR1 and BCRP and SLC (solute carrier) uptake transporters OATP1B1, OATP1B3, OAT1, OAT3 and OCT2. Abametapir and abametapir carboxyl have the potential to inhibit various transporters at high concentrations. Abametapir has the potential to inhibit OCT2 (IC50 = 35.4 μM) and OAT3 (IC50 = 57.5 μM), but the ratio of the unbound Cmax to the IC50 is less than 0.1. Abametapir carboxyl has the potential to inhibit OAT3 (IC50 = 17.1 μM), OCT2, OAT1, OATP1B1, and MDR1, however the unbound Cmax / IC50 ratios for OAT3, OCT2, and OAT1 also are all less than 0.1. Abametapir carboxyl IC50 values were not determined for MDR1 and OATP1B1(i.e., IC50 >100 μM) due to solubility limitations; the total Cmax / IC50 ratios for both transporters are <0.24. Overall, the data suggest low risk of interaction with drug transporters following topical application of Abametapir lotion, 0.74% for treatment of head lice infestation.

Exposure to benzyl alcohol:
Benzyl alcohol is an excipient in the formulation of Abametapir lotion, 0.74%. Because systemic exposure to benzyl alcohol can lead to neonatal gasping syndrome, serum benzyl alcohol was measured following application of Abametapir lotion, 0.74% to assess this risk. Benzyl alcohol serum concentrations were assessed in PK samples from trials Ha03-003 and Ha03-004 using an

assay with LLOQ of 0.5 mcg/mL. In trial Ha03-003, one of 9 evaluable subjects had measurable concentration of 0.536 and 0.726 mcg/mL at 0.5 hour and 1 hour post dose, respectively. In trial Ha03-004, six of 30 subjects had measurable concentrations of 0.524, 0.664, 0.826, 0.877, 1.39, and 3.57 mcg/mL. Only one measurable concentration was seen in each subject.

These observed concentrations of benzyl alcohol do not appear to be a safety concern. Systemic exposure to benzyl alcohol at concentration of ~109.2 µg/mL (1.01 mmol/L) has been associated with neonatal gasping syndrome (Gershanik et al., N Engl J Med 1982; 307:1384-1388).

QT interval:
The Applicant conducted a thorough QT study Ha02-005 and reported that administration of Abametapir lotion, 0.74% for 60 minutes to the scalp and back area in healthy adults without head lice did not prolong cardiac repolarization (QTc interval). The results of this study were reviewed by interdisciplinary review team for QT (IRT-QT) under IND 77510 on 6/14/2013, which concurred with the Applicant's conclusion. The mean observed abametapir Cmax in this study was 432 ±137 ng/mL, which exceeded those observed under maximal use conditions in subjects with active head lice infestation. Therefore, the results of this study are applicable to the target population and it can be concluded that there is no concern regarding QTc prolongation with Abametapir lotion, 0.74% for treatment of head lice infestation.

Pediatrics:
The Applicant conducted Phase 3 safety and efficacy trials and PK trials in subjects 6 months of age and older. The Applicant requests a waiver of studies in pediatrics <6 months of age. The waiver request is reasonable. The waiver request was discussed at a meeting of the Pediatric Review Committee (PeRC) 0n 3/23/2016 and the PeRC agreed with the waiver.

Clinical vs. to-be-marketed formulation:
The to-be-marketed formulation was used in all clinical studies, except for an initial tolerability Phase 1 study Ha01-001. Study Ha01-001 was not essential to support the NDA.

Method validation:
The plasma samples from the human PK studies were analyzed for abametapir, abametapir hydroxyl and abametapir carboxyl using tandem mass spectrometry (LC-MS/MS) methods. Serum samples from the human PK studies were analyzed for benzyl alcohol by gas chromatography-mass spectrometric procedures (GC-MS). All bioanalytical methods were adequately validated.

Analysis of abametapir in plasma samples in all clinical trials were conducted within established long term storage stability. For analysis of benzyl alcohol, samples from 19 of 22 subjects were analyzed within the 452 days demonstrated storage stability. Samples from the remaining 3 subjects were analyzed after up to 472 days of storage. This is a minor deviation from the demonstrated storage duration of 452 days and all data were considered acceptable for review.

For analysis of abametapir carboxyl, samples from trials Ha03-003 and Ha03-004 were analyzed within the demonstrated storage stability duration of 568 days. Samples from trial Ha02-003 were collected in 2011 and retained in storage for 1251 days prior to analysis for abametapir

carboxyl. Therefore, there is insufficient demonstrated stability to support the analysis of abametapir carboxyl in trial Ha02-003. The sponsor suggested that since stability was demonstrated for extended period of 568 days the stability may be inferred out to 1251 days. This reviewer also note that the AUC and Cmax for pediatric subjects (aged 3 – 12 years) in trial Ha02-003 was similar to and in between those observed for the 3 - 17 years age group in trials Ha03-003 and Ha03-004, which were analyzed within the demonstrated stability period. The same order among the 3 trials was seen for the parent abametapir. These data suggest that there were no overt degradation of abametapir carboxyl samples from trial Ha02-003 and the data may be used for review. However, the sponsor should continue to evaluate the storage stability to fully support the storage duration as a post marketing commitment.

Office of Clinical Pharmacology (OCP) briefing:
An Optional Inter-Divisional OCP briefing was held on 4/21/2016 with the following in attendance: Kevin Clark, Yanhui Lu, Dinko Rekic, Chinmay Shukla, Sam Raney, Steven Li, Sudharshan Hariharan, Markham Luke, Martina Sahre, Dennis Bashaw, and Doanh Tran

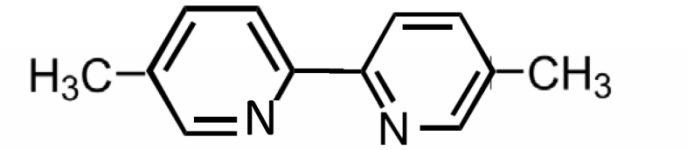
2 Question-Based Review

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance abametapir?

Abametapir, the active compound in Abametapir lotion 0.74%, is a bipyridyl compound with the chemical name 5,5'-dimethyl-2,2'-bipyridyl and an international nonproprietary name (INN) of abametapir. It has appearance of a white to pale yellow solid. Abametapir has a molecular formula of $C_{12}H_{12}N_2$ and a molecular weight of 184.24 g/mol. The chemical structure is shown in Figure 1.

Figure 1: Structural formula of abametapir



Abametapir is a metalloproteinase inhibitor. Metalloproteinases have a role in physiological processes critical to egg development and survival of lice.

2.1.2 What are the proposed indication and dosing regimen for Abametapir lotion, 0.74%?

Abametapir lotion, 0.74% is indicated for the topical treatment of head lice infestation (*Pediculosis humanis capitis*) in patients 6 months of age and older. The dosing instruction is to apply Abametapir lotion, 0.74% to dry hair in an amount sufficient to thoroughly coat the hair and scalp and massage into the scalp and throughout the hair. Leave on the hair and scalp for 10 minutes and then rinse off with warm water.

2.2 General Clinical Pharmacology

2.2.1 What were the design features of the clinical pharmacology and clinical trials used to support Abametapir lotion, 0.74%?

The abametapir lotion formulation has been evaluated in a Phase 2a study (Ha02-002) and a Phase 2b study (Ha02-003) in both a 0.37% and 0.74% strength. Based on superior efficacy and equivalent safety, the higher concentration (0.74%) was chosen for commercial development. The abametapir lotion 0.74% formulation was evaluated for safety and efficacy in 2 Phase 3 studies (Ha03-001 and Ha03-002), a Phase 2 study investigating ovicidal activity (Ha03-008) as well as 2 Phase 2 pediatric pharmacokinetic (PK) studies (Ha03-003 and Ha03-004), a cardiac safety (TQT) study (Ha02-005) and 2 dermal safety studies (Ha03-006 and Ha03-007). A prototype formulation, referred to as "Ha44 Lotion", was also evaluated in a Phase 1 study (Ha01-001). A summary of clinical pharmacology studies is shown in Table 2.

Table 2: Tabular summary of clinical pharmacology studies

Study / Phase	Primary Endpoint	% abametapir[1] Application Time Application Area	Population / Age	Study Purpose and Design	~# Subjects
Ha01-001/ 1[2]	To determine the safety and tolerability of Ha44 Lotion when applied topically to the hair and scalp.	0.37%, 0.74% 10, 20 minutes Scalp	Healthy Volunteers / Adults	ECG, PK, Safety R, DB, PC, SED	32
Ha02-002/ 2a	Primary Objective: To determine the safety and tolerability of abametapir lotion after a single topical application to the hair and scalp of adult subjects with head lice infestation.	0.37%, 10 minutes 0.74%, 20 minutes Scalp	Patients / Adults	ECG, PK, Safety R, DB, PC, 1D	30
Ha02-003/ 2b	Proportion of subjects who were lice free at all follow-up visits through the Day 14 visit.	0.37%, 10 minutes 0.74%, 10 minutes Scalp	Patients / Ages 3 years and older	PK, Safety R, DB, VC, PL	142
Ha02-005/ 2	Assess the safety and tolerability of single doses of abametapir lotion 0.74% with increasing exposure durations in healthy male and female subjects to determine the supratherapeutic dose that would be used in Part 2.	0.74% 20, 40, 60 minutes Scalp, Back	Healthy Volunteers / Adults	ECG, PK, Safety R, DB, PC, AC, XR	81
Ha03-003/ 2	Evaluate the safety and tolerability of a single application of abametapir lotion 0.74% under maximal use conditions for the treatment of head lice.	0.74% 10 minutes Scalp	Patients / Peds 6 mos to <17 years of age	PK, Safety OL, 1D	22
Ha03-004/ 2	Evaluate the safety and tolerability of a single application of abametapir lotion 0.74% under maximal use conditions for the treatment of head lice.	0.74% 10 minutes Scalp	Patients / Peds 6 mos to <17 years of age	PK, Safety OL, 1D	38

Abbreviations: AC = active controlled; DB = double blind; EB = evaluator blind; ECG = electrocardiogram; mos = months; OL = open label; PC = placebo controlled; peds = pediatrics; PL = parallel; R = randomized; 1D = single dose; SED = single escalating dose; VC = vehicle controlled; XR = cross-over.

[1] abametapir concentration is expressed as %w/v for the Ha01-001 study and %w/w for all other studies. Abametapir 0.74% w/v is equivalent to (b) (4) (b) (4)

[2] Ha01-001 used a prototype abametapir lotion formulation that differs to the other clinical studies listed in this table (refer to 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 1).

2.2.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

A Phase 2b study (Ha02-003) was conducted to evaluate the safety and efficacy of a single, 10 minute treatment of abametapir lotion at 2 concentrations (0.37% and 0.74%) compared with a vehicle control in adult and pediatric subjects (2 years of age and older). 67.4% (31/46) of subjects in the abametapir lotion 0.37% treatment group and 85.7% (42/49) of subjects in the abametapir lotion 0.74% treatment group achieved treatment success compared to 23.4% (11/47) of subjects in the vehicle lotion group. Both treatment group differences were statistically significant (both p-values were <0.001) and demonstrated the efficacy of Abametapir lotion, 0.37% and Abametapir lotion, 0.74%. Because the 0.74% strength product showed higher rate of success and no apparent safety concerns, it was chosen for further development.

The safety and efficacy of Abametapir lotion, 0.74% was further evaluated in 2 Phase 3 trials (Ha03-001 and Ha03-002). In Study Ha03-001, 81.1% (43/53) of index subjects in the Abametapir lotion, 0.74% group compared to 50.9% (28/55) of index subjects in the vehicle lotion group achieved treatment success (no live lice present at any post-Baseline Visit). This result was significant (p=0.001) and demonstrated the efficacy of Abametapir lotion, 0.74%.

In Study Ha03-002 , 81.8% (45/55) of index subjects in the Abametapir lotion 0.74% treatment group as compared to 47.2% (25/53) of subjects in the vehicle lotion group achieved treatment success (no live lice present at any post-Baseline Visit). This result was significant (p<0.001) and demonstrated the efficacy of Abametapir lotion, 0.74% while confirming the results obtained in the Ha03-001 study.

According to the medical officer, Dr. Kevin Clark, most of the adverse effects were local reactions, except for vomiting which occurred in 6 of 349 (1.7%) subjects on Abametapir lotion, 0.74%. In contrast, vomiting occurred in 2 of 350 (0.6%) subjects in the Vehicle group. In the Phase 3 trials, laboratory evaluation (hematology, blood chemistry including electrolytes, liver and renal function) were checked at baseline and on day 14 with no significant changes. Complete physical exams were performed at Baseline and Day 14, and brief exams at Days 1 and 7.

2.2.3 What is the systemic bioavailability of Abametapir lotion, 0.74% under maximal use conditions?

The pharmacokinetics of Abametapir lotion, 0.74% were evaluated in 3 trials, namely Trials Ha02-003, Ha03-003 and Ha03-004. Each trial enrolled lice infested subjects who received a single 10 minute application of Abametapir lotion, 0.74%. Pharmacokinetic samplings were carried out to 72 hours post dose in adults and 8 hours post dose in pediatrics for all trials.

Trial Ha02-003 evaluated pharmacokinetics in 6 adult and 10 pediatric subjects aged 6 to 12 years of age and 2 pediatric subjects 3 – 5 years of age. The PK profiles out to 72 hours are shown in Figure 2 (note: the figure also include plot for a lower strength 0.37% product not discussed further in this review). There appears to be a biphasic distribution for abametapir. Figure 3 show the PK profile for adults and pediatrics for up to 8 hours post dose, the last time point measure in pediatrics (note: the figure also include plot for a lower strength 0.37% product not discussed further in this review). The pediatric group had higher systemic exposure to abametapir compared to adults.

The mean (%CV) abametapir plasma maximum concentration (Cmax) and area under the concentration time curve from 0 to 8 hours post dose (AUC0-8h) in the adult group were 41 (66%) ng/mL and 121 (50%) ng*h/mL, respectively (Table 3). The mean (%CV) Cmax and AUC0-8h in the pediatric group were 73 (57%) ng/mL and 264 (67%) ng*h/mL, respectively, and were higher compared to the values for adults. The mean (%CV) terminal half-life in adults was 21 (11%) hours.

