CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206966Orig1s000

NON-CLINICAL REVIEW(S)

Memorandum

To:	NDA 206966 / Class 2 Resubmission
Sponsor:	Dr. Reddy's Laboratories, Inc.
Trade name:	Xeglyze Lotion, 0.74%
Generic name:	abametapir
Indication:	treatment of head lice
From:	Jill C Merrill, PhD, reviewing toxicologist, DDD
Through:	Barbara Hill, PhD, Pharmacology/Toxicology Supervisor, DDD
Re:	Recommendations on Approvability and Labeling

Background:

NDA 206966 received a Complete Response on August 30, 2016 for facility deficiencies. The applicant submitted a Class 2 Resubmission package on November 12, 2019 (SDN28) under section 505(b)(1) of the Public Health Service Act for Xeglyze Lotion, 0.74% indicated for the treatment of head lice infestation (*pediculosis capitis*) in patients 6 months of age and older. The active pharmaceutical ingredient in the drug product is abametapir (5,5'-dimethyl-2,2'-bipyridyl), a new chemical entity. The applicant has conducted repeat-dose nonclinical studies in both a rodent and nonrodent species. Abametapir has been tested in the complete ICH battery of genotoxicity tests and is not considered genotoxic. Abametapir has been tested in the complete battery of reproductive toxicology tests with no significant findings independent of maternal toxicity.

Xeglyze Lotion, 0.74% is approvable from a pharmacology/toxicology perspective. There are no recommended nonclinical PMCs/PMRs for this NDA.

Label:
Revisions to the sponsor's proposed wording for the nonclinical and related sections of the label are provided below. The clinical reviewer will determine appropriate modifications to the clinical portions of Section 8 of the label. Except as where designated by PLLR format, reviewer proposed deletions are annotated as ~~strikeout~~ text and reviewer proposed additions are annotated as <u>underlined</u> text.

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE
XEGLYZE (b) (4) is a pediculicide indicated for the topical treatment of head lice infestation in patients 6 months of age and older.

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on XEGLYZE (b) (4) use in pregnant women to (b) (4) evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In embryofetal development studies conducted with oral administration of abametapir during organogenesis, no evidence of fetal harm or malformations, independent of maternal toxicity were observed in pregnant rats and rabbits at doses that produced exposures up to 50 times and equivalent to the maximum recommended human dose (MRHD) in rats and rabbits, respectively. The highest dose evaluated in rabbits was limited due to maternal toxicity associated with the vehicle used in the study *[(see Data)]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Systemic embryofetal development studies were performed in rats and rabbits. Oral doses of 10, 25 and 75 mg/kg/day abametapir were administered during the period of organogenesis (gestational days 6 – 17) to pregnant rats. In the presence of maternal toxicity, embryofetal toxicity (lower fetal body weights and delayed ossification) was noted at 75 mg/kg/day. No treatment related effects on malformations were noted at 75 mg/kg/day (50 times the MRHD based on C_{max} comparisons).

Oral doses of 4, 16 and 40 mg/kg/day abametapir were administered during the period of organogenesis (gestational days 6 – 19) to pregnant rabbits. No treatment related effects on embryofetal toxicity or malformations were noted at 40 mg/kg/day (~1 time the MRHD based on C_{max} comparisons). Maternal toxicity related to the vehicle limited the maximum dose in pregnant rabbits.

In a perinatal and postnatal development study in rats, oral doses of 10, 25 and 75 mg/kg/day were administered from the beginning of organogenesis (gestational day 6) through the end of lactation (lactation day 20). In the presence of maternal toxicity, embryofetal lethality, and decreased fetal body weight gain were noted at 75 mg/kg/day. No treatment related effects on

postnatal development were noted at 75 mg/kg/day (47 times the MRHD based on C_{max} comparisons).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been conducted to evaluate the carcinogenic potential of XEGLYZE (b) (4) or abametapir.

Abametapir was not mutagenic or clastogenic based on the results of two in vitro genotoxicity tests (Ames test and human lymphocyte chromosomal aberration assay) and one in vivo genotoxicity test (rat micronucleus assay).