Figure 2: Mean abametapir (Ha44) plasma concentration time plots in adults (Ha02-003)

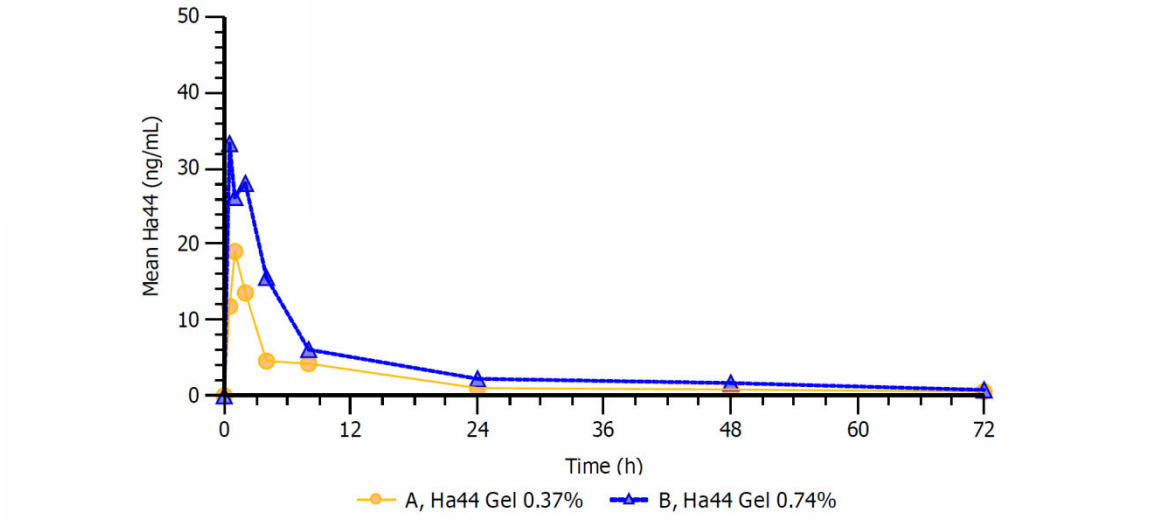


Figure 3: Mean abametapir plasma concentration time plots by treatment and age group (Ha02-003)

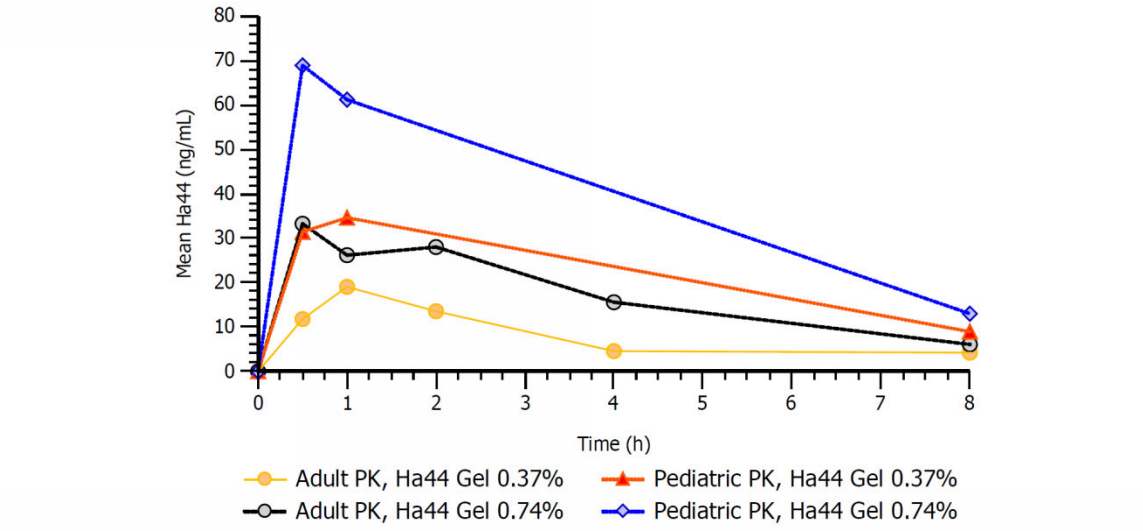


Table 3: Mean (%CV) abametapir PK parameters (Ha02-003)

Group	Cmax (ng/mL)	Tmax[a] (h)	$T_{1/2}$ (h)	AUC0-tlast (h*ng/mL)	AUC0-inf (h*ng/mL)	AUC0-8h (h*ng/mL)
Adults (n=6)	41.0 (66%)	1.54 (0.48-4.02)	21.3 (11%)	278.8 (44%)	302.5 (42%)	120.7 (50%)
Pediatrics (n=12)	72.6 (57%)	0.58 (0.42-1.03)	Not calculated	263.2 (63%)	NA	263.9 (62%)

[a] Median (range)

Trials Ha03-003 and Ha03-004 evaluated pharmacokinetics in pediatric subjects aged 6 months to 17 years of age. The pharmacokinetic results for plasma abametapir are shown in Table 4. As expected, even though the values varied between the 2 trials, abametapir exposure increased as the age of the subject decreased. Abametapir absorption was rapid with a median Tmax of 0.57 to 1.54 hours. The PK profile is similar to those seen in trial Ha02-003 (data not shown).

Table 4: Abametapir pharmacokinetic parameters in subjects with head lice infestation (Ha03-003 and Ha03-004)

Study	Age Group	n	C_{max} (ng/mL) Mean (%CV)	AUC0-8h (ng*h/mL) Mean (%CV)
HA03-003	6 months to <1 year	1	418	1057
HA03-004		5	228 (50%)	688 (43%)
HA03-003	1 year to <2 years	3	209 (62%)	446 (65%)
HA03-004		8	147 (49%)	406 (37%)
HA03-003	2 years to <3 years	6	206 (66%)	633 (57%)
HA03-004		8	160 (48%)	602 (51%)
HA03-003	3 years to 17 years	12	121 (60%)	330 (49%)
HA03-004		7	52 (45%)	254 (67%)

Abametapir hydroxyl and abametapir carboxyl:

Abametapir hydroxyl and abametapir carboxyl are metabolites of abametapir. The concentrations of abametapir hydroxyl are low compared to abametapir and will not be discussed further here (see individual study reviews in section 4 for details).

The concentration of abametapir carboxyl (MW 214.2) was much higher compared to abametapir. Based on data in adults in trial Ha02-003, where samplings was carried out to 72 hours, the ratios of Cmax and AUC0-72h between abametapir carboxyl and abametapir were about 30 and 250, respectively. The mean PK profile from trial Ha03-003 is shown in Figure 4. As seen with the parent, abametapir carboxyl concentration increased with decreasing age. At the last sampling time of 8 hour, the concentration appears to be still rising. Even sampling out to 72 hours in trial Ha02-003 did not adequately capture the full profile of abametapir carboxyl (Figure 5). The elimination half-life of abametapir carboxyl has not been well characterized but is estimated to be approximately (mean ± SD) 71 ± 40 hours or longer in adults. In some subjects the plasma abametapir carboxyl concentrations appears to be at a plateau out to 72 hours. The summary of PK parameters for abametapir carboxyl from the 3 PK trials is shown in Tables 5 to 7. The Cmax values noted in these tables may not represent the true Cmax because the sampling times were not adequate to capture Tmax in all pediatric and some adult subjects.

Figure 4: Mean plasma abametapir carboxyl concentration-time plot by age group (Ha03-003) (Group 1: <12 months, group 2: 1 to <2 years, group 3: 2 to <3 years, group 4: 3 to <18 years)

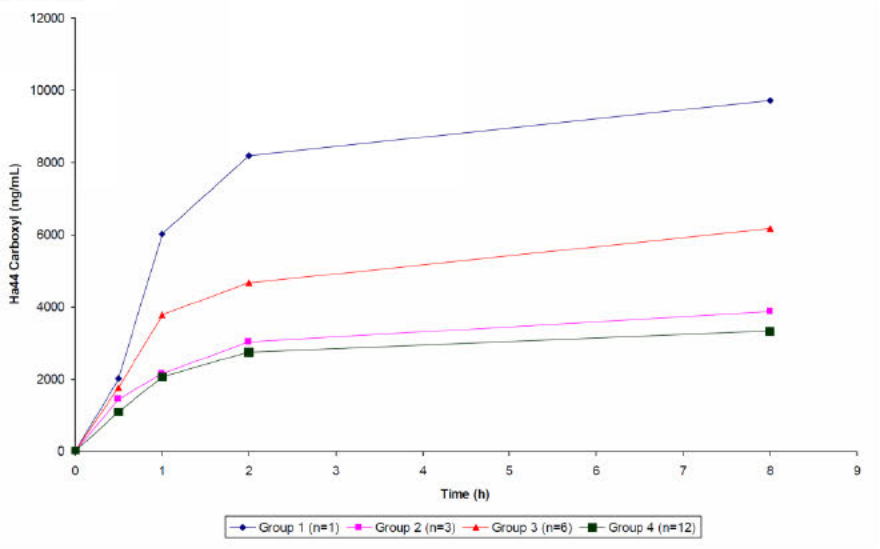


Figure 5: Mean (±SD) plasma abametapir carboxyl concentration-time plot in adults (Ha02-003)

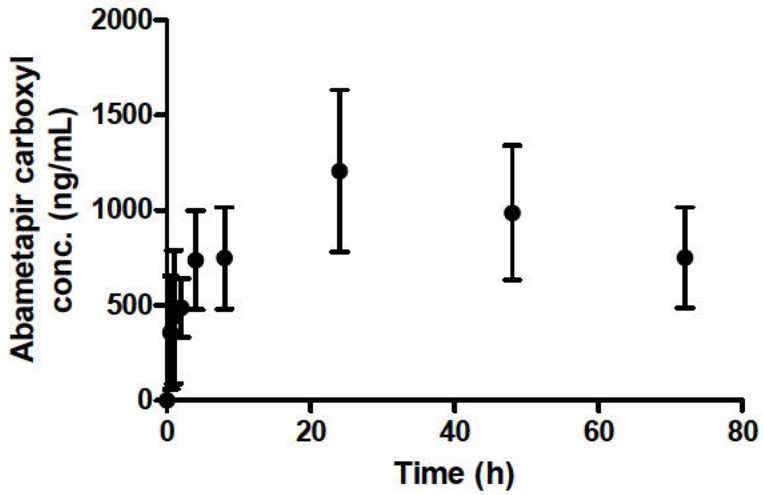


Table 5: Abametapir carboxyl PK parameters in adults and pediatrics for Abametapir Lotion 0.74% from trial Ha02-003.

n	Age Group	C_{max} (ng/mL) Mean ± SD	T_{max} (hours) Median ± SD	AUC_{0-8} (ng*h/mL) Mean ± SD
6	Adults	1130 ± 397	28.7 ± 16.9	4900 ± 1680
12	2 to 12 years	2000 ± 1140	8.0 ± 0.0	11400 ± 6550

Abbreviations: n= number of subjects; SD = standard deviation.

Table 6: Abametapir carboxyl PK parameters for Abametapir lotion, 0.74% from trial Ha03-003.

Age Group	n	C_{max} (ng/mL) Mean (CV%)	T_{max} (hours) Median (Range)	AUC_{0-8} (ng*h/mL) Mean (CV%)
6 to <12 months	1	9710	7.92	62408
1 to <2 years	3	3863 (41%)	7.97 (7.90 - 8.03)	24158 (30%)
2 to <3 years	6	6172 (34%)	7.99 (7.90 - 8.02)	38334 (37%)
3 to <18 years	12	3353 (58%)	7.89 (2.00 - 8.03)	21369 (64%)

Abbreviations: CV = coefficient of variation; n = number of subjects.

Table 7: Abametapir carboxyl PK Parameters for Abametapir lotion, 0.74% from trial Ha03-004.

Age Group	n	C_{max} (ng/mL) Mean (%CV)	T_{max} (hour) Median (range)	AUC_{0-8} (ng*h/mL) (%CV)
6 to <12 months	1	6830	8.00 (8.00 - 8.00)	37500
1 to <2 years	2	3550 (1.8%)	5.00 (2.03 - 7.97)	24600 (0.3%)
2 to <3 years	7	4290 (46.7%)	8.00 (7.85 - 8.00)	26000 (49.5%)
3 to 17 years	7	1760 (41.9%)	8.00 (7.83 - 8.08)	10000 (46.4%)

Abbreviations: CV = coefficient of variation; n = number of subjects.

2.2.4 What are protein binding and distribution properties of abametapir?

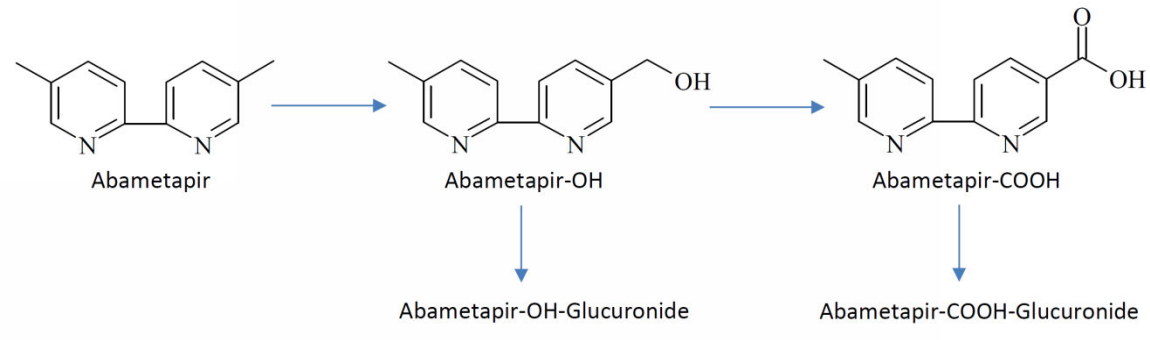
Abametapir plasma protein binding was assessed using equilibrium dialysis over 2 hours. The protein binding in human plasma was similar over the tested concentration range of 50 – 800 ng/mL and ranged from 91.3 – 92.3% (report (b) (4) 0014).

Abametapir carboxyl plasma protein binding was assessed using equilibrium dialysis over 4 hours. The protein binding in human plasma was similar over the tested concentration range of 1000 – 13000 ng/mL and ranged from 96.0 – 97.5% (report (b) (4) 0021).

2.2.5 What is the metabolic pathway for abametapir?

Incubation of abametapir with liver microsomes in vitro showed that both abametapir hydroxyl (abametapir-OH) and abametapir carboxyl (abametapir-COOH) are formed under permissive phase I metabolism conditions and glucuronide conjugates of both abametapir-OH and abametapir-COOH are formed under permissive Phase II metabolism conditions. It is proposed that the metabolic pathway of abametapir involves the sequential formation of abametapir-OH followed by abametapir-COOH catalyzed by phase I oxidative metabolism enzymes with glucuronidation of both metabolites mediated by Phase II metabolism catalyzed by UDP-Glucuronosyltransferases (UGTs) (Report (b) (4) -036B). Additional in vitro studies using liver microsomes showed that abametapir is extensively metabolized, primarily by CYP1A2 and to a lesser extend CYP2B6 (Report (b) (4) 0013). The proposed metabolic pathway is shown in Figure 6.

Figure 6: Proposed metabolic pathway of abametapir



Mass spectrometry screening of human plasma following topical administration of Abametapir lotion, 0.74% found 3 moieties, namely abametapir and metabolites abametapir-OH and abametapir-COOH (Report (b) (4) 0011). In vitro studies identified the capacity for glucuronidation of both metabolites, but in vivo data suggests glucuronidated metabolites contribute only a small proportion of total drug related exposure and their overall levels are low. In vivo, unconjugated abametapir carboxyl accounts for the vast majority of drug related plasma exposure in humans.

Abametapir carboxyl is not metabolized by CYP450s or other NADPH-dependent microsomal enzymes (Report (b) (4) 0020).

2.2.6 What is the effect of Abametapir lotion, 0.74% on QT interval?

The Applicant conducted a thorough QT study Ha02-005 and reported that administration of abametapir lotion, 0.74% for 60 minutes to the scalp and back in healthy adults without head lice did not prolong cardiac repolarization (QTc interval). The results of this study were reviewed by IRT-QT under IND 77510 on 6/14/2013, which concurred with the Applicant's conclusion. The mean observed abametapir Cmax in this study was 432 ± 137 ng/mL, which exceeded those observed under maximal use conditions in subjects with active head lice infestation. The metabolite abametapir carboxyl Cmax was 6010 ± 1120 ng/mL, which covered most subjects except for those <1 year of age. Therefore, the results of this study are applicable to the target population and it can be concluded that there is no concern regarding QTc prolongation with Abametapir lotion, 0.74% for treatment of head lice infestation.

2.2.7 What is the systemic exposure of benzyl alcohol following application of Abametapir lotion, 0.74%?

Benzyl alcohol is an excipient in the formulation of Abametapir lotion, 0.74%. Because systemic exposure to benzyl alcohol can lead to neonatal gasping syndrome, serum benzyl alcohol was measured following application of Abametapir lotion, 0.74% to assess this risk. Benzyl alcohol serum concentrations were assessed in PK samples from trials Ha03-003 and Ha03-004 using an assay with LLOQ of 0.5 µg/mL. In trial Ha03-003, one of 9 evaluable subjects (13 subjects from site 02 were excluded due to inadvertent use of saline flush containing benzyl alcohol) had measurable concentration of 0.536 and 0.726 mcg/mL at 0.5 hour and 1 hour post dose, respectively. In trial Ha03-004, six of 30 subjects had measurable concentrations of 0.524, 0.664, 0.826, 0.877, 1.39, and 3.57 µg/mL. Only one measurable concentration was seen in each

subject. Four of the samples were seen at 0.5 hours post dose and two samples (the highest 2 concentrations) were seen at 8 hours post dose.

These observed concentrations of benzyl alcohol do not appear to be a safety concern. Systemic exposure to benzyl alcohol at concentration of ~109.2 µg/mL (1.01 mmol/L) has been associated with neonatal gasping syndrome (Gershanik et al., N Engl J Med 1982; 307:1384-1388). The highest benzyl alcohol observed in the current trial of 3.57 µg/mLis about 30 fold lower. For reference, the highest plasma benzyl alcohol observed in studies with Natroba and Uleasfia, two other products approved for treatment of head lice infestation, were 2.37 µg/mL and 2.99 µg/mL, respectively.

2.3 Intrinsic Factors

2.3.1 What is the systemic exposure of Abametapir lotion, 0.74% in pediatrics?

The systemic exposure of abametapir and its metabolites was higher in pediatrics and increased with decreasing age. See section 2.2.3 for further details.

2.3.2 What is the effect of hepatic and renal impairment on Abametapir lotion, 0.74% PK?

The effect of hepatic and renal impairment on PK of Abametapir lotion, 0.74% was not evaluated by the applicant.

2.4 Extrinsic Factors

2.4.1 What is the effect of CYP enzymes inhibition on the pharmacokinetics of Abametapir lotion, 0.74%?

The effects of CYP enzyme inhibition on the PK of Abametapir lotion, 0.74% were not evaluated. Since abametapir is metabolized mainly by CYP1A2, inhibition of this enzyme may lead to increased systemic exposure to abametapir.

2.4.2 What is the effect of Abametapir lotion, 0.74% on the PK of other drugs?

There is low risk of in vivo CYP inhibition for abametapir and low risk of CYP induction for both abametapir and abametapir carboxyl. However, there is a potential risk of CYP3A4 inhibition due to high and sustained plasma concentration of abametapir carboxyl following application of Abametapir lotion, 0.74%. The potential of Abametapir lotion, 0.74% to inhibit CYP3A4 should be further evaluated in vivo. A brief discussion of this recommendation is presented below followed by additional details of in vitro inhibition and induction results for abametapir and abametapir carboxyl, respectively.

Briefly, in human liver microsomes studies, the results showed no significant (>30%) inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 at concentration up to 200 µM for abametapir carboxyl. Based on highest clinically observed plasma total Cmax of 45.3 µM (9710 ng/mL) or unbound concentration of 1.81 µM, the Cmax/Ki (assuming Ki=IC50/2) would be <0.227 based on total drug and <0.0181 based on unbound drug

concentration. Given that this was based on the highest observed clinical sample, it suggests the risk of CYP inhibition for abametapir carboxyl is low.

However, in a study with human hepatocytes to evaluate the induction potential, abametapir carboxyl showed concentration dependent inhibition of all 3 tested enzymes, namely CYP1A2, CYP2B6 and CYP3A4 with 50% inhibition of enzyme activity at concentrations in the range of 50 – 200 μM and 50% inhibition of mRNA expression as low as in the range of 5 – 15 μM. A similar trend of CYP enzyme inhibition (primarily CYP3A4) in hepatocytes was also seen at the highest concentration tested for abametapir (i.e., 40 μM). It is not clear the reason for this discrepancy between results of hepatocyte studies and microsomal studies. It is possible that hepatocytes could form metabolites and lead to the observed inhibition. Abametapir carboxyl may also be acting as a suppressor of CYP enzyme expression as both enzyme activity and mRNA expression was inhibited. The potential for Abametapir lotion, 0.74% to inhibit CYP enzymes, particularly, CYP3A4 should be further evaluated in vivo.

CYP inhibition potential of abametapir:

The potential for abametapir to inhibit CYP450 enzymes commonly active in the metabolism of xenobiotics was assessed in vitro using pooled human liver microsomes (Report (b) (4) 0009). Abametapir (0, 40 μM) was incubated with human liver microsomes (pooled from 50 donors) in the presence of NADPH for 0 and 0.5 hours, in duplicate. Subsequently, CYP450 specific chemical substrates were added to the incubations. The inhibition results are shown in Table 8.

Abametapir reversibly inhibited the activity of CYP1A2 (Ki = 39 μM). It did not inhibit the activity of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5 at up to 40 μM. Considering the highest mean Cmax (in subjects <1 year of age) in maximal use PK trials Ha03-003 and Ha03-004 was 1.41 μM, the [I]/Ki is <0.1 suggesting low risk of in vivo CYP inhibition.

Table 8: CYP450-Specific Substrates Utilized to Identify Abametapir Potential for CYP450 Inhibition and results of inhibition

Study Number	(b) (4)0009			
Type of Study	Inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5 activity levels in human liver microsomes			
Method	Enzyme activity assay: LC-MS/MS analysis of enzyme substrate levels over time Inhibition potential was assessed at an abametapir concentration of 40 µM. Abametapir was subsequently titrated from 0 to 120 µM to further characterize its potential for the inhibition of CYP1A2.			
Compound	% Inhibition			
Cytochrome P450 Type	Enzyme	Abametapir		Selective Inhibitor
		0 min pre-incubation	30 min pre-incubation	
CYP1A2	Phenacetin O-deethylase	63	51	78[1] (Furafylline, 3 µM)
CYP2B6	Bupropion hydroxylase	10	8	97[1] (Thio-TEPA, 50 µM)
CYP2C8	Taxol 6α-hydroxylase	6	-3	36[2] (Trimethoprim, 80 µM)
CYP2C9	Diclofenac 4'-hydroxylase	-1	0	95[2] (Sulphaphenazole, 20 µM)
CYP2C19	S-Mephenytoin 4'-hydroxylase	6	3	91[2] (Benzylnirvanol, 5 µM)
CYP2D6	Bufuralol 1'-hydroxylase	10	6	61[2] (Quinidine, 5 µM)
CYP3A4/5	Testosterone 6β-hydroxylase	15	6	95[2] (Ketoconazole, 1 µM) 97[1](Troleandomycin, 100 µM)
CYP3A4/5	Midazolam 1'-hydroxylase	-23	-18	94[2](Ketoconazole, 1 µM) 95[1](Troleandomycin, 100 µM)

Additional Information: Abametapir (at 40 µM) reversibly (competitively) inhibits CYP1A2. Abametapir was titrated (0 to 120 µM) to characterize the inhibition potential against CYP1A2 and the resulting Ki was determined to be 39 µM.

[1] Mechanism-based selective chemical inhibitor requiring 30 minutes pre-incubation.

[2] Direct selective chemical inhibitor requiring 0 minutes pre-incubation.

CYP inhibition potential of abametapir carboxyl:

The potential for abametapir carboxyl to inhibit CYP450 enzymes commonly active in the metabolism of xenobiotics was assessed in vitro using pooled human liver microsomes (Report (b) (4)0017). Abametapir carboxyl (0, 200 µM) was incubated with human liver microsomes (pooled from 150 donors) in the presence of NADPH for 0 and 0.5 hours, in duplicate. Subsequently, CYP450 specific chemical substrates were added to the incubations. The inhibition results are shown in Table 9.

No significant (>30%) inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 was observed at either time point. Thus, abametapir carboxyl is not a competitive/reversible or time-dependent inhibitor of human CYP450 enzymes at up to 200 µM. In vivo systemic exposure of abametapir carboxyl under clinical use condition resulted in concentration up to 9710 ng/mL or 45.3 µM. Based on protein binding of 96%, the unbound concentration is equal to 1.81 µM and the calculated unbound Cmax/Ki (assuming Ki=IC50/2) is <0.0181 suggesting low risk of in vivo inhibition. However, in a study with human hepatocyte to evaluate the induction potential, abametapir carboxyl showed unexpected concentration dependent inhibition of all 3 tested enzymes, namely CYP1A2, CYP2B6 and CYP3A4 with 50% inhibition of enzyme activity at concentrations in the range of 50 – 200 µM (see discussion of hepatocyte induction study below).

Table 9: CYP450-Specific Substrates Utilized to Identify Abametapir Carboxyl Potential for CYP450 Inhibition and inhibition results

Study Number	(b) (4)0017			
Type of Study	Inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5 activity levels in human liver microsomes			
Method	Enzyme activity assay: LC-MS/MS analysis of enzyme substrate levels over time Inhibition potential was assessed at an abametapir carboxyl concentration of 200 µM			
Compound	% Inhibition			
Cytochrome P450 Type	Enzyme	Abametapir carboxyl		Selective Inhibitor
		0 min pre-incubation	30 min pre-incubation	
CYP1A2	Phenacetin O-deethylase	-5	-26	69[1] (Furafylline, 3 µM)
CYP2B6	Bupropion hydroxylase	-13	-5	97[1] (Thio-TEPA, 50 µM)
CYP2C8	Amodiaquine N-deethylase	11	12	83[2] (Montelukast, 1 µM)
CYP2C9	Diclofenac 4'-hydroxylase	-10	7	100[2] (Sulphaphenazole, 20 µM)
CYP2C19	S-Mephenytoin 4'-hydroxylase	-9	5	90[2] (Benzylnirvanol, 5 µM)
CYP2D6	Bufuralol 1'-hydroxylase	-23	-12	50[2] (Quinidine, 5 µM)
CYP3A4/5	Testosterone 6β-hydroxylase	-2	11	97[2] (Ketoconazole, 1 µM) 97[1](Troleandomycin, 100 µM)
CYP3A4/5	Midazolam 1'-hydroxylase	1	-6	96[2] (Ketoconazole, 1 µM) 97[1] (Troleandomycin, 100 µM)

Additional Information: Abametapir carboxyl (at 200 µM) does not inhibit the activity of any of the cytochrome P450s tested.
[1] Mechanism-based selective chemical inhibitor requiring 30 minutes pre-incubation.
[2] Direct selective chemical inhibitor requiring 0 minutes pre-incubation .

CYP induction potential of abametapir:

The potential for abametapir to induce CYP450 mRNA and enzyme activity levels was assessed in vitro using cryopreserved human hepatocytes (Report (b) (4)0010). Abametapir (0.4, 1.3, 4.0, 12, and 40 µM) was incubated with cultured hepatocytes from 3 donors (male and female) for 48 hours, with medium changes at 24 hours. Subsequently, cells were washed and chemical substrates for CYP1A2 (phenacetin), CYP2B6 (buproprion), and CYP3A4 (midazolam) were added to the cultures for 0.25, 0.33, and 1 hour, respectively. Following these incubations, reactions were quenched and samples either were analyzed for substrate metabolites (acetaminophen, hydroxybuproprion, and 1-hydroxymidazolam) using LC-MS/MS or were analyzed for CYP1A2, CYP2B6, and CYP3A4 mRNA expression using quantitative RT-PCR and SYBR-green technology. Positive and negative controls were assessed concurrently. Results are shown in Table 10.

Abametapir did not markedly (≥2-fold) induce CYP1A2, CYP2B6, or CYP3A4 activity (most cases were ≤1.4-fold except for CYP1A2) and did not markedly induce (≥20% of that elicited by the positive control) CYP1A2, CYP2B6, or CYP3A4 mRNA expression. There was no evident of positive concentration response relationship for any enzymes tested. Thus, at up to 40 µM, abametapir is not considered an inducer of human CYP450s.

Table 10

Study Number	(b) (4)0010					
Type of Study	Induction of CYP1A2, 2B6, and 3A4/5 mRNA and activity levels in human hepatocytes					
Method	mRNA assay: quantitative-PCR using SYBR®-green technology Enzyme activity assay: LC-MS/MS analysis of enzyme substrate levels over time Induction potential was assessed at abametapir concentrations of 0.4, 1.3, 4.0, 12 and 40 µM					
Assay	mRNA expression			Enzyme activity		
	Abametapir Concentration with Maximal Induction (µM)	Fold Induction	Relative Potency (%)	Abametapir Concentration with Maximal Induction (µM)	Fold Induction	Relative Potency (%)
CYP1A2						
Donor (b) (6)	12	1.7	2.1	12	1.5	5.5
Donor	12	1.9	3.1	12	1.7	21
Donor	12	1.9	2.9	12	1.4	4.5
CYP2B6						
Donor (b) (6)	4.0	1.3	2.0	4.0	1.1	7.1
Donor	4.0	1.5	2.2	4.0	1.2	6.6
Donor	4.0	1.8	2.3	1.3	1.3	7.8
CYP3A4/5						
Donor (b) (6)	4.0	1.2	1.3	12	1.1	1.2
Donor	4.0	2.0	2.9	4.0	1.2	1.7
Donor	1.3	2.0	3.6	0.4	1.1	1.7

CYP induction potential of abametapir carboxyl:

The potential for abametapir carboxyl to induce CYP450 mRNA and enzyme activity levels was assessed in vitro using cryopreserved human hepatocytes using same method outline for abametapir above except incubation duration was 72 hours (Report (b) (4)0018). Abametapir carboxyl was tested at concentrations of 5, 15, 50, 100, and 200 µM, each in duplicate.

Abametapir carboxyl did not markedly (≥2-fold) induce CYP1A2, CYP2B6, or CYP3A4 activity and did not markedly induce (≥20% of that elicited by the positive control) CYP1A2, CYP2B6, or CYP3A4 mRNA expression. There were 2 cases where it exceeded the above thresholds, namely a 40.7% relative potency for CYP2B6 in one donor and a 20.7% relative potency for CYP3A4 in another donor. There was no positive concentration induction response trend. Thus, abametapir carboxyl, at up to 200 µM, is not considered an inducer of human CYP450s. In contrast, it appears that there were significant inhibition of activity and mRNA expression of all 3 CYP enzymes tested. Results of maximum enzyme inhibition are shown in Table 11 below. Evaluation of CYP enzyme activities at all concentrations tested showed that there appears to be concentration dependent inhibition with 50% inhibition of enzyme activity occurred at concentrations in the range of 50 – 200 µM, with CYP3A4 being most sensitive. Similar results were seen with mRNA expression, where CYP3A4 was most sensitive with 50% mRNA inhibition in the range of as low as 5 – 15 µM.

Table 11: CYP enzyme inhibition in hepatocytes due to abametapir carboxyl.

Study Number	[redacted]0018					
Type of Study	Induction of CYP1A2, 2B6, and 3A4/5 mRNA and activity levels in human hepatocytes					
Method	mRNA assay: quantitative-PCR using SYBR®-green technology Enzyme activity assay: LC-MS/MS analysis of enzyme substrate levels over time Induction potential was assessed at abametapir concentrations of 5, 15, 50, 100, and 200 µM					
Assay	mRNA expression			Enzyme activity		
	Abametapir Carboxyl Concentration with Maximal Induction (µM)	Fold Induction	Suppression (%)	Abametapir Carboxyl Concentration with Maximal Induction (µM)	Fold Induction	Suppression (%)
CYP1A2						
Donor [redacted]	200	0.48	52	200	0.52	48
Donor	200	0.27	73	200	0.48	52
Donor	200	0.19	81	200	0.11	89
CYP2B6						
Donor [redacted]	200	0.08	92	200	0.16	84
Donor	200	0.21	79	200	0.40	60
Donor	200	0.28	72	200	0.09	91
CYP3A4/5						
Donor [redacted]	200	0.02	98	200	0.17	83
Donor	200	0.05	95	200	0.23	77
Donor	200	0.02	98	200	0.10	90

2.4.3 Are abametapir and abametapir carboxyl substrates of drug transporters?

The applicant conducted studies to assess whether abametapir and major metabolite abametapir carboxyl are substrate of drug transporters. The results showed that neither abametapir nor abametapir carboxyl are substrates for ABC (ATP binding cassette) efflux transporters MDR1 and BCRP and SLC (solute carrier) uptake transporters OATP1B1, OATP1B3, OAT1, OAT3 and OCT2. Additional details for abametapir and abametapir carboxyl are shown separately below.

Abametapir:

The potential for abametapir to be a substrate for efflux and uptake transporters was assessed in vitro in a series of assays using liquid scintillation counting (LSC) (Report [redacted]0008). ^{14}C-abametapir (0.4, 4 and 40 µM) was administered to the apical or basolateral chambers of monolayers of MDCKII cells transfected with MDR1 (P-glycoprotein) or BCRP, and the bidirectional transport of abametapir was determined via LSC after 0, 0.25, 0.5, 1, and 2 hours of incubation. Appropriate positive and negative controls were conducted concurrently and verified the validity of the assay. Background-corrected efflux ratios of abametapir were approximately 1 in both MDCKII-MDR1 and MDCKII-BCRP monolayers at all concentrations tested. Therefore, abametapir is not considered a substrate of the ABC efflux transporters MDR1 and BCRP at concentrations up to 40 µM.