No effects on fertility have been observed in rats following repeated oral doses of up to 75 mg/kg/day abametapir (50 times the MRHD based on C_{max} comparisons).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JILL C MERRILL
05/01/2020 08:37:25 AM

BARBARA A HILL
05/01/2020 09:00:29 AM

Pharmacology/Toxicology Supervisory Memorandum

NDA number:	206966
Supporting document:	1
CDER Stamp Date:	September 14, 2015
Type of submission:	Original NDA; 505(b)(1)
Applicant:	Dr. Reddy's Laboratories
Supervisor name:	Barbara Hill, PhD
Review Division:	Dermatology and Dental Products
Date:	April 13, 2016
Product:	Xeglyze (abametapir) lotion, 0.74%
Pharmacologic class:	Pediculicide
Indication:	Topical treatment of head lice infestation in patients 6 months of age and older

General comments:

- I concur with the overall assessment and conclusions contained in Dr. Jill Merrill's Pharmacology/Toxicology review for this drug product.
- I concur that there are no nonclinical approval issues for this drug product and that this NDA is approvable from a Pharmacology/Toxicology perspective.
- I concur that there are no nonclinical Post-Marketing Requirements recommended for this NDA.
- I concur with the recommended nonclinical labeling changes proposed by Dr. Merrill for Xeglyze contained in Section 1.3.3 of her review which include:
    - Pharmacologic Class designation of "pediculicide"
    - The revisions proposed for Sections 8.1, 8.2, 12.1, 12.3 and 13.1 of the label

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BARBARA A HILL
04/13/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	206966
Supporting document/s:	SDN 1, 4, 5
Applicant's letter date:	9-14-2015, 12-16-2015, 12-30-2015
CDER stamp date:	9-14-2015, 12-16-2015, 12-30-2015
Product:	Abametapir Lotion 0.74% (XEGLYZE™)
Indication:	Head lice infestation in patients 6 months of age and older
Applicant:	Dr. Reddy's Laboratories
Review Division:	DDDP
Reviewer:	Jill Merrill, PhD
Supervisor/Team Leader:	Barbara Hill, PhD
Division Director:	Kendall Marcus, MD
Project Manager:	Cristina Attinello

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 206966 are owned by Dr. Reddy's Laboratories or are data for which Dr. Reddy's Laboratories has obtained a written right of reference. Any information or data necessary for approval of NDA 206966 that Dr. Reddy's Laboratories does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 206966.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Dr. Reddy's Laboratories is submitting abametapir lotion 0.74% for the topical treatment of head lice infestation (*pediculosis capitis*) in subjects 6 months of age and older. The active pharmaceutical ingredient in the drug product is abametapir (5,5'-dimethyl-2,2'-bipyridyl), a new chemical entity. Abametapir is a metalloproteinase inhibitor, chelating metal cations at the active center of metalloproteinases critical to louse egg development, hatching and survival.

1.2 Brief Discussion of Nonclinical Findings

All nonclinical studies enormously exaggerated exposure under clinical conditions of use. The drug-related nonclinical effects observed after extended repeat testing would not be a cause for concern for this drug product under the clinical conditions of use which is one time use on scalp and hair for 10 minutes and then rinsed off.

In a 28-day repeat-dose dermal study in minipigs, abametapir lotion (0%, 0.74%, 0.74% (administered twice/day), 3.7%) was applied to a clipped dorsal surface area approximating 10% total body surface area (0, 14.2, 28.4, 71.0/35.5 mg/kg/day; reviewed under Section 6.2). Dermal effects associated with topical administration included erythema and flaking with histological observations of epidermal hyperplasia, hyperkeratosis, erosion and/or ulceration. These effects were dependent on dosing parameters (*i.e.*, strength, frequency and contact time) and were reversible. Systemic effects included tremors, decreased activity and decreased feed consumption in both males and females. In males, extended dosing (>10 days) was associated with penile protrusion and related secondary microscopic findings in the penis and bone marrow. Reversibility of these systemic effects could not be assessed in males due to early termination in affected animals based on ethical considerations. Reversibility of clinical signs was demonstrated in females. It is unclear how much of the systemic exposure noted in this dermal minipig study may have been due to oral ingestion of the topically applied abametapir lotion. Also, abametapir lotion was repeatedly applied to the skin of minipigs for up to 24 hours per day compared to the one-time clinical use of 10 minutes applied to the scalp/hair and subsequently washed off. This increase in exposure in the dermal minipig study probably contributed to the noted systemic effects. **No clinical signs consistent with gastrointestinal targets or smooth muscle function were observed in the clinical program**. Therefore, the systemic effects noted in the dermal minipig study are not a cause for concern for the clinical single topical application of abametapir lotion which is subsequently washed off after 10 minutes.

Abametapir and abametapir-COOH, the major human metabolite, were not mutagenic in the Ames test. Abametapir caused increases in chromosome aberrations in human lymphocytes at cytotoxic concentrations and was negative in the in vivo rat micronucleus assay when administered orally at doses up to 160 mg/kg/day. The

overall interpretation of the conducted genotoxicity studies is that abametapir and abametapir-COOH do not exhibit a genotoxic signal.

Abametapir has been tested for reproductive and developmental toxicology in rats and rabbits after oral administration with no significant findings independent of maternal toxicity.

1.3 Recommendations

1.3.1 Approvability

NDA 206966 is approvable from a pharmacology/toxicology perspective.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

Revisions to the sponsor's proposed wording for the nonclinical and related sections of the label are provided below. With the exception of titles which are underlined based on the label template, nonclinical recommendations are shown as underlined text. It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the XEGLYZE label text. A clean copy of these revised labeling sections is provided in Appendix #2.

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Xeglyze (b) (4) is a (b) (4) pediculicide (b) (4) indicated for the topical treatment of head lice infestation (b) (4) in patients 6 months of age and older. (b) (4)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

(b) (4) There are no available data (b) (4) on Xeglyze (b) (4) use in pregnant women to inform a drug associated risk. In embryofetal development studies conducted with oral administration of abametapir during organogenesis no evidence of fetal harm or malformations, independent of maternal toxicity, were observed in pregnant rats and rabbits at doses that produced exposures up to 50 times and equivalent to the maximum recommended human dose (MRHD) in

rats and rabbits, respectively. The highest dose evaluated in rabbits was limited due to maternal toxicity associated with the vehicle used in the study *[see Data]*. ~~The background risk of major birth defects and miscarriage for the indicated population is unknown;~~ (b) (4)

Data

Animal Data

Systemic ~~E~~embryofetal development studies were performed in rats (b) (4) and rabbits. Oral doses of 10, 25, and 75 mg/kg/day abametapir were administered during the period of organogenesis (gestational days 6 – 17) to pregnant rats. In the presence of maternal toxicity, embryofetal toxicity (lower fetal body weights and delayed ossification) was noted at 75 mg/kg/day. No treatment related effects on malformations were noted at 75 mg/kg/day (50 times (b) (4) the MRHD based on C_{max} comparisons). (b) (4)

Oral doses of 4, 16 and 40 mg/kg/day abametapir were administered during the period of organogenesis (gestational days 6 – 19) to pregnant rabbits. No treatment related effects on embryofetal toxicity or malformations were noted at 40 mg/kg/day (~1 times the MRHD based on C_{max} comparisons). Maternal toxicity related to the vehicle limited the maximum dose in pregnant rabbits.

(b) (4)

In a perinatal and postnatal development study in rats, oral doses of 10, 25, and 75 mg/kg/day were administered from the beginning of organogenesis (gestation day 6) through the end of lactation (lactation day 20). In the presence of maternal toxicity, embryofetal lethality and decreased fetal body weight gain were noted at 75 mg/kg/day. No treatment related effects on postnatal development were noted at 75 mg/kg/day (47 times the MRHD based on C_{max} comparisons).

Lactation

Risk Summary

No data are available regarding the presence of (b) (4) abametapir (b) (4) in human milk, or the effects of abametapir on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Xeglyze (b) (4) and any potential adverse effects on the breastfed child from Xeglyze (b) (4) or from the underlying maternal condition.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

Excretion

Excretion of abametapir and its human metabolites was not examined in patients. [redacted]

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term [redacted] studies in animals have not been conducted to evaluate the carcinogenic potential [redacted] of Xeglyze [redacted] or abametapir.

Abametapir was not mutagenic or clastogenic based on the results of two in vitro genotoxicity tests (Ames test and human lymphocyte chromosomal aberration assay) and one in vivo genotoxicity test (rat micronucleus assay). [redacted]

No effects on fertility have been observed in rats following repeated oral doses of up to 75 mg/kg/day abametapir (50 times the MRHD based on C_{max} comparisons).

2 Drug Information

2.1 Drug

CAS Registry Number: 1762-34-1

Generic Name: abametapir

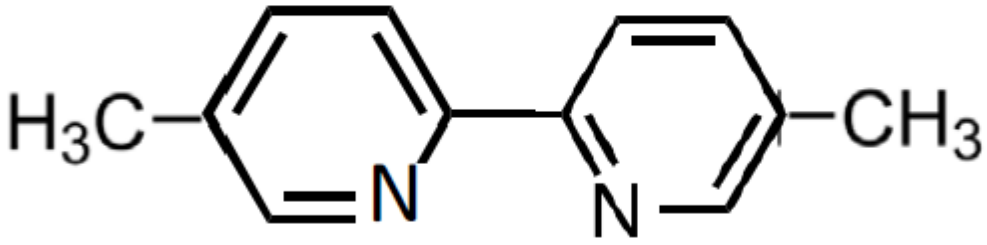
Code Name: Ha44 (CLBI1)

Chemical Name: 5,5'-dimethyl-2,2'-bipyridyl

Molecular Formula/Molecular Weight: $C_{12}H_{12}N_2$/ 184.24 g/mol

Structure

Figure 1 Structural Formula of Abametapir



Pharmacologic Class: pediculicide

Reviewer's comment: The drug product has demonstrated both ovidical and pediculicidal activity in in vitro tests.