^{14}C-abametapir (0.4 and 40 µM) was administered to Chinese hamster ovary (CHO) cells transfected with human OATP1B1, human OATP1B3, human OAT1, or human OCT2 and HEK293 cells transfected with human OAT3 for 2 and 20 minutes of incubation. The accumulation of abametapir was detected through LSC of cell lysates. Appropriate positive and negative controls were conducted concurrently and verified the validity of the assay. Less than 2-fold accumulation of abametapir was observed in any of the cell cultures. Therefore, abametapir

is not considered a substrate of the SLC uptake transporters OATP1B1, OATP1B3, OAT1, OCT2 and OAT3 at concentrations up to 40 μM.

Abametapir carboxyl:
The potential for abametapir carboxyl to be a substrate for ABC efflux and SLC uptake transporters was assessed in vitro (Report OPT-2014-056). Abametapir carboxyl (5 and 50 μM) was administered to MDCKII monolayers transfected with MDR1 or Caco-2 cells endogenously expressing BCRP for 2 hours in the absence or presence of transporter-specific inhibitors. Positive controls consisted of radiolabeled transporter-specific probe substrates. Reactions were quenched, and samples from the basal and apical wells were measured for abametapir carboxyl by LC-MS/MS and for positive controls by radiometric detection. Transport was measured in both the apical-to-basal and basal-to-apical directions. MDR1 efflux ratios for abametapir carboxyl were less than 2. BCRP efflux ratios for abametapir carboxyl were slightly >2 at 5 μM and <2 at 50 μM, but the presence of the BCRP-specific inhibitor did not impact the efflux. Therefore, abametapir carboxyl is not considered a substrate of the ABC transporters MDR1 and BCRP at concentrations up to 50 μM.

Abametapir carboxyl (5 and 50 μM) was administered to MDCKII monolayers transfected with OATP1B1, OATP1B3, OAT1, OCT2, or OAT3 for 5 minutes in the absence and presence of transporter-specific inhibitors. Identical treatments were made to MDCKII monolayers which did not express the transporters. Positive controls consisted of radiolabeled transporter-specific probe substrates. Reactions were quenched, and quantities of abametapir carboxyl in cell extracts were determined by LC-MS/MS, while quantities of positive controls in cell extracts were measured by radiometric detection. Net transporter mediated uptake was calculated by subtracting concentrations in monolayers not expressing transporters from concentrations in monolayers expressing the transporter of interest. Net transporter mediated cellular accumulation was minimal. Therefore, abametapir carboxyl is not considered a substrate of the SLC uptake transporters OATP1B1, OATP1B3, OAT1, OCT2 and OAT3 at concentrations up to 50 μM.

2.4.4 What is the effect of Abametapir lotion, 0.74% on drug transporters?

The applicant conducted studies to assess whether abametapir and major metabolite abametapir carboxyl can inhibit or induce the function of drug transporters MDR1(P-gp), BCRP, OATP1B1, OATP1B3, OAT1, OCT2 and OAT3. The results showed that abametapir and abametapir carboxyl have the potential to inhibit various transporters at high concentrations. Abametapir has the potential to inhibit OCT2 (IC50 = 35.4 μM) and OAT3 (IC50 = 57.5 μM), but the ratio of the unbound Cmax to the IC50 is less than 0.1. Abametapir carboxyl has the potential to inhibit OAT3 (IC50 = 17.1 μM), OCT2, OAT1, OATP1B1, and MDR1, however the unbound Cmax / IC50 ratios for OAT3, OCT2, and OAT1 also are all less than 0.1. Abametapir carboxyl IC50 values were not determined for MDR1 and OATP1B1(i.e., IC50 >100 μM) due to solubility limitations; the total Cmax / IC50 ratios for both transporters are <0.24. Overall, the data suggest low risk of interaction with drug transporters following topical application of Abametapir lotion, 0.74% for treatment of head lice infestation. Additional details for abametapir and abametapir carboxyl are shown separately below.

Abametapir:

The potential for abametapir to inhibit ABC efflux and SLC uptake transporters was assessed in a series of in vitro assays using vesicles and cell monolayers (Report [redacted]0008). Abametapir (0.16 to 120 μM) was administered to membrane vesicles prepared from mammalian K and M cells overexpressing MDR1 or BCRP in the presence of transporter-specific probe substrates and ATP or AMP for 3 or 1 minute, respectively. Positive controls consisted of transporter-specific inhibitors, and negative controls consisted of vehicle. Identical treatments were made to vesicles which did not express the transporters. Reactions were quenched, and the amount of transporter-specific substrate inside the vesicles was measured using LSC. Abametapir stimulated MDR1 transport in a dose-dependent manner with a maximum stimulation of about 2-fold relative to vehicle control. Abametapir weakly inhibited BCRP transport with a maximum inhibition of 22% at 120 μM.

Abametapir (40 μM) was administered to the apical or basolateral chambers of monolayers of MDCKII cells transfected with MDR1 or BCRP for 2 or 1 hours of incubation, respectively, and the bidirectional transport of radiolabeled probe substrates was detected through LSC. Identical treatments were made to monolayers which did not express the transporters. Positive controls consisted of transporter-specific inhibitors, and negative controls consisted of vehicle. Due to equivocal results, this experiment was conducted twice. After appropriately correcting for background in the second set of experiments, this study confirmed abametapir carboxyl did not affect the apparent permeability in either direction for MDR1 and the efflux ratio for BCRP was approximately 1. Therefore, abametapir was not considered an inhibitor of the ABC efflux transporters MDR1 and BCRP at 40 μM.

For SLC uptake transporters, abametapir (0.16 to 120 μM) was administered to CHO cells transfected with human OATP1B1, OATP1B3, OAT1, or OCT2, and HEK293 cells transfected with human OAT3 for 5 or 10 minutes of incubation in the presence of radiolabeled transporter-specific probe substrates. Reactions were quenched, and the accumulation of transporter-specific probe substrates was detected through LSC of cell lysates. Identical treatments were made to cells which did not express the transporters. Positive controls consisted of transporter-specific inhibitors, and negative controls consisted of vehicle. OATP1B1, OATP1B3, and OAT1-mediated transport were inhibited by less than 30% at abametapir concentrations up to 120 μM. OCT2 and OAT1-mediated transport were weakly inhibited by abametapir carboxyl, with IC50 values determined as 35.4 and 57.5 μM, respectively. Detailed results are shown in Table 12.

Table 12: Results of abametapir vesicular transport and uptake transport inhibition assays

Study Number		(b) (4)-0008								
Type of Study		Transporter inhibition potential								
Method		Abametapir (0.16 to 120 µM) inhibition of vesicular transport and uptake transport in CHO or HEK293 cells transfected with P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2.								
Vesicular Transport and Uptake Transport Inhibition Assays										
Abametapir Concentration		0 (DMSO)	0.16 µM	0.49 µM	1.48 µM	4.44 µM	13.33 µM	40.00 µM	120.00 µM	Inhibitor
P-gp	Transporter specific transport (pmol/mg/min)	92.59 ± 5.72	98.13 ± 12.5	163.31 ± 11.62	201.67 ± 18.82	220.76 ± 9.5	253.43 ± 5.63	285.94 ± 3.33	291.99 ± 31.86	6.53 ± 2.96 (Verapamil, 100 µM)
	Relative transport (% of control)	100 ± 8.74	105.98 ± 15	176.38 ± 16.63	217.81 ± 24.38	238.43 ± 17.96	273.71 ± 17.98	308.82 ± 19.43	315.36 ± 39.55	7.06 ± 3.22 (Verapamil, 100 µM)
BCRP	Transporter specific transport (pmol/mg/min)	234.94 ± 7.67	245.46 ± 39.76	292.9 ± 74.85	250.11 ± 4.9	224.7 ± 41.39	247.55 ± 24.88	229.39 ± 7.8	182.87 ± 4.56	1.87 ± 0.94 (Ko134, 1 µM)
	Relative transport (% of control)	100 ± 4.62	104.48 ± 17.26	124.67 ± 32.12	106.46 ± 4.05	95.64 ± 17.89	105.37 ± 11.13	97.64 ± 4.6	77.84 ± 3.2	0.79 ± 0.4 (Ko134, 1 µM)
OATP1B1	Transporter specific transport (cpm)	843 ± 68.8	894 ± 16.27	875.67 ± 93.9	909.67 ± 25.41	860.67 ± 53.28	833 ± 83.08	762 ± 52.97	623.67 ± 76.02	51.67 ± 17.7 (Cerivastatin, 100 µM)
	Relative transport (% of control)	100 ± 11.54	106.05 ± 8.87	103.88 ± 14.00	107.91 ± 9.31	102.10 ± 10.46	98.81 ± 12.73	90.39 ± 9.69	73.98 ± 10.85	6.13 ± 2.16 (Cerivastatin, 100 µM)

Study Number		(b) (4)-0008								
Type of Study		Transporter inhibition potential								
OATP1B3	Transporter specific transport (AFU)	151,273.33 ± 6,950.29	146,740.00 ± 10,227.79	148,179.67 ± 13,306.32	155,885.67 ± 9,213.47	145,939.00 ± 11,225.04	154,044.67 ± 2,131.00	166,256.33 ± 6,136.75	151,381.67 ± 13,219.15	7,057.67 ± 931.84 (Fluvastatin, 30 µM)
	Relative transport (% of control)	100 ± 6.50	97.00 ± 8.10	97.95 ± 9.88	103.05 ± 7.71	96.47 ± 8.64	101.83 ± 4.89	109.90 ± 6.48	100.07 ± 9.87	4.67 ± 0.65 (Fluvastatin, 30 µM)
OAT1	Transporter specific transport (cpm)	1,303.00 ± 13.93	1,265.33 ± 57.97	1,273.33 ± 120.07	1,284.00 ± 25.47	1,201.67 ± 26.43	1,207.33 ± 19.12	1,113.67 ± 69.12	961.67 ± 40.86	81.67 ± 18.74 (Probenecid, 200 µM)
	Relative transport (% of control)	100 ± 1.51	97.11 ± 4.57	97.72 ± 9.27	98.54 ± 2.22	92.22 ± 2.25	92.66 ± 1.77	85.47 ± 5.38	73.80 ± 3.23	6.27 ± 1.44 (Probenecid, 200 µM)
OAT3	Transporter specific transport (cpm)	500.33 ± 11.08	611.33 ± 39.16	549.67 ± 69.20	525.67 ± 31.46	492.83 ± 39.63	462.00 ± 39.38	331.00 ± 27.31	207.33 ± 5.60	37.00 ± 16.66 (Probenecid, 200 µM)
	Relative transport (% of control)	100 ± 3.13	122.19 ± 8.28	109.86 ± 14.04	105.06 ± 6.7	98.50 ± 8.22	92.34 ± 8.13	66.16 ± 5.65	41.44 ± 1.45	7.40 ± 3.3 (Probenecid, 200 µM)
OCT2	Transporter specific transport (pmol/mg/min)	603.00 ± 62.38	597.67 ± 24.47	617.67 ± 37.31	545.67 ± 39.79	521.67 ± 31.15	430.33 ± 13.2	292.67 ± 13.98	147.00 ± 8.29	24.00 ± 12.04 (Verapamil, 100 µM)
	Relative transport (% of control)	100 ± 14.63	99.12 ± 11.03	102.43 ± 12.27	90.49 ± 11.45	86.51 ± 10.33	71.37 ± 7.70	48.54 ± 5.53	24.38 ± 2.87	3.98 ± 2.04 (Verapamil, 100 µM)

Abbreviations: P-gp = P-glycoprotein; BCRP - Breast Cancer Resistance Protein; OAT1= Organic Anion Transporter 1; OAT3 = Organic Anion Transporter 3; OATP1B1 = Organic Anion Transporting Polypeptide 1B1; OATP1B3 = Organic Anion Transporting Polypeptide 1B3; OCT2 = Organic Cation Transporter 2.
Additional Information: Abametapir OCT2 IC_{50} = 35.4 µM. Abametapir OAT3 IC_{50} = 57.5 µM.

Abametapir carboxyl:

The potential for abametapir carboxyl to function as an inhibitor of ABC efflux and SLC uptake transporters was assessed in vitro (Reports OPT-2014-055 and OPT-2014-081). Abametapir carboxyl (100 µM) was administered to MDCKII monolayers transfected with MDR1 or Caco-2 cells endogenously expressing BCRP for 2 hours in the presence of radiolabeled transporter-

specific probe substrates. Positive controls consisted of transporter-specific inhibitors, and negative controls consisted of vehicle and, for MDR1, non-transfected monolayers. Reactions were quenched, and samples from the basal and apical wells were measured for probe substrates by radiometric detection. Transport was measured in both the apical-to-basal and basal-to-apical directions. BCRP transport was not inhibited, while MDR1 transport was inhibited only 18.7% by abametapir carboxyl at 100 μM.

Abametapir carboxyl (100 μM) was administered to MDCKII monolayers transfected with OATP1B1, OATP1B3, OAT1, OCT2, or OAT3 for 5 minutes in the presence of radiolabeled transporter-specific probe substrates. Positive controls consisted of transporter-specific inhibitors in the presence of probe substrates. Negative controls consisted of probe substrates without candidate inhibitors. Identical treatments were made to MDCKII monolayers which did not express the transporters. Reactions were quenched, and quantities of probe substrates in cell extracts were measured by radiometric detection. OAT1, OCT2, and OATP1B1-mediated transport were inhibited by less than 30% (OAT1 by 25.4%, OCT2 by 28.7%, OATP1B1 by 21.8%). OAT3-mediated transport was inhibited by 77.4% ($p=0.0016$) at a concentrations of 100 μM. Inhibition of OAT3-mediated transport was further characterized over the abametapir carboxyl concentration range of 3 to 200 μM in the same manner as described above, and the IC50 was determined to be 17.1 μM. Detailed results are shown in Table 13.

Table 13: Results of abametapir carboxyl transporter inhibition

Study Numbers	**OPT-2014-055, OPT-2014-081**		
Type of Study	Transporter inhibition potential		
Method	Abametapir carboxyl (100 µM) was incubated with polarized monolayers of MDCK-II cells expressing OAT1, OAT3, OCT2, OAT1B1, or OATP1B3; Caco-2 cells expressing BCRP; and MDCK-MDR1 cells expressing P-gp. The transport of each substrate was determined by radiometric detection. Additionally, OAT3 inhibition was examined over the concentration range of 3 to 200 µM.		
Transporter	Test condition	Net Transporter Mediated Cellular Accumulation (pmol/min/cm^2)	Inhibition (%)
OAT1	Vehicle	1.01 ± 0.101	-
	Abametapir carboxyl, 100 µM	0.753 ± 0.0920	25.4 ± 9.11
	Probenecid, 100 µM	0.114 ± 0.0365	88.7 ± 3.61
OAT3	Vehicle	0.418 ± 0.0512	-
	Abametapir carboxyl, 100 µM	0.0948 ± 0.0522	77.4 ± 12.5
	Probenecid, 100 µM	0.0255 ± 0.0148	93.9 ± 3.53
	Vehicle	0.371 ± 0.0486	-
	Abametapir carboxyl, 3 µM	0.329 ± 0.0302	11.4 ± 8.15
	Abametapir carboxyl, 10 µM	0.218 ± 0.0443	41.2 ± 11.9
	Abametapir carboxyl, 30 µM	0.128 ± 0.0202	65.6 ± 5.46
	Abametapir carboxyl, 60 µM	0.105 ± 0.0273	71.8 ± 7.36
	Abametapir carboxyl, 100 µM	0.0941 ± 0.0395	74.6 ± 10.7
	Abametapir carboxyl, 200 µM	0.0209 ± 0.0277	94.4 ± 7.47
	Probenecid, 100 µM	0.00535 ± 0.0240	98.6 ± 6.47
OCT2	Vehicle	9.84 ± 0.327	-
	Abametapir carboxyl, 100 µM	7.02 ± 0.175	28.7 ± 1.77
	Quinidine, 1000 µM	0.233 ± 0.0760	97.6 ± 0.773

Study Numbers	**OPT-2014-055, OPT-2014-081**		
Type of Study	Transporter inhibition potential		
OATP1B1	Vehicle	1.39 ± 0.0453	-
	Abametapir carboxyl, 100 µM	1.09 ± 0.0968	21.8 ± 6.95
	Rifampicin, 100 µM	0.0201 ± 0.00711	98.6 ± 0.511
OATP1B3	Vehicle	1.73 ± 0.124	-
	Abametapir carboxyl, 100 µM	1.57 ± 0.133	9,62 ± 7.69
	Rifampicin, 100 µM	0.0372 ± 0.0127	97.9 ± 0.732
Transporter	Test condition	Efflux Ratio (Papp B -> A) / (Papp A -> B)	Inhibition (%)
BCRP	Vehicle	5.44 ± 0.142	-
	Abametapir carboxyl, 100 µM	4.67 ± 0.225	-1.07 ± 6.19
	Chrysin, 100 µM	1.07 ± 0.0347	94.3 ± 2.65
P-gp	Vehicle	36.8 ± 2.04	-
	Abametapir carboxyl, 100 µM	7.88 ± 0.0185	18.7 ± 0.22
	Verapamil, 100 µM	1.43 ± 0.0527	90.1 ± 1.22

Abbreviations: P-gp = P-glycoprotein; BCRP - Breast Cancer Resistance Protein; OAT1= Organic Anion Transporter 1; OAT3 = Organic Anion Transporter 3; OATP1B1 = Organic Anion Transporting Polypeptide 1B1; OATP1B3 = Organic Anion Transporting Polypeptide 1B3; OCT2 = Organic Cation Transporter 2.
Additional Information: The OAT3 IC_{50} for abametapir carboxyl was 17.1 µM.