2.2 Relevant INDs, NDAs, and MFs

IND 77510, 7-09-2008, Hatchtech Pty Ltd, treatment of head lice infestation

2.3 Drug Formulation

Table 1 Drug Product 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.

2.4 Comments on Novel Excipients

There are no novel excipients.

The drug product, abametapir lotion, which is restricted to children 6 months of age and older, contains (b) (4) benzyl alcohol. Benzyl alcohol has been associated with neonatal gasping syndrome in premature infants (Gershanik *et al.*, 1982). Benzyl alcohol serum concentrations were assessed in pharmacokinetic samples from clinical trials Ha03-003 and Ha03-004 using an assay with a lower limit of quantification of 0.5 µg/mL. In trial Ha03-003, one of nine evaluable subjects (13 subjects from a single site were excluded due to inadvertent use of benzyl alcohol- containing saline flush) had measurable concentrations of up to 0.726 µg/mL. In trial Ha03-004, six of 30 subjects had measurable concentrations of up to 3.57 µg/mL. It is not clear if this value is real as the value was seen only at 8 hours postdose while most other measureable concentrations were seen at 0.5 hour postdose; the next highest value (in a different subject) was 1.39 µg/mL.

However, assuming the observed high value of 3.57 µg/mL from Ha03-003 is real, it still does not appear to be a safety concern for neonatal gasping syndrome which has been associated with systemic exposure to benzyl alcohol at a concentration of ~109.2 µg/mL (1.01 mmol/L; Gershanik *et al.*, 1982). The highest benzyl alcohol observed in the current trial, 3.57 µg/mL, is about 30.6 fold lower. For reference, the highest plasma benzyl alcohol levels observed in clinical studies with Natroba (NDA 22408, approved January 18, 2011) and Ulesfia (NDA 22129, approved April 9, 2009) were 2.37 µg/mL and 2.99 µg/mL, respectively. Thus in this reviewer's opinion the infant gasping

syndrome associated with benzyl alcohol and low birth weight premature infants with limited ability to metabolize benzyl alcohol and subsequently conjugate benzoic acid to hippuric acid is not expected to be a problem in the indicated population.

2.5 Comments on Impurities/Degradants of Concern

Two potential toxicological impurities, (b) (4) have been identified by the Applicant. (b) (4) has been identified during forced degradation studies. (b) (4) has not been seen in any forced degradation studies to date. Given the proposed Clinical use conditions for Xeglyze (*i.e.*, topical product to be washed off after 10 minutes contact time on the hair and scalp) and the fact these impurities have not been identified under recommended storage conditions, they are not considered a toxicological concern.

2.6 Proposed Clinical Population and Dosing Regimen

Xeglyze Lotion 0.74% is indicated for the topical treatment of head lice infestation in patients 6 months of age and older. Instructions for use include the following:

- Shake well before use.
- Apply Xeglyze Lotion to dry hair in an amount sufficient to thoroughly coat the hair and scalp.
- Massage Xeglyze Lotion into the scalp and throughout the hair
- Avoid contact with eyes.
- Leave on the hair and scalp for 10 minutes and then rinse off with warm water.
- The bottle is intended for single use only. Discard any unused portion.

2.7 Regulatory Background

June 20, 2007 pre-IND meeting
December 20, 2007 –original IND submission
April 15, 2008- teleconference clinical hold
July 9, 2008, release of clinical hold for adult studies
August 1, 2012 – End of Phase 2 meeting
January 21, 2015- pre-NDA meeting
December 30, 2015– change in ownership

3 Studies Submitted

3.1 Studies Reviewed

Pharmacology

Ovicidal activity of (b) (4) Formulation/ (b) (4)

Reviewer's comment: (b) (4) *was a previous name for XEGLYZE™.*

Ovicidal activity of abametapir (formerly Ha44)/ (b) (4)

Secondary Pharmacology

An assessment of the effects of abametapir and abametapir-COOH in selected enzyme and uptake assays (100012149)

Further evaluation of abametapir and abametapir-COOH cytotoxicity against HEK-293 cells (100015139)

Cytotoxicity assay in two mammalian cell lines (HEK-293 and BJ cells) – Study of abametapir and abametapir-COOH (100017066)

Study of the agonism and antagonism potential of selected biological receptors related to smooth muscle function by abametapir and abametapir-COOH (100016477)

Investigation of the effect of abametapir and abametapir-COOH on endothelin converting enzyme-1 (ECE-1) in an ex vivo smooth muscle assay (100017514)

Pharmacokinetics/ADME/Toxicokinetics

Targeted open scan metabolite investigation of phase II metabolism of two phase I metabolites of abametapir (Htc-036A)