2.5 General Biopharmaceutics

2.5.1 What is the formulation composition of Abametapir lotion, 0.74%?

Abametapir lotion 0.74% is a white to off white lotion consisting of an oil-in-water emulsion. The formulation of the drug product is shown in Table 14. Notably the formulation contains (b) (4) w/w benzyl alcohol.

Table 14: Abametapir lotion 0.74% formulation composition

Component	Quantity		Function	Quality Standard
	Amount per unit (g/bottle)	%w/w		
Abametapir (5,5′-Dimethyl-2,2′-dipyridyl)	(b) (4)	0.74	Active	In-house
Light mineral oil (b) (4)		(b) (4)		NF
Polysorbate 20				NF
Benzyl Alcohol				NF
Butylated hydroxytoluene				NF
Carbomer 980 (b) (4)				NF
Trolamine				NF
Purified Water				USP

Abbreviations: NF = National Formulary; USP = United States Pharmacopeia; %w/w = weight per weight.

2.5.2 Was the to-be-marketed formulation used in the clinical trials?

Yes. The to-be-marketed formulation was used in all clinical studies, except for an initial tolerability Phase 1 study Ha01-001. Study Ha01-001 was not essential to support the NDA.

2.6 Analytical

2.6.1 What bioanalytical methods were used to assess abametapir and its metabolites abametapir hydroxyl and abametapir carboxyl and were they adequately validated?

The plasma samples from the human PK studies were analyzed for abametapir by tandem mass spectrometry (LC-MS/MS) procedures in methods V508 v1, V508 v2, V555, and V580. Method V580 also included analysis of metabolites abametapir hydroxyl and abametapir carboxyl in plasma samples. Serum samples from the human PK studies were analyzed for benzyl alcohol by gas chromatography-mass spectrometric procedures (GC-MS). All bioanalytical methods were adequately validated. A summary of results are shown in Tables 15, 16 and 17 for abametapir, abametapir metabolites and benzyl alcohol, respectively.

Table 15: Summary of plasma abametapir assay performance

Parameter/Methods	V508 v1	V508 v2	V555	V 580
Affected studies	Ha01-001	Ha02-002	Ha02-003, Ha02-005, Ha03-004	Ha03-003
Assay range	1 - 500 ng/mL	1 - 100 ng/mL	0.25 – 100 ng/mL	0.25 – 1000 ng/mL
Intra-run precision	1.91 to 5.63%	2.9 to 11.6%	4.5 to 5.4%	0.8 to 11.8%
Intra-run accuracy	+6.72 to +8.12%	-10.7 to -0.1%	-5.8 to +4.8%	-8.2 to +11.9%, except for

				+17.6% at LLOQ for one run.
Inter-run precision	6.41 to 8.13%	Not tested (partial revalidation after v1)	2.6 to 8.0%	1.3 to 8.5%
Inter-run accuracy	-6.83 to 2.40%	Not tested (partial revalidation after v1)	+2.7 to +6.4%	-7.4 to +12.2%
Long term storage stability	106 days at -80 ºC	106 days at -80 ºC	259 days at -80 ºC	568 days at -80 ºC

Table 16: Summary of plasma abametapir carboxyl and abametapir hydroxyl assay performance in method V 580.

Parameter/Analyte	Abametapir carboxyl	Abametapir hydroxyl
Affected studies	Ha02-003, Ha02-005, Ha03-003, Ha03-004	
Assay range	0.25 - 1000 ng/mL	0.50 – 1000 ng/mL
Intra-run precision	0.9 to 8.6%	0.7 to 6.5%
Intra-run accuracy	-10.3 to +9.1%	-7.1 to +15.0%
Inter-run precision	2.5 to 7.6%	2.6 to 7.2%
Inter-run accuracy	-8.1 to +5.8%	-4.5 to +10.1%
Long term storage stability	568 days at -80 ºC	

Table 17: Summary of serum benzyl alcohol assay performance

Parameter/Analyte	Benzyl alcohol
Affected studies	Ha03-003 and Ha03-004
Assay range	0.5 – 5 µg/mL
Intra-run precision	1.7 to 2.7%
Intra-run accuracy	-2.2 to +9.3%
Inter-run precision	1.9 to 6.1%
Inter-run accuracy	+5.6 to +7.7%
Long term storage stability	452 days at -80 ºC

Storage stability:
Analysis of abametapir in plasma samples in all clinical trials were conducted within established long term storage stability. For analysis of benzyl alcohol, samples from 19 of 22 subjects were analyzed within the 452 days demonstrated storage stability. Samples from the remaining 3 subjects were analyzed after up to 472 days of storage. This is a minor deviation from the demonstrated storage duration of 452 days and all data were considered acceptable for review.

For analysis of abametapir carboxyl, samples from trial Ha03-003 were analyzed in real time and were analyzed within the demonstrated storage stability duration of 568 days. Samples from trial Ha03-004 were analyzed retrospectively but were also within the demonstrated stability period.

Samples from trial Ha02-003 were collected in 2011 and retained in storage for 1251 days prior to analysis for abametapir carboxyl. Therefore, there is insufficient demonstrated stability to support the analysis of abametapir carboxyl in trial Ha02-003. The sponsor suggested that since stability was demonstrated for extended period of 568 days the stability may be inferred out to 1251 days. This reviewer also note that the AUC and Cmax for pediatric subjects (aged 3 – 12 years) in trial Ha02-003 was similar to and in between those observed for the 3 - 17 years age group in trials Ha03-003 and Ha03-004 (see Table 18), which were analyzed within the demonstrated stability period. The same order among the 3 trials was seen for the parent abametapir (Table 19). These data suggest that there were no overt degradation of abametapir carboxyl samples from trial Ha02-003 and the data may be used for review. However, the sponsor should continue to evaluate the storage stability to fully support the storage duration as a post marketing commitment.

Table 18: Summary of abametapir carboxyl exposure in pediatric subjects ≥3 years of age

Study	Age group	N	Cmax (ng/mL) Mean (%CV)	AUC0-8h (ng*h/mL) Mean (%CV)
Ha02-003	3 to 12 years	12	2000 (57%)	11400 (57%)
Ha03-003	3 to <17 years	12	3353 (58%)	21369 (64%)
Ha03-004	3 to <18 years	7	1760 (42%)	10000 (46%)

Table 19: Summary of abametapir exposure in pediatric subjects ≥3 years of age

Study	Age group	N	Cmax (ng/mL) Mean (%CV)	AUC0-8h (ng*h/mL) Mean (%CV)
Ha02-003	3 to 12 years	12	65 (57%)	254 (67%)
Ha03-003	3 to <17 years	12	121 (60%)	330 (49%)
Ha03-004	3 to <18 years	7	52 (45%)	194 (39%)

3 Detailed Labeling Recommendations

The following changes are recommended for sections 5, 8 and 12 of the label. Deletions are noted as ~~strikethrough~~ and additions are noted as double underline.

7 DRUG INTERACTIONS

In vitro studies suggest there is a potential for inhibition of cytochrome P450 (CYP) 3A4, 2B6 and 1A2 enzyme following a single application of XEGLYZE (b) (4) Use of XEGLYZE (b) (4) with drugs that are substrate of these enzymes may lead to increased systemic concentration of the interacting drugs. Avoid administration of drugs that are substrates of CYP3A4, CYP2B6, or CYP1A2 within 2 weeks after application XEGLYZE (b) (4). If this is not feasible, avoid use of XEGLYZE (b) (4) *[see Clinical Pharmacology 12.3]*.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Abametapir (5,5'-dimethyl 2,2'-bipyridinyl) is a metalloproteinase inhibitor (b) (4) Metalloproteinases have (b) (4) a (b) (4) role in (b) (4) physiological processes (b) (4) critical to egg development and survival of crawling lice. (b) (4)

(b) (4)

12.3 Pharmacokinetics

Absorption

(b) (4)

The pharmacokinetics of XEGLYZE [redacted] were evaluated in 3 trials, namely Trials A, B, and C. Each trial enrolled lice infested subjects who received a single 10 minute application of XEGLYZE [redacted]. Pharmacokinetic samplings were carried out to 72 hours post dose in adults and 8 hours post dose in pediatrics for all trials.

Trial A evaluated pharmacokinetics in 6 adult and 12 pediatric subjects 3 to 12 years of age. The mean (%CV) abametapir plasma maximum concentration (Cmax) and area under the concentration time curve from 0 to 8 hours post dose (AUC0-8h) in the adult group were 41 (66%) ng/mL and 121 (50%) ng*h/mL, respectively. The mean (%CV) Cmax and AUC0-8h in the pediatric group were 73 (57%) ng/mL and 264 [redacted]%) ng*h/mL, respectively, [redacted] adults. The mean (%CV) terminal half-life in adults was 21 (11%) hours.

Trials B and C evaluated pharmacokinetics in pediatric subjects 6 months to 17 years [redacted]. The pharmacokinetic results for plasma abametapir are shown in Table [redacted], even though the values varied between the 2 trials, abametapir exposure increased as the age of the subject decreased. Abametapir absorption was rapid with a median Tmax of 0.57 to 1.54 hours.

Table 21 Abametapir pharmacokinetic parameters in subjects with head lice infestation

Study	Age Group	n	C_{max} (ng/mL) Mean (%CV)	AUC_{0-8} (ng*h/mL) Mean (%CV)
[redacted]	6 months to <1 year	1	418	1057
		5	228 (50%)	688 (43%)
	1 year to <2 years	3	209 (62%)	446 (65%)
		8	147 (49%)	406 (37%)
	2 years to <3 years	6	206 (66%)	633 (57%)
		8	160 (48%)	602 (51%)

Study	Age Group	n	C_{max} (ng/mL) Mean (%CV)	AUC_{0-8} (ng*h/mL) Mean (%CV)
(b) (4)	3 years to 17 years	12	121 (60%)	330 (49%)
		7	52 (45%)	(b) (4)

Serum concentration of benzyl alcohol, an excipient in the formulation of XEGLYZE (b) (4) was assessed in Trials B and C. Benzyl alcohol in serum was measurable (limit of quantitation = 0.5 µg/mL) in 7 subjects out of 39 evaluable subjects. The Cmax of benzyl alcohol in these 7 subjects ranged from 0.52 to 3.57 µg/mL *[see Warnings and Precautions (5.X) and Use in Specific Populations (8.4)].*

Distribution

Abametapir and its primary human metabolite, abametapir carboxyl, are highly bound to proteins in (b) (4) plasma. Abametapir is 91.3 – 92.3% bound to plasma proteins, and abametapir carboxyl is 96.0% – 97.5% bound to plasma proteins.

Elimination

~~Metabolism~~Metabolism

Abametapir is extensively (b) (4) metabolized, primarily by the cytochrome P450 enzyme CYP1A2 to a mono-hydroxylated metabolite (abametapir hydroxyl) and further to a mono-carboxylated metabolite (abametapir carboxyl). Abametapir carboxyl is cleared slowly from the systemic circulation resulting in plasma concentration (b) (4) higher than that of abametapir. Based on data in adults in Trial A above, where samplings was carried out to 72 hours, the ratios of Cmax and AUC0-72h between abametapir carboxyl and abametapir were about 30 and 250, respectively. The elimination half-life of abametapir carboxyl has not been well characterized but is estimated to be approximately (mean ± SD) 71 ± 40 hours or longer in adults.

~~Excretion~~Excretion

Excretion of abametapir and its human metabolites was not examined in patients. (b) (4)

Drug interaction:

In vitro studies suggest that there is a potential for inhibition of cytochrome P450 3A4, 2B6, and 1A2 enzyme following application of XEGLYZE (b) (4) due to high and prolonged systemic exposure of the metabolite abametapir carboxyl *[seeDrug Interactions (7)].*

4 Appendix

4.1 Individual Study Reviews

4.1.1 Trial Ha02-003

Title: An Efficacy and Safety Study of Ha44 Gel Administered Topically for the Treatment of Head Lice Infestation.

Studied period:

Date of first enrolment: 13 Apr 2011
Date of last completed: 16 Aug 2011

Objectives:

Primary objective: To evaluate the efficacy of Ha44 Gel
Secondary objective: To evaluate the safety, tolerability and the pharmacokinetics of Ha44 Gel

Study design:

This was a Phase 2b, multicenter, double-blind, randomized, vehicle-controlled, parallel study. The study consisted of 2 identical, consecutive stages (Stage 1 and Stage 2), with a planned interim analysis between the 2 stages. Stage 1 was to enroll approximately 43 subjects and Stage 2 was to enroll approximately 89 subjects, for a total of 132 study subjects. Subjects could only be enrolled once in the study and could not participate in both stages of the study. Enrollment was suspended at the completion of Stage 1 to allow these subjects to complete all study visits. The number of subjects enrolled in Stage 1 was dependent on the size of the last household enrolled in Stage 1. In each stage, subjects were randomized at 1:1:1 ratio to the Ha44 Gel 0.37% w/v (Group A), Ha44 Gel 0.74% w/v (Group B) and the vehicle control (Group C) treatment groups.

The study was designed to assess the efficacy, safety, and tolerability of a single application of Ha44 Gel at 2 different dose levels (0.37% and 0.74%) compared to a vehicle control. The treatment groups are identified as Ha44 Gel 0.37%, Ha44 Gel 0.74% and Control in the study result sections.

The study also assessed the pharmacokinetics (PK) of Ha44 Gel in 2 subsets of subjects: Pediatric PK subset (2-12 years of age) and Adult PK subset (≥ 18 years of age). PK assessments were performed only at 1 study center. The Pediatric PK subset was to be comprised of 33 pediatric subjects enrolled from 1 of the 2 study centers, which was to include at least 11 subjects 2-5 years of age and 22 subjects 6-12 years of age. To ensure a sufficient number of subjects ≤5 years of age, the Pediatric PK subset could include more than 33 enrolled subjects. Subjects could be enrolled into the Pediatric PK subset from either Stage 1 or Stage 2 of the study. The Adult PK subset was to be comprised of 20 adult subjects enrolled from the same study center. Subjects could be enrolled into the Adult PK subset from either Stage 1 or Stage 2 of the study.

All PK sampling times were determined by the investigational product (IP) application start time, i.e. when the IP was first applied to the hair and scalp. Pediatric PK sampling time points were: 0 (predose), 30, 60 minutes and 8 hours and the Adult PK sampling time points were: 0 (predose); 30; 60 minutes; and 2; 4; 8; 24, 48 and 72 hours. PK assessment windows were ±5 min for the 30

and 60 min assessments; ±10 min for 2, 4 and 8 hr assessments; and ±1 hr for the 24, 48 and 72 hr assessments.

All household members were to be consented and screened for study eligibility. Eligible subjects within each household were enrolled and randomized to the same treatment group. The youngest member of the household who was between 2 and 12 years of age and met the eligibility criteria (including the presence of at least 3 live lice on Day 0) was the index subject for that household. Each family was required to have an eligible index subject to qualify for enrollment. Non-index household members were to have at least 1 live louse present on Day 0 to participate in the trial.