In vitro Phase I and Phase II metabolism of abametapir, abametapir-OH and abametapir-COOH in liver microsomes (Htc-036B)

In vitro interaction studies of Ha44 with human MDR1 and BCRP ABC (efflux) transporters, and with human OATP1B1, OATP1B3, OCT2, OAT1 and OAT3 uptake transporters (b) (4) 0008)

Ha44: Potential inhibition of cytochromes P450 in human liver microsomes ((b) (4) 0009)

Ha44: Potential induction of cytochromes P450 in cultured human hepatocytes ((b) (4) 0010)

Ha44: metabolism studies in rat, rabbit, minipig and human after repeated dermal or oral dosing (b) (4) 0011)

[^{14}C]Ha44: Distribution and excretion study in the pigmented rat after application of a single dermal dose (b) (4) 0012)

[^{14}C]Ha44: Investigation of the human cytochromes P450 involved in the in vitro microsomal metabolism of [^{14}C]Ha44 (b) (4) 0013)

[^{14}C]Ha44 (abametapir) - Investigation of plasma protein binding in vitro in rat, rabbit, minipig and human by equilibrium dialysis (b) (4) 0014)

Analysis of abametapir and its metabolites in minipig plasma samples and rat plasma samples from Hatchtech preclinical study [redacted]0011 (Htc-034)

Analysis of abametapir and its metabolites in rat plasma samples from Hatchtech preclinical study [redacted]0003 (Htc-040)

Analysis of abametapir and its metabolites in rat plasma samples from HatchTech preclinical study 70658 (Htc-039)

In vitro Phase I and Phase II metabolism of abametapir, abametapir-OH and abametapir-COOH in liver microsomes (Htc-036B)

Abametapir-COOH: Potential induction of cytochromes P450 in human liver microsomes [redacted]0017)

Abametapir-COOH: Potential induction of cytochromes P450 in cultured human hepatocytes [redacted]0018)

Abametapir-COOH: Investigation of the human cytochromes P450 involved in its in vitro microsomal metabolism [redacted]0020)

Abametapir-COOH: Investigation of plasma protein binding in vitro in rat, rabbit, minipig, and human plasma by rapid equilibrium dialysis [redacted]0021)

Assessment of dermal absorption in rats following topical application of Ha44 emulsion (Htc01005)

Toxicology

A fourteen-day GLP dermal toxicokinetic study of Ha44 lotion in Gottingen minipigs (1370-13220)

A 7-day tolerability study of abametapir lotion, 0.74% in Gottingen minipigs (1370-13240)

Toxicokinetic study in male and female Sprague-Dawley rats following repeat dose oral gavage administration of abametapir (HTCH0001:001:2107)

Comparative acute subcutaneous toxicity study of three formulations of Ha44 in the rat ([redacted]636.A)

7-day repeated dose intraperitoneal toxicity study of Ha44 in the Sprague-Dawley rat [redacted]612)

A 28-day toxicity study of Abametapir Lotion by dermal administration to minipigs with a 16-day recovery (20049509)

Genetic Toxicology

Evaluation of the genotoxicity of abametapir-COOH in a bacterial reverse mutation (AMES) test with five *Salmonella typhimurium* strains with and without metabolic activation (±S9) at five concentrations (HTCH0001-002-2130)

Special Toxicology

Topical application ocular irritation screening assay of abametapir lotion using the EpiOcular™ human cell construct (14AB04-AB05.015001)

Primary eye irritation study in rabbits (0421LH27.001)

Ha44: Assessment of skin sensitization potential using the local lymph node assay in the mouse (b) (4) 0012/063738/LN)

3.2 Studies Not Reviewed

The following studies have been previously reviewed. Summaries of pivotal studies are provided in the corresponding section of this document.

Pharmacology

Screening of the ovicidal activity of emollient vehicles (Htc01001)

Dose response evaluation of ovicidal activity of Ha44 (b) (4) emulsion (Htc01002)

Assessment of ovicidal activity of Ha44 (b) (4) Emulsion (Htc01003)

Assessment of the lousicidal activity of Ha44 Emulsion (Htc1004)

Assessment of ovicidal activity of Ha44 Emulsion against head lice (Htc1006)

Assessment of ovicidal activity of Ha44 emulsion against body lice (Htc01006a)

The lousicidal effects of formulations containing varying levels of (b) (4) (Htc01013)

Optimisation of a formulation of Ha44 suitable for use in a Phase IIa clinical trial (Htc01023b)

The lousicidal and ovicidal effects of formulated Ha44 (Htc01024)

In vitro – Assessment of ovicidal activity of Ha44 against head lice (Htc02002)

Safety Pharmacology
Irwin dose range in rats including body temperature and locomotor assessment (b) (4) 0013/063633)

Evaluation of respiratory parameters in the conscious rat using whole body bias flow plethysmography (b) (4) 0014)

Effects on hERG tail current recorded from stably transfected HEK-293 cells (b) (4) 0017/072680)

The effects of Hatchtech compound Ha44 on cardiovascular parameters in rats (2006-001).