Eligible subjects from each household were treated together on the same day with a single application of IP by the study staff. This was the only application of IP in the study. All subjects then returned to the study center for at least 3 follow-up clinic visits on Days 1, 7 and 14 (i.e. at least 4 visits in total). The adult PK subset had 2 additional clinic visits on Day 2 and 3 (i.e. at least 6 visits in total).

Number of subjects (planned and analyzed): Approximately 132 pediatric and adult subjects, 2 years of age or older, with an active head lice infestation were planned to be enrolled into the study.

A total of 142 subjects were registered from 2 study centers in the US. All subjects met the eligibility criteria and were randomized to the Ha44 Gel 0.37% (46), Ha44 Gel 0.74% (49), and the Vehicle (47) treatment groups. A total of 134 subjects (Ha44 Gel 0.37%, 42; Ha44 Gel 0.74%, 48; Vehicle, 44) completed all of the study visits.

A total of 55 (Ha44 Gel 0.37%, 18; Ha44 Gel 0.74%, 19; Vehicle, 18) subjects from Center 2 participated in the PK analysis. The Pediatric PK subset included 11 subjects (Ha44 Gel 0.37%, 4; Ha44 Gel 0.74%, 3; Vehicle, 4) 2-5 years and 24 subjects (Ha44 Gel 0.37%, 10; Ha44 Gel 0.74%, 10; Vehicle, 4) 6-12 years of age. A total of 20 subjects (Ha44 Gel 0.37%, 4; Ha44 Gel 0.74%, 6; Vehicle, 10) >18 years of age were included in the Adult PK subset.

Diagnosis and main criteria for inclusion:

1. Male or female.
2. 2 years of age or older.
3. Be in good health, as determined by medical history and physical examination.
4. Body weight of at least 33 pounds.
5. Had an active head lice infestation at Day 0 as determined by an experienced evaluator. An active infection was defined as at least 3 live lice for the index subject and at least 1 live louse for the other household members.
6. Female subjects were:
    a. of non-childbearing potential (no history of menstrual periods, post-hysterectomy, or, post-menopausal for at least 2 years) OR,
    b. if of childbearing potential, had to have a negative urine pregnancy test prior to treatment and agreed to use a highly effective method of contraception from Day 0 through the Day 14 visit. Acceptable methods of contraception included abstinence, vasectomized partner, tubal ligation, combined oral hormonal contraceptive,

contraceptive injection, contraceptive patch or IUD. If a hormonal contraception was the only method, the subject had to be on a stable dose for at least 3 months.

7. If the subject was in the Pediatric PK subset, parent/guardian agreed to have serial blood samples collected for PK analysis on Day 0.
8. Signed an informed consent and/or assent form (ICF).

Test product, dose and mode of administration, batch number: The volume of the Ha44 Gel applied to each subject had to be sufficient to achieve saturation of the scalp and hair. No more than 200 mL (1 bottle) of IP was to be applied to each subject's scalp and hair regardless of their hair length and/or thickness. Total time of IP exposure is the time it took to apply the IP (expected to be less than 5 minutes), followed by the 10 minute treatment period.

The batch number of the 0.37% Ha44 Gel was RD-10091 and 0.74% Ha44 Gel was RD-10092.

Duration of treatment: The duration of the study for each subject from screening (Day 0) to the follow-up visit was approximately 14 days.

Reference therapy, dose and mode of administration, batch number: The vehicle control is identical in appearance, odor and formulation to Ha44 Gel except without the active ingredient.

The batch number of the vehicle control was RD-10090.

Criteria for evaluation:
Primary Efficacy Endpoint: The primary efficacy endpoint was the proportion of subjects who were lice free at all follow-up visits through the Day 14 visit.
Secondary Efficacy Endpoints:
1. Proportion of index subjects who were lice free at all follow-up visits through the Day 14 visit.
2. Proportion of all subjects who were lice free at each follow-up study visit (Day 1, 7, 14).
Safety Endpoints: The assessment of safety and tolerability of Ha44 Gel included treatment emergent adverse events (TEAEs), scalp/eye irritation assessment, clinical laboratory safety test results, vital signs, physical examination and ECG.

PK analysis:
Ha44 plasma concentrations were summarized using descriptive statistics (including N, mean, standard deviation (SD), coefficient of variation (CV%), median, minimum, and maximum) for each treatment. Post hoc analysis for abametapir carboxyl was also conducted.

Results:
Review note: This section focuses only on the PK results. For safety and efficacy results, please see clinical review.

Protocol deviation:
There were no major protocol deviations.

Ha44 pharmacokinetics:

Fifty-five (55) subjects enrolled in this study provided PK samples for analysis of Ha44 plasma concentrations. Of the 55 subjects, plasma concentrations were evaluated for a subset of 33 subjects who received Ha44 Gel and had sufficient data points to determine concentration-time profiles. This group of 33 subjects was comprised of 24 children aged 3-12 years (Ha44 Gel 0.37%, 12; Ha44 Gel 0.74%, 12) and 9 adults aged ≥18 years (Ha44 Gel 0.37%, 3; Ha44 Gel 0.74%, 6) [Note: the trial allowed enrollment of subjects ≥2 years of age but the youngest subject enrolled was 3 years of age]. Due to practical and ethical limitations on the number of blood samples that can be drawn from pediatric subjects, PK sampling was conducted only through 8 hours post dosing. The longest measure of exposure for the pediatric subjects was AUC(0-8).

The mean Ha44 concentration-time profiles for adults (through 72 hours post-dose) showed rapid absorption into the systemic circulation followed by a biphasic distribution (Figure 7). Median Tmax values were 0.97 to 1.54 hours in adults and 0.58 to 0.98 hours in pediatric subjects across the 2 dose levels demonstrating rapid absorption of Ha44 Gel for all age groups. The mean t½ of Ha44 Gel in adults was 28.8 and 21.3 hours for the 0.37% and 0.74% doses, respectively, indicating a relatively long terminal phase component for the systemic concentration-time profile. For the individual adult subjects, AUC(0-8) represents 24% to 57% of AUCinf while the percent extrapolation from AUClast to AUCinf in the terminal phase was 25% or less. Ha44 exposure was higher in pediatrics compared to adults (Figure 8). The t½ of Ha44 Gel in pediatric subjects could not be accurately estimated due to the short PK sampling time of only 8 hours post-dose (Table 22).

Exposure to Ha44 Gel in plasma measured by mean Cmax and AUC(0-8) approximately doubled when the concentration of Ha44 Gel doubled from 0.37% to 0.74%. This increase in exposure was seen in both the pediatric and adult populations. For adult subjects, AUClast and AUCinf approximately doubled with increase in dose from 0.37% and 0.74%.

Ha44 Gel exposure (AUC(0-8) and Cmax) increased with decreasing age, body weight, body mass index (BMI), and with increasing weight adjusted Ha44 Gel dose levels. The strongest correlations were found to exist between Ha44 Gel exposure and body weight, and Ha44 Gel exposure and dose normalized by body weight (mg/kg) (data not shown).

Exposure (measured by both Cmax and AUC(0-8)) was higher in the pediatric group compared to the adult group at both dose levels of Ha44 Gel 0.37% and 0.74%. When comparing within the same dose level, the pediatric age group (3-12 years of age) had approximately 2-fold higher mean Cmax and AUC(0-8) values compared to those seen in the adult age group (≥18 years of age).

Figure 7: Mean Ha44 plasma concentration time plots by treatment in adults

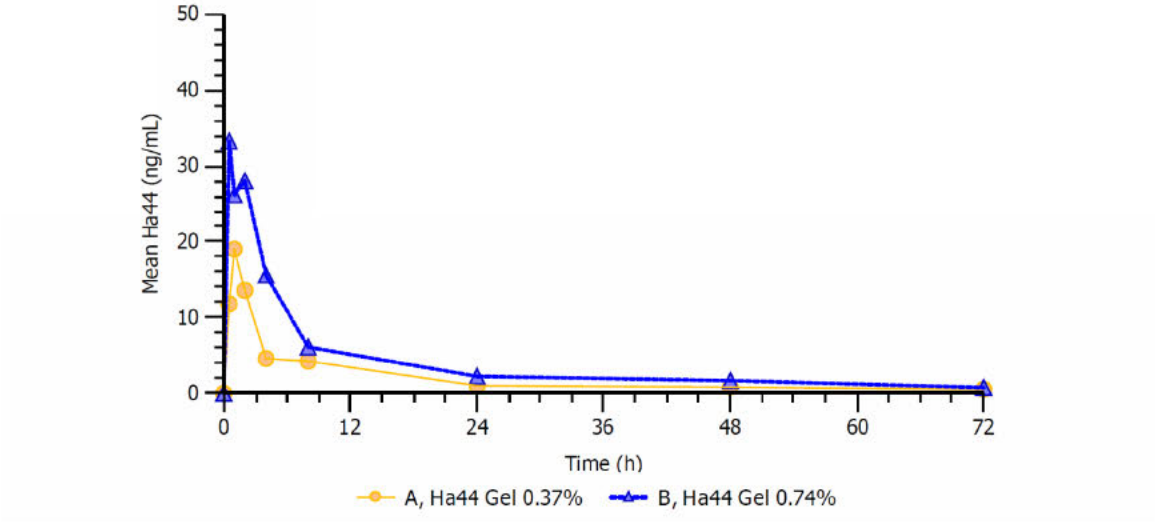


Figure 8: Mean Ha44 plasma concentration time plots by treatment and age group

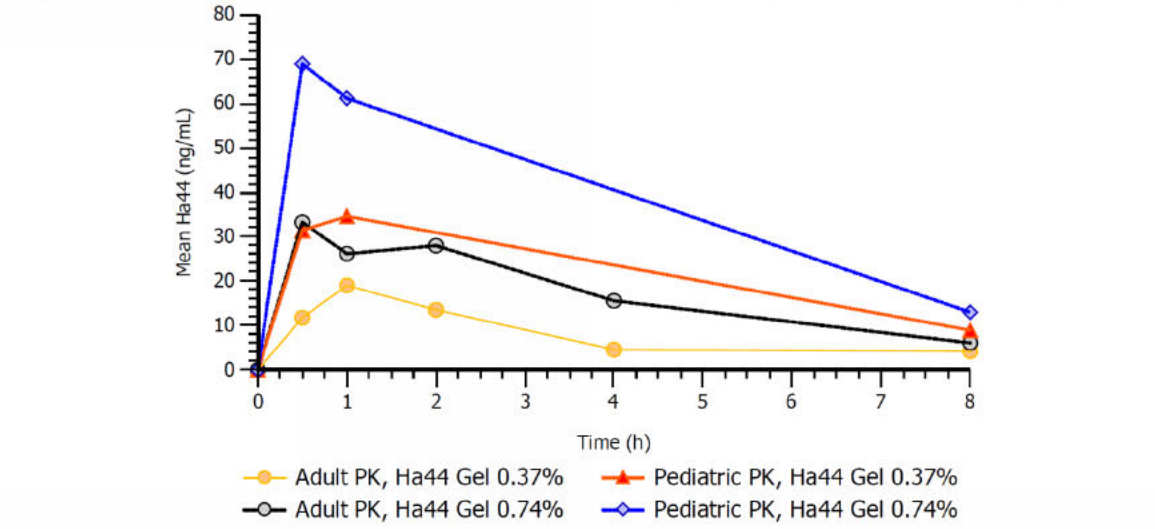


Table 22: Mean (%CV) Ha44 parameters of all groups

Group	Ha44 Dose	Cmax (ng/mL)	Tmax[a] (h)	λz (1/h)	t½ (h)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	AUC(0-8) (h*ng/mL)
Adults A (N=3)	0.37%	19.0 (8.3%)	0.97 (0.93-1.02)	0.036 (72%)	28.8 (76%)	124.6 (44%)	143.9 (41%)	59.0 (27%)
Adults B (N=6)	0.74%	41.0 (66%)	1.54 (0.48-4.02)	0.033 (11%)	21.3 (11%)	278.8 (44%)	302.5 (42%)	120.7 (50%)
Peds A (N=12)	0.37%	37.0 (69%)	0.98 (0.47-1.12)	NC	NC	153.9 (63%)	NA	154.2 (63%)
Peds B (N=12)	0.74%	72.6 (57%)	0.58 (0.42-1.03)	NC	NC	263.2 (62%)	NA	263.9 (62%)

%CV listed in parentheses
NC = not calculated
[a] Median (range)

Ha44 carboxyl pharmacokinetics:
Abametapir metabolites were identified after study Ha02-003 was complete. Archived samples were analyzed for abametapir carboxyl several years after. Only the archived plasma samples for subjects treated with the to-be-marketed formulation of abametapir lotion 0.74% were analyzed for metabolites. Stability data for abametapir metabolites did not extend to the duration of frozen storage of plasma samples used in retrospective analyses of study Ha02-003, however all data collected to date indicate robust long-term stability of both the abametapir carboxyl and abametapir hydroxyl metabolites in plasma and support the interpretation that the metabolite concentration data determined retrospectively in stored samples are indeed accurate (see additional discussion in section 2.6.1 of this review).

The Cmax and AUC0-8 of the primary metabolite, abametapir carboxyl, were higher in pediatrics compared to adults (Table 23). There was insufficient data from pediatrics to calculate AUCinf, t1/2 and λz. The concentrations of abametapir carboxyl appear to be much greater than that of the parent abametapir. Based on data in adults, where samplings was carried out to 72 hours, the ratios of Cmax and AUC0-72h between abametapir carboxyl and abametapir were about 30 and 250, respectively (Table 24). The elimination half-life of abametapir carboxyl has not been well characterized but is estimated to be approximately (mean ± SD) 71 ± 40 hours in adults.

Table 23: Abametapir carboxyl PK parameters in adults and pediatrics for Abametapir Lotion 0.74%

n	Age Group	C_{max} (ng/mL) Mean ± SD	T_{max} (hours) Median ± SD	AUC_{0-8} (ng*h/mL) Mean ± SD
6	Adults	1130 ± 397	28.7 ± 16.9	4900 ± 1680
12	2 to 12 years	2000 ± 1140	8.0 ± 0.0	11400 ± 6550

Abbreviations: n= number of subjects; SD = standard deviation.

Table 24: Ratio of abametapir carboxyl metabolite to parent in adults (Source: Table 15 of report HATC201401)

Study	Subject ID	Age (yrs)	Weight (kg)	Abametapir C_{max} (ng/mL)	Abametapir AUC_{0-Last} (hr*ng/mL)	Abametapir $AUC_{0-\infty}$ (hr*ng/mL)	Abametapir-COOH C_{max} (ng/mL)	Abametapir-COOH AUC_{0-Last} (hr*ng/mL)	Abametapir-COOH $AUC_{0-\infty}$ (hr*ng/mL)	C_{max} Met:Parent Ratio	AUC_{0-Last} Met:Parent Ratio	$AUC_{0-\infty}$ Met:Parent Ratio
Ph2b	(b) (6)	29	122.9	17.4	180.9	200.4	674	43700	101477.76	38.74	241.57	506.38
Ph2b		27	117.46	47.6	435.7	455.4	947	53000	235076.4	19.89	121.64	516.20
Ph2b		28	75.74	37.8	396	430.9	1540	91800	186265.42	40.74	231.82	432.27
Ph2b		26	107.94	90	315.2	339.2	1630	85600	140234.95	18.11	271.57	413.43
Ph2b		24	107.03	38	214.1	247.4	1210	68400	130855.45	31.84	319.48	528.92
Ph2b		51	42.99	15.3	131.2	141.5	779	42100	66330.84	50.92	320.88	468.77
	N	6	6	6	6	6	6	6	6	6	6	6
	Mean	30.83	95.68	41.02	278.85	302.47	1130	64100	143373.47	33.37	251.16	477.66
	SD	10.03	30.56	27.13	122.67	126.96	397.27	21313.85	60177.26	12.71	73.74	47.33
	%CV	32.52	31.94	66.15	43.99	41.97	35.16	33.25	41.97	38.09	29.36	9.91
	Median	27.5	107.48	37.9	264.65	293.3	1078.5	60700	135545.2	35.29	256.57	487.57
	Min	24	42.99	15.3	131.2	141.5	674	42100	66330.84	18.11	121.64	413.43
	Max	51	122.9	90	435.7	455.4	1630	91800	235076.4	50.92	320.88	528.92

Efficacy and Safety: Please see clinical review.

4.1.2 Trial Ha03-003

Title: A Pediatric Safety and Pharmacokinetic Study of Ha44 Gel Administered Topically for the Treatment of Head Lice Infestation.

Studied period:
Date of first enrolment: 8 Apr 2013
Date of last completed: 2 Jul 2014

Objectives:
Primary objective: To evaluate the safety and tolerability of a single application of Ha44 Gel 0.74% w/w for the treatment of head lice

Secondary objective: To evaluate the pharmacokinetics of Ha44, its metabolites and benzyl alcohol (contained in the Ha44 Gel vehicle) under conditions of maximal exposure in a pediatric population.

Design: This was an open-label safety and pharmacokinetic (PK) study of a single application of Ha44 Gel in a pediatric population.

All participants had to have an active head lice infestation (at least 3 live lice) and scalp erythema with evidence of excoriation or inflammation and be 6 months to < 18 years of age. The study enrolled 22 pediatric subjects in order to ensure at least 19 PK-evaluable subjects. The first 3 subjects enrolled (all in group 3) did not have scalp erythema with evidence of excoriation or inflammation. The study enrolled subjects in the following age groups:

Group	Age Range	Number of Subjects
1	6 to < 12 months	1
2	1 to < 2 years	3
3	2 to < 3 years	6
4	3 to 17 years	12

More than one household member with an active lice infestation and scalp erythema with evidence of scalp excoriation or inflammation could participate in the study. Eligible subjects were to be treated at the study site on Day 0 with a single application of the maximum feasible amount of Ha44 Gel, to ensure saturation of the scalp and hair. This was to be the only application of Ha44 Gel in the study. All subjects were to return to the study site for three follow-up clinic visits at Days 1, 7 and 14.

PK samplings:
PK samples for Ha44, Ha44 metabolites and benzyl alcohol were to be collected at 0 (predose), 30 and 60 min and 2 and 8 hr time points following the investigational product (IP) application, with the exception that a 2 hour benzyl alcohol sample was not to be collected in infants weighing less than 29 lb if the subject was enrolled in protocol amendment 1, but 16lbs if the subject was enrolled in amendment 2 or 3. PK assessment windows were ± 5 min for the 30 and

60 min assessments and ± 10 min for the 2 and 8 hr assessments. Note: All post-treatment assessments were to be performed at time points relative to the start of the IP application, which was defined as the time at which the IP was first applied to the scalp and/or hair.

Number of subjects (planned and analyzed): Approximately 22 pediatric subjects were planned to be enrolled into the study in order to ensure that 19 PK-evaluable pediatric subjects. Twenty nine (29) pediatric subjects were screened and 22 of these subjects were eligible for enrollment and received treatment. All 22 subjects completed the study were included in the safety and PK analyses.

Diagnosis and main criteria for inclusion:
1. Male or female, 6 months to <18 years of age
2. Be in good health, as determined by medical history and physical examination
3. Had an active head lice infestation at screening as determined by an experienced evaluator. An active infestation is defined as the presence of at least 3 live lice.
4. Had a primary or secondary eczematous dermatological condition of the scalp at Screening including, but not limited to eczema, atopic dermatitis or active head lice infestation and had at least Grade 2 erythema or pruritus (scratching) with evidence of excoriation/inflammation
5. The parent/guardian agreed to allow serial blood samples collected from subject for PK analysis during study.
6. Parent or guardian signed an Informed Consent Form (ICF).

Test product, dose and mode of administration, batch number: The application of the Ha44 Gel was performed by study staff. A single application of the maximum feasible amount of Ha44 Gel up to 200 g (one container) was administered to each subject ensuring complete saturation of the scalp and hair. The amount of product applied to each subject and time of application were recorded. The Ha44 Gel was in contact with the subject's scalp and hair for the time it took to apply the Ha44 Gel (expected to be less than 5 minutes), followed by the 10 minute treatment period.

The batch number for the Ha44 Gel used in this study was RD 13-003.

Duration of treatment: The duration of the study for each subject from screening (Day 0) to the follow-up visit (Visit 3) was approximately 14 days.

Criteria for evaluation:
PK endpoint: Blood samples were analyzed for concentrations of Ha44, Ha44 metabolites (plasma) and benzyl alcohol (serum).
Safety endpoints: The assessment of safety and tolerability of Ha44 Gel included treatment emergent adverse events (TEAEs), scalp/eye irritation assessment, clinical laboratory safety test results, vital signs, physical examination and ECG.

Statistical methods: Descriptive statistics for continuous variables, sample size (n), mean, standard deviation, median and range are presented; for categorical variables, count and percentage are presented.
Two planned study populations were defined as follows:

- Safety Population: all subjects who received Ha44 Gel.
- PK Population: all subjects who received Ha44 Gel and had sufficient concentration-time profiles to derive the PK parameters (Cmax, Tmax, and AUC0-8) for Ha44 and Ha44 metabolites (abametapir carboxylic and abametapir hydroxyl) and benzyl alcohol.

Bioanalytical methods:
See section 2.6.1 of this review.

Results:

Protocol Deviation:
The sponsor noted that 9 of 13 subjects from Site 02 had at least one reported benzyl alcohol value that was probably due to the bacteriostatic saline solution (NaCl + 0.9% benzyl alcohol) inadvertently used for flushing the catheter between blood sample drawings. The study coordinator responsible for blood draws at this site did not document the use of the bacteriostatic saline solution. The site could not identify those subjects that were affected. To avoid bias, the sponsor excluded values from site 02 in the summary statistics and plots for benzyl alcohol.

Demographic:
The majority of subjects were Caucasian (95.5%) and female (90.9%). The mean weight was 30.1 kg with a range from 9 to 87 kg and the mean height was 111.2 cm with a range from 69 to 165 cm. The mean age was 6.4 years (range: 0.9 - 17.0 years): one subject was 6 to <12 months of age, 3 subjects were 1 to <2 years, 6 subjects were 2 to <3 years and 12 subjects were 3 to <18 years of age.

Treatment compliance:
Ha44 Gel was applied by the clinic staff; all subjects (100%) were compliant to treatment.

PK parameters:
Due to practical and ethical limitations on the number of blood samples that can be drawn from pediatric subjects, blood sampling for PK analysis was conducted only from pre-dose through 8 hours after dosing. Therefore, the longest measure of exposure for the pediatric subjects was AUC0-8. This duration adequately captured the PK profile for abametapir but was inadequate for the major metabolite abametapir carboxyl.

Abametapir (also denoted as Ha44):
PK analysis of plasma concentrations of Ha44 showed the mean Cmax was 169.5 ng/mL (range: 43.9 - 423.0 ng/mL), the median Tmax was 0.50 hours (range: 0.45 - 7.93 hr) and the mean AUC0-8 was 461.7 ng*h/mL (range: 113.1 - 1226.5 ng*h/mL).

Table 25: PK parameters of Ha44

		Ha44 (N = 22)
Cmax (ng/mL)	N	22
	MEAN	169.5
	SD	116.7
	MEDIAN	158.5
	RANGE	(43.9, 423.0)
	CV%	68.8
Tmax (h)	N	22
	MEAN	0.93
	SD	1.57
	MEDIAN	0.50
	RANGE	(0.45, 7.93)
	CV%	168.6
AUC(0-8) (h*ng/mL)	N	22
	MEAN	461.7
	SD	297.6
	MEDIAN	391.3
	RANGE	(113.1, 1226.5)
	CV%	64.5

Abametapir carboxyl:
PK analysis of plasma concentrations of Ha44 carboxyl showed the mean Cmax was 4480.1 ng/mL (range: 833.0 – 9710.0 ng/mL), the median Tmax was 7.93 hours (range: 2.00 – 8.03 hr) and the mean AUC0-8 was 28241.5 ng*h/mL (range: 5286.1 – 62407.8 ng*h/mL).

Table 26: PK parameters of abametapir carboxyl

		Ha44 (N = 22)
Cmax (ng/mL)	N	22
	MEAN	4480.1
	SD	2486.4
	MEDIAN	4190.0
	RANGE	(833.0, 9710.0)
	CV%	55.5
Tmax (h)	N	22
	MEAN	7.67
	SD	1.27
	MEDIAN	7.93
	RANGE	(2.00, 8.03)
	CV%	16.5
AUC(0-8) (h*ng/mL)	N	22
	MEAN	28241.5
	SD	16264.6
	MEDIAN	25471.1
	RANGE	(5286.1, 62407.8)
	CV%	57.6

Abametapir hydroxyl:
PK analysis of plasma concentrations of Ha44 hydroxyl showed the mean Cmax was 1.79 ng/mL (range: 0 - 4.23 ng/mL), the median Tmax was 1.00 hours (range: 0.50 - 8.02 hr) and the mean AUC0-8 was 6.76 ng*h/mL (range: 0 - 19.73 ng*h/mL).

Table 27: PK parameters of abametapir hydroxyl

		Ha44 (N = 22)
Cmax (ng/mL)	N	22
	MEAN	1.79
	SD	1.32
	MEDIAN	1.73
	RANGE	(0.00, 4.23)
	CV%	73.9
Tmax (h)	N	18
	MEAN	1.23
	SD	1.71
	MEDIAN	1.00
	RANGE	(0.50, 8.02)
	CV%	138.4
AUC(0-8) (h*ng/mL)	N	22
	MEAN	6.76
	SD	5.89
	MEDIAN	5.96
	RANGE	(0.00, 19.73)
	CV%	87.1

The individual subject metabolite to parent and metabolite to metabolite ratios for Cmax and AUC0-8 confirms that Ha44 hydroxyl is a minor metabolite (Ha44 hydroxyl AUC0-8/Ha44 AUC0-8 < 0.10) and that Ha44 carboxyl is a major metabolite (Ha44 carboxyl AUC0-8/Ha44 AUC0-8 > 0.10).

Benzyl alcohol:
Of the 9 evaluable subjects from Site 01, only one (b) (6) had measurable serum benzyl alcohol at 0.5 (0.536 µg/mL) and 1.0 (0.726 µg/mL) hours post treatment time points.

Table 28: evaluable subject with measurable benzyl alcohol concentrations

Subject	Time (h)	Plasma Ha44 Concentration (ng/mL)	Plasma Ha44 Hydroxyl Concentration (ng/mL)	Plasma Ha44 Carboxyl Concentration (ng/mL)	Serum Benzyl Alcohol Concentration (µg/mL)
(b) (6)	0.5	266	2.27	2030	0.536
	1.0	418	4.23	6020	0.726

PK parameters values by age:
Mean Ha44 and Ha44 metabolites plasma concentration-time profiles for all age groups are presented over the 0 to 8 hour post-dose period (Table 29). The mean Ha44 and Ha44 metabolites Cmax and AUC0-8 tended to increase with decreasing age. Mean Ha44 and Ha44 metabolites plasma concentrations were approximately 2 fold higher in the younger groups (<3

years of age) compared to the older group (3 to <18 years). Ha44 was rapidly absorbed in all groups. Mean concentration time profiles for Ha44, Ha44 hydroxyl, and Ha44 carboxyl by age are shown in Figures 9 – 11.

Table 29: Mean (%CV) Ha44 and Ha44 metabolites PK parameters (Group 1: <12 months, group 2: 1 to <2 years, group 3: 2 to <3 years, group 4: 3 to <18 years)

Group	Analyte	C_{max} (ng/mL)	T_{max}[a] (h)	AUC_{0-8} (ng*h/mL)
1 (N=1)	Ha44	418	0.98	1056.8
	Ha44 Hydroxyl	4.23	0.98	19.73
	Ha44 Carboxyl	9710	7.92	62407.83
2 (N=3)	Ha44	209.27 (62)	0.50 (0.50-1.02)	446.47 (65)
	Ha44 Hydroxyl	2.57 (44)	0.50 (0.50-1.02)	8.05 (68)
	Ha44 Carboxyl	3863.33 (41)	7.97 (7.90-8.03)	24157.56 (30)
3 (N=6)	Ha44	205.58 (66)	0.54 (0.48-1.00)	632.83 (57)
	Ha44 Hydroxyl	2.16 (51)	0.99 (0.50-8.02)	9.19 (56)
	Ha44 Carboxyl	6171.67 (34)	7.99 (7.90-8.02)	38334.19 (37)
4 (N=12)	Ha44	120.89 (60)	0.50 (0.45-7.93)	330.26 (49)
	Ha44 Hydroxyl	1.21 (98)	1.00 (0.50-1.00)	4.14 (114)
	Ha44 Carboxyl	3352.75 (58)	7.89 (2.00-8.03)	21368.86 (64)

%CV listed in parentheses
[a] Median (range)

Figure 9: Mean Ha44 plasma concentration-time plot by age group

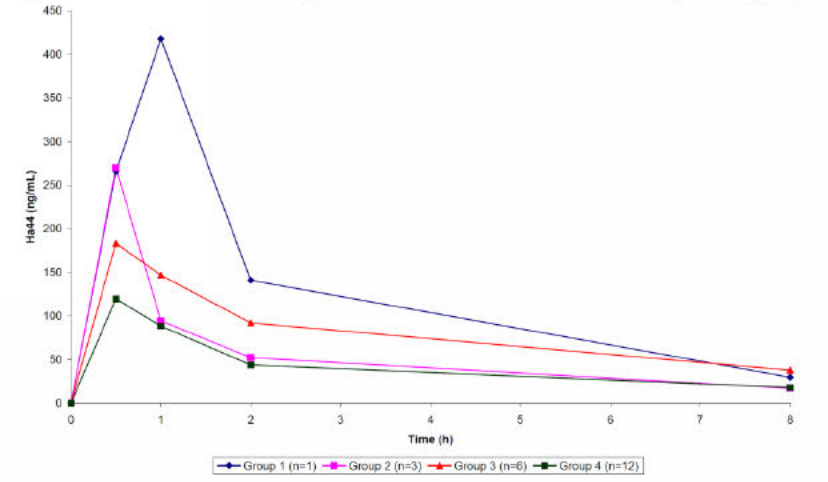


Figure 10: Mean Ha44 hydroxyl plasma concentration-time plot by age group

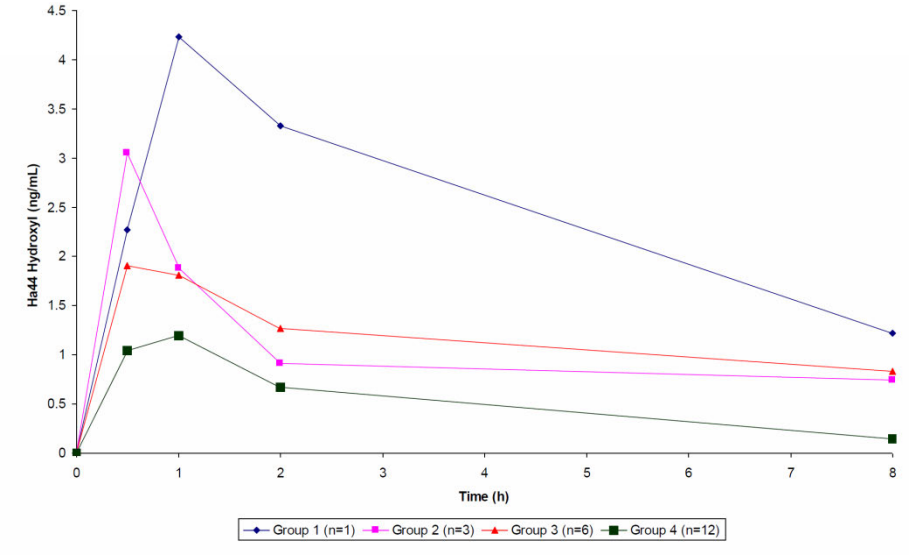
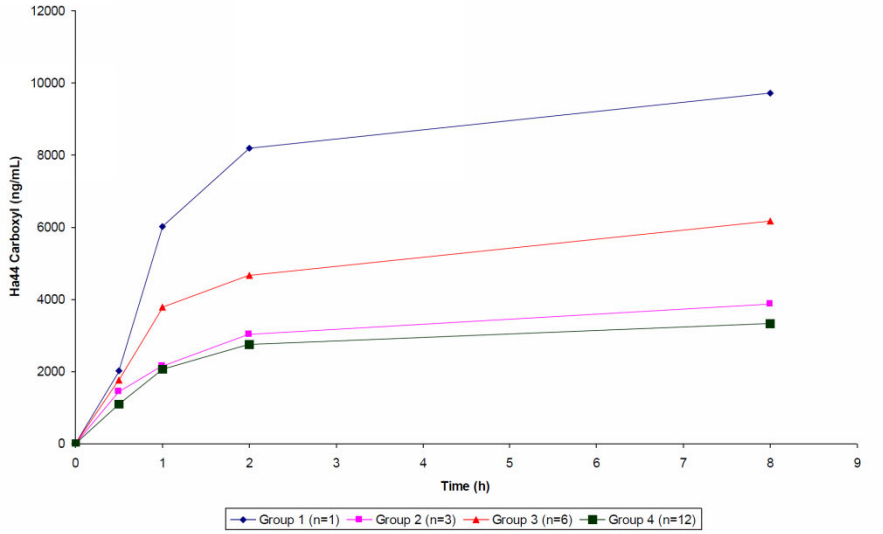


Figure 11: Mean Ha44 carboxyl plasma concentration-time plot by age group



Safety:

The sponsor states that there were no clinically significant findings in physical examinations or vital signs; no abnormalities in laboratory safety tests were reported as TEAEs. There were no SAEs reported during the study. No subjects discontinued from the study due to a TEAE. See Clinical review for further details.