Cardiovascular study in minipigs using telemetry (69698)

Cardiovascular study in minipigs using telemetry (71456)

Pharmacokinetics/ADME/Toxicokinetics

Determination of the human epidermal penetration and retention of Ha44 following topical application (081)

Ha44: Combined Pharmacokinetic/DRF study in minipigs (71422)

In vitro metabolic stability of Ha44 using cryopreserved human, rat and minipig hepatocytes (HTC-003/A/FR-01)

Structural conformation report for Ha44/CLBI1/abametapir (Document No. I-CLBI-13-0200)

Toxicology

Preliminary dose range finding toxicity study in the rat using the oral gavage route of administration (b) (4) 0005)

Toxicity study by oral gavage administration to CD rats for 2 weeks (b) (4) 0006/063736)

Maximum tolerated dosage study by topical (dermal) application to minipigs (b) (4) 0008/060138)

Toxicity study by topical (dermal) application to minipigs for 2 weeks [(b) (4)] 0007/063497)

Toxicity study in juvenile rats with a recovery period (70658)

Pilot dose range-finding juvenile study in rats (71387)

Genetic Toxicology

Ha44: In vitro mammalian chromosome aberration test in human lymphocytes ([(b) (4)]0010/063565)

Ha44: Bacterial reverse mutation test [(b) (4)]0011/063429)

Ha44: Rat micronucleus test [(b) (4)]0015/063770)

Reproductive and Developmental Toxicity

Ha44: Study for effects on fertility and early embryonic development in the CD rat by oral administration ([(b) (4)]0006)

Ha44: Preliminary study for effects on embryofetal and pre- and postnatal development following oral administration to the CD rat [(b) (4)]0001)

Ha44: Preliminary study for effects on embryofetal development in the New Zealand White rabbit by oral administration [(b) (4)]0002)

Ha44: Study for effects on embryofetal development in the CD rat by oral administration ([(b) (4)]0003)

Ha44: Study for effects on embryofetal development in the New Zealand White rabbit by oral administration [(b) (4)]0004)

Ha44: Study for effects on pre- and post-natal development in the CD rat by oral gavage administration [(b) (4)]0005)

Special Toxicology

Ha44 (50 mM) eye irritation to the rabbit [(b) (4)]0009/063655)

Acute dermal irritation/corrosion of Ha44 formulation Nos.23-06-02, 23-06-03, and 23-06-04 in the rabbit (OECD404) ([(b) (4)]636)

Ha44: A fourteen day study to evaluate the skin irritation/corrosion potential of 0.74% Ha44 Gel following a four hour dermal exposure on the rabbit (PC 149)

3.3 Previous Reviews Referenced

IND 77510

4 Pharmacology

4.1 Primary Pharmacology

Abametapir forms complexes with transition metal ions and inhibits the activity of metal-dependent enzymes. Its mechanism of action in the treatment of head lice infestation is believed to be through the chelation of zinc ions specifically required at the active center of various metalloproteases critical to hatching and subsequent development of the head louse.

Head lice employ a range of proteolytic enzymes to digest the contents of their blood meal. These include endoproteases and exoproteases which require metal ions (typically zinc) at their active sites (Williamson *et al*., 2003). Metalloproteases are also involved in other developmental stages including insect molting (Sui *et al.*, 2009) and hatching (Bowles *et al.*, 2008), and have been identified as important targets in the control of parasites (Williamson *et al.*, 2003).

Based on in vitro tests the sponsor has previously demonstrated both pediculicidal and ovicidal activity of abametapir prototype formulations against lice.

The ovicidal activity of the to-be-marketed formulation, abametapir lotion 0.74%, was investigated using three different developmental stages of a permethrin-and-DDT-resistant strain of head lice eggs (*Pediculus humanus capitis*, SF-HL strain eggs; 0-2, 3-5, and 6-8 days post oviposition; Htc02025). Individual hair tufts with eggs (0 – 2, 3 – 5, or 6 – 8 days old) were completely immersed in 2-3 mL abametapir lotion 0.74% and its dilutions (0.55%, 0.37%, 0.18%, 0.15%, 0.09% and 0%) for 10 minutes. Treated hair tufts were then air dried on filter paper at room temperature for 1 hr. Dried hair tufts with eggs were allowed to hatch in an incubator (31ºC, 70-80% relative humidity). Percent hatchability values were determined 7-10 days post oviposition. The number of 1st instars that hatch from eggs were recorded and used to determine the percent hatchability of eggs. Undeveloped eggs and stillborn lice were recorded as dead. All experiments were performed in triplicate.

Regardless of the developmental stage, abametapir lotion, 0.74% and its dilutions (0.55%, 0.37%, 0.18% and 0.09% Ha44) showed high ovicidal activity against SF-HL eggs (Table 1, taken directly from the study report). All replicated treatment groups except one (Group 2, 1st replication) were 100% efficacious. Comparatively, untreated SF-HL eggs showed consistently high hatchability (80.0-90.1%).

SF-HL eggs treated with placebo (abametapir lotion vehicle) exhibited increasing ovicidal responses (30.4-55.4%) as they matured. This moderate ovicidal action is not unexpected given the presence of solubilizing agents present in the vehicle formulation.

Despite these vehicle effects, the results demonstrate that abametapir is the critical ovicidal component in this formulation.

Table 1. Comparisons of the percent hatch of DDT- and permethrin-resistant SF-HL eggs treated with various concentrations of DeOvo™ formulation, placebo (a vehicle formulation without the active ingredient, abametapir), Nix®(a formulation containing 1 % permethrin) and ddH_2O.

Egg developmental stage groups (days since oviposition)	Concentration of abametapir: 0.74 %	0.55 %	0.37 %	0.18 %	0.09 % (b) (4)	Placebo	Nix®	ddH_2O
	Percent hatch (Mean ± SD)[1,2]							
Group 1 (0-2)	0	0	0	0	0	$69.6 \pm 5.5^{a*}$	$72.8 \pm 3.4^{a*}$	$90.1 \pm 1.9^{b*}$
Group 2 (3-5)	0	0	0	0	1.4 ± 2.4^{a}	$55.3 \pm 2.5^{b\#}$	$63.3 \pm 7.1^{bc+\#}$	$80.0 \pm 10.1^{c*}$
Group 3 (6-8)	0	0	0	0	0	$44.6 \pm 3.5^{a+}$	$41.5 \pm 14.8^{a\#}$	$89.7 \pm 3.9^{b*}$

[1] Means ± SD in the same row followed by the same letter are not statistically different by ANOVA ($P > 0.05$).
[2] Means ± SD in the same column followed by the same symbol are not statistically different by ANOVA ($P > 0.05$).

Study Htc02026 was conducted to determine the dose-dependent ovicidal activity of abametapir (0.74%, 0.55%, 0.37%, 0.18%, 0.15%, 0.09%, and 0.009%) without the formulation vehicle on SF-HL eggs. Using the same treatment protocol as previously described (Htc02025), the numbers of 1st instars hatching from SF-HL eggs treated with varying abametapir concentrations formulated in isopropanol were recorded to determine the percent hatchability of eggs. Undeveloped eggs and stillborn lice were recorded as dead. All experiments were performed in triplicate.

Treatment of head louse eggs with abametapir 0.74% formulated in isopropanol resulted in complete inhibition of hatching (100% ovicidal) in all stages of egg development from day 0 to day 8 (Table 1, taken directly from the study report). At 0.55% abametapir, approximately 5.4% of the 6-8 day old eggs hatched in contrast to none of the 0-2 and 3-5 day old eggs hatching. As the concentration of abametapir declined, percent egg hatch increased in a concentration-dependent manner.

Table 1. Comparisons of the percent hatch of DDT- and permethrin-resistant SF-HL eggs treated with various concentrations of abametapir in isopropanol

Egg developmental stage groups (days since oviposition)	Concentration of abametapir							
	0.74 %	0.55 %	0.37 %	0.18 %	0.15%	0.11%	0.09%	0.009%
	Percent hatch (Mean ±SD)[1,2]							
Group 1 (0-2)	0	0	0	11.4±6.9[a]	30.1±19.7[a]	35.3±18.8[a]	72.6±3.3[b]	75.3±2.3[b]
Group 2 (3-5)	0	0	2.1±3.6[a]	27.6±11.9[b]	43.3±4.8[b]	49.1±5.2[b]	70.7±5.7[c]	82.5±11.2[c]
Group 3 (6-8)	0	5.4±4.8[a]	15.3±5.6[b*]	44.5±8.6[c]	55.2±5.7[a]	60.9±13.4[a]	81.7±8.5[d]	89.6±1.7[d]

Egg developmental stage groups (days since oviposition)	Isopropanol	ddH_2O
	Percent hatch (Mean ±SD)[1,2]	
Group 1 (0-2)	84.6±2.3[c]	92.1±0.5[d]
Group 2 (3-5)	95.8±3.7[c#]	96.0±2.9[e]
Group 3 (6-8)	96.3±3.2[d#]	94.3±7.6[d]

[1] Means ± SD in the same row followed by the same letter are not statistically different by ANOVA ($P > 0.05$).
[2] Means ± SD in the same column followed by the same symbol are not statistically different by ANOVA ($P > 0.05$).
[3] Isopropanol is a solvent vehicle for application.
[4] ddH_2O (distilled deionized water) is a no treatment control.

Results from this study indicate that isopropanol alone had no apparent effect on the hatch rate of the 3-5 and 6-8 day old eggs when compared to the water control-treated eggs. However, the 0-2 day old eggs were more susceptible to treatment with isopropanol compared to treatment with the water control.

4.2 Secondary Pharmacology

The effects of abametapir and abametapir-COOH (primary human metabolite) on the in vitro activity of a range of metalloproteinases and cell uptake assays were investigated to assess potential off-target effects of metalloproteinase inhibition (100012149). For this in vitro pharmacology screen, achieving a nominal value of at least 50% inhibition of the control value was considered to indicate a potential effect of the test compound against the target and warranted development of an IC_{50} value. Inhibition values between 25% to 50% were considered to have a weak-to-moderate effect, while values <25% were considered insignificant and associated with variation in the signal.

In the in vitro pharmacology screen, 10 µM abametapir inhibited the activity of cyclooxygenase-1 (COX1) by 52.3% while 10 µM abametapir-COOH inhibited this target by 47.7% (see table below, taken directly from the study report). The same 10 µM analyte concentrations inhibited endothelin converting enzyme-1 (ECE-1) by at least 25%. Therefore, IC_{50} values for the potential interaction of abametapir or abametapir-COOH against either COX1 or ECE-1 were determined. Based on literature information suggesting 2,2-bipyridyl compounds could potentially inhibit acetylcholinesterase (AChE) (Wermuth and Brodbeck, 1973), IC_{50} values were also developed for AChE, although neither abametapir or abametapir-COOH showed significant inhibition of AChE in the in vitro screen.

Assay	Test Article	% Inhibition of Control value at 10µM	IC_{50} (µM)
COX1	abametapir	52.3%	32*
	abametapir-COOH	47.7%.	N.C.
ECE-1	abametapir	26.8%	51
	abametapir-COOH	33.9%	N.C.
MMP-2	abametapir	-	N.C.
	abametapir-COOH	-	N.C.
MMP-9	abametapir	-24.4%	>500
	abametapir-COOH	-37.9%	N.C.
MMP-13	abametapir	-	130
	abametapir-COOH	-	130
AChE	abametapir	0.5%	>500
	abametapir-COOH	11.5%	N.C.

N.C.: IC_{50} value not calculable; the concentration-response curve shows less than 25% effect at the highest validated testing concentration.
> *Conc.*: IC_{50} value above the highest test concentration; concentration-response curve shows less than 50% effect at the highest

In Clinical study Hatch201401 the mean C_{max} of the clinical cohort age group showing the highest concentration (≥6 months and <2 years) of total abametapir is 198 ng/mL; the mean C_{max} of the clinical cohort age group showing the highest concentration (≥2 and <4 years) of total abametapir-COOH is 5,055 ng/mL. Both abametapir and abametapir-COOH bind to plasma proteins. In humans abametapir is 91.3% to 92.3% bound (b) (4) 0014) and abametapir-COOH is 96% to 97.5% bound (b) (4) 0021). Expressed as molar concentrations, the highest free abametapir concentration is 0.087 µM and the highest free abametapir-COOH is 0.733 µM (see Calculations, below).

Calculations

Abametapir – mol wt = 184.24 g
1 M = 184.24 g/L

I µM = 184.24 µg/1000 mL = 184.24 ng/mL

Total (bound + free) C_{max} = 198 ng/mL

Free C_{max} = 198 ng/mL x 8.2% = 16.2 ng/mL

C_{max} =16 ng/mL = 0.087 µM

Abametapir-COOH – mol wt = 214.2 g

1 µM = 214.2 µg/ 1000 mL = 214.2 ng/mL

Total (bound + free) C_{max} = 5,055 ng/mL

Free C_{max} =5,055 x 3.25% =157 ng/mL

Free C_{max} =157 ng/mL = 0.733 µM

Since the estimated IC_{50} values of abametapir against these enzymes were defined in excess of the greatest human cohort mean "free" C_{max} (16 ng/mL, 0.087 µM) it is unlikely abametapir would significantly inhibit these enzymes in patients treated with Xeglyze. Similarly, since the IC_{50} values of abametapir-COOH are in excess of the highest human cohort mean "free" C_{max} (157 ng/mL, 0.733 µM), it is unlikely abametapir-COOH would significantly inhibit these enzymes in patients.

The sponsor investigated the potential for abametapir (10 µM) and abametapir-COOH (10 µM) to act as either an agonist or antagonist