4.1.3 Trial Ha03-004

Title: A Safety and Pharmacokinetic Study of Ha44 Gel Administered Topically Under Maximal Use Conditions for the Treatment of Head Lice Infestation.

Studied period:

Date of first enrolment: 15 Mar 2013
Date of last completed: 15 Jul 2013

Objectives:

Primary objective: To evaluate the safety and tolerability of a single application of Ha44 Gel 0.74% w/w under maximal use conditions for the treatment of head lice

Secondary objective: To evaluate the pharmacokinetics of both Ha44 and benzyl alcohol (contained in the Ha44 Gel vehicle) under maximal use conditions

Study design:

This was a Phase 2, open-label, safety and PK study involving a single application of Ha44 Gel 0.74% administered under maximal use conditions. All participants had to have an active head lice infestation (at least 3 live lice) and be 6 months to 17 years of age. More than one household member with an active lice infestation could participate in the study. Subjects were consented and screened for study eligibility on Day 0 (Visit 1) and were treated at the study site on the same day (Day 0). This was the only application of Ha44 Gel in the study.

Ha44 Gel was applied to the scalp and hair of subjects for 10 minutes. Administration of the investigational product (IP) under maximal use conditions was achieved by a single application of one whole container (~200 mL) of Ha44 Gel 0.74% to each subject where feasible. Otherwise, the maximum feasible volume was applied ensuring that there was complete saturation of the scalp and hair. The amount of product applied to each subject was recorded.

PK samples for plasma Ha44 level and benzyl alcohol level were collected at 0 (predose), 30 and 60 minute and 2 and 8 hour time points, except that a 2 hour sample for benzyl alcohol level was not collected in infants weighing less than 16 lb. Not collecting a 2 hour sample in infants weighing less than 29 lb was due to IRB requirement referring to guidelines for daily blood volumes collected from children. PK assessment windows were ± 5 minutes for the 30 and 60 minute assessments and ± 10 minutes for the 2 and 8 hour assessments. Note: all post-treatment assessments were performed at time points relative to the start of the IP application (when the IP was first applied to the scalp and hair).

All treated subjects returned to the study site for three follow-up clinic visits at Days 1, 7 and 14.

Number of subjects (planned and analyzed): Approximately 36 pediatric subjects were planned to be enrolled into the study in order to ensure that 21 PK-evaluable pediatric subjects between the ages of 6 months and 2 years were enrolled.

Fifty (50) subjects were screened and 38 of these subjects were eligible for enrollment and received treatment. All 38 subjects completed the study were included in the safety analysis. Twenty eight (28) subjects who had sufficient concentration-time profiles were included for PK analyses.

Diagnosis and main criteria for inclusion:
1. Male or female
2. 6 months to 17 years of age
3. Be in good health, as determined by medical history and physical examination
4. Had an active head lice infestation at screening as determined by an experienced evaluator. An active infestation is defined as the presence of at least 3 live lice.
5. Female subjects were:
    a. Of non-childbearing potential (no history of menstrual periods, post-hysterectomy, or post-menopausal for at least 2 years) OR,
    b. If of childbearing potential, had to have a negative urine pregnancy test prior to treatment and agreed to use a highly effective method of contraception from Day 0 through the Day 14 visit. Acceptable methods of contraception included abstinence, vasectomized partner, tubal ligation, combined oral hormonal contraceptive, contraceptive injection, contraceptive patch, or IUD. If a hormonal contraception was the only method, the subject had to be on a stable dose for at least 3 months.
6. The parent/guardian agreed to allow serial blood samples collected from subject for PK analysis during study.
7. Signed an informed consent and/or assent form (ICF).

Test product, dose and mode of administration, batch number: The application of the Ha44 Gel was performed by study staff. A single application of one whole container (~200 mL) of Ha44 Gel 0.74% was administered to each subject where feasible. For subjects for whom it was not feasible to apply the full 200 mL of Ha44 Gel 0.74%, the maximum feasible volume was applied ensuring that there was complete saturation of the scalp and hair. The amount of product applied to each subject was recorded. No more than one container of IP (200 mL) could be applied to each subject's scalp and hair regardless of their hair length and/or thickness. The Ha44 Gel was in contact with the subject's scalp and hair for the time it took to apply the Ha44 Gel (expected to be less than 5 minutes), followed by the 10 minute treatment period.

The batch number for the Ha44 Gel used in this study was RD 13-003.

Duration of treatment: The duration of the study for each subject from screening (Day 0) to the follow-up visit (Visit 3) was approximately 14 days.

Criteria for evaluation:
Primary PK endpoint: Blood samples were analyzed for concentrations of Ha44 (plasma) and benzyl alcohol (serum). Post-hoc analysis for plasma Ha44 carboxyl concentrations were performed as well.

Safety endpoints: The assessment of safety and tolerability of Ha44 Gel included treatment emergent adverse events (TEAEs), scalp/eye irritation assessment, clinical laboratory safety test results, vital signs and physical examination.

Statistical methods: Descriptive statistics for continuous variables, sample size (n), mean, standard deviation, median and range are presented; for categorical variables, count and percentage are presented.
Two planned study populations were defined as follows:

- Safety Population: all subjects who received Ha44 Gel.
- PK Population: all subjects who received IP and had sufficient concentration-time profiles to derive the PK parameters (Cmax, Tmax, and AUC0-8) for Ha44 and/or benzyl alcohol.

Bioanalytical methods:
See section 2.6.1 of this review.

Results:

Protocol Deviation:
There were no major protocol deviations.

Demographic:
The majority of subjects were Caucasian (89.5%), 47.4% were male, and the mean age was 3.75 years (0.6 – 15.8 years). Of the 38 treated subjects, 8 subjects were <12 months of age, 9 subjects were 1 to <2 years, 11 subjects were 2 to <3 years and 10 subjects were 3 to 17 years of age. The mean weight was 42.5 lbs with a range from 16 to 173 lbs.

Demographic characteristics for the PK population are similar to Safety Population and details are shown in Table 30.

Table 30: Demographic – PK population

		Ha44 (N = 28)
AGE (year)	N	28
	MEAN	3.83
	SD	4.15
	MEDIAN	2.13
	RANGE	(0.6, 15.6)
	N	28
	6 months to < 12 months	5 (17.9%)
	1 year to < 2 years	8 (28.6%)
	2 years to < 3 years	8 (28.6%)
	3 years to 17 years	7 (25.0%)
GENDER	N	28
	MALE	12 (42.9%)
	FEMALE	16 (57.1%)
RACE	N	28
	WHITE	24 (85.7%)
	BLACK	2 (7.1%)
	ASIAN/PACIFIC ISLANDER	0 (0.0%)
	INDIAN / ALASKA NATIVE	0 (0.0%)
	MULTI RACIAL	2 (7.1%)
	OTHER	0 (0.0%)
ETHNICITY	N	28
	HISPANIC	25 (89.3%)
	NOT HISPANIC	3 (10.7%)
HEIGHT (inches)	N	28
	MEAN	38.5
	SD	10.1
	MEDIAN	35.0
	RANGE	(27.0, 62.5)
WEIGHT (pounds)	N	28
	MEAN	42.6
	SD	31.9
	MEDIAN	30.0
	RANGE	(19.0, 142.0)

Treatment compliance:
Ha44 Gel was applied by the clinic staff; all subjects (100%) were compliant to treatment.

PK parameters:

Abametapir (also denoted as Ha44):
Thirty (30) subjects provided samples for PK analysis of plasma concentrations of Ha44, 28 subjects were evaluable for Cmax and 24 subjects had an 8 hour sample considered evaluable for calculation of AUC0-8. Of the 28 subjects, 5 subjects were 6 to <12 months of age, 8 subjects were 1 to <2 years, 8 subjects were 2 to <3 years and 7 subjects were 3 to 17 years of age. Two subjects each in the 1 to <2 years and 2 to <3 years age groups did not have an 8 hour sample for AUC0-8 analysis.

Overall, the mean Cmax was 141.4 ng/mL (range: 16 - 397 ng/mL) and the Tmax was 0.8 hours (range: 0 - 2 hr) showing rapid absorption into the systemic circulation. The mean AUC0-8 was 447.5 ng*h/mL (range: 80 - 971 ng*h/mL). The mean Cmax and AUC0-8 increased with decreasing age (Figure 12 and Table 31).

Figure 12: Mean Ha44 plasma concentration-time plot by age group

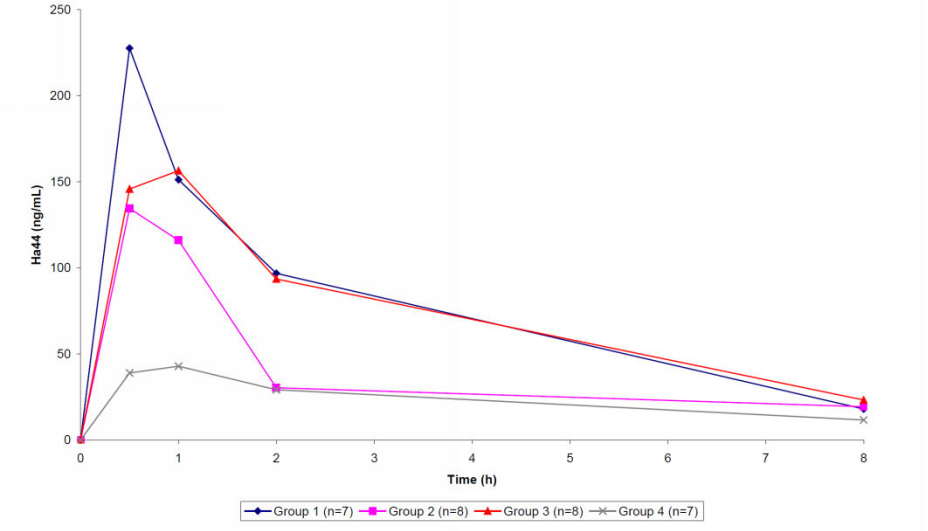


Table 31: Mean (%CV) Ha44 PK parameters (Group 1: <12 months, group 2: 1 to <2 years, group 3: 2 to <3 years, group 4: 3 to 17 years)

Group (C_{max}/AUC_{0-8})	C_{max} (ng/mL)	T_{max}[a] (h)	AUC_{0-8} (ng*h/mL)
1 (N=5/5)	227.74 (50)	0.50 (0.50-0.57)	668.24 (43)
2 (N=8/6)	147.33 (49)	0.59 (0.48-2.00)	405.53 (37)
3 (N=8/6)	160.01 (48)	0.55 (0.50-2.05)	601.79 (51)
4 (N=7/7)	51.61 (45)	1.00 (0.50-1.08)	193.71 (39)

%CV listed in parentheses
[a] Median (range)

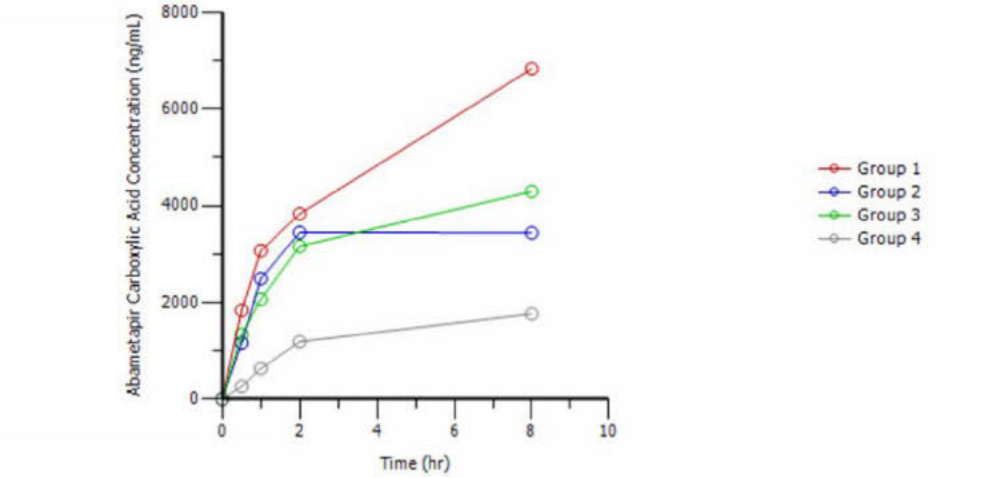
Abametapir carboxyl:
The mean abametapir carboxyl Cmax and AUC0-8 appeared to increase with decreasing age (Figure 13 and Table 32). The median abametapir carboxyl Tmax value was similar for all groups (range 5.00 to 8.00 hours) and reflected the time of the final PK sample taken rather than a true maximum concentration. While most subjects had a Tmax between 7.83 to 8.08 hours, 1 subject in the 1 to <2 years age group had an unusually early Tmax of 2.03 hours. The plasma concentrations of abametapir carboxyl were much greater than that of the parent abametapir.

Table 32: Ha03-004 Abametapir Carboxyl PK Parameters for Abametapir Lotion 0.74%

Age Group	n	C_{max} (ng/mL) Mean (%CV)	T_{max} (hour) Median (range)	AUC_{0-8} (ng*h/mL) (%CV)
6 to <12 months	1	6830	8.00 (8.00 - 8.00)	37500
1 to <2 years	2	3550 (1.8%)	5.00 (2.03 - 7.97)	24600 (0.3%)
2 to <3 years	7	4290 (46.7%)	8.00 (7.85 - 8.00)	26000 (49.5%)
3 to 17 years	7	1760 (41.9%)	8.00 (7.83 - 8.08)	10000 (46.4%)

Abbreviations: CV = coefficient of variation; n = number of subjects.

Figure 13: Ha03-004 Mean Abametapir Carboxyl Concentration vs Time by Age Group



Group 1 = 6 to <12 months, Group 2 = 1 to <2 years, Group 3 = 2 to <3 years, Group 4 = 3 to 17 years.

Benzyl alcohol:
Thirty (30) subjects provided samples for benzyl alcohol analysis, 6 subjects (01-401, 01-406, 02-404, 02-406, 02-407 and 03-420) had sufficient data points to evaluate Cmax however none had an 8 hour sample and were not evaluable for AUC0-8. The measurable concentrations are shown in Table 33.

Overall, the mean Cmax was 1.3 µg/mL (range: 0.7 – 3.6 µg/mL) with Tmax range of 0.5 – 8 hr.

Table 33: Subjects with measurable benzyl alcohol concentrations

Subject	Time (h)	Plasma Ha44 Concentration (ng/mL)	Serum Benzyl Alcohol Concentration (µg/mL)
(b) (6)	0.5	397	0.877
	8	16.3	1.39
	8	21.9	3.57
	0.5	239	0.826
	0.5	242	0.664
	0.5	201	0.524

Safety:
The sponsor states that there were no SAEs reported during the study. No subjects discontinued from the study due to a TEAE. See Clinical review for further details.

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/s/

DOANH C TRAN
04/26/2016

EDWARD D BASHAW
04/26/2016

Concur with the need for two PMRs and the analytical PMC. As the target population is primarily (but not exclusively children) the obtaining of adequate pk data in the pediatric population is important in addition to clarifying the potential for drug drug interactions in light of the conflicting data from the in vitro metabolism studies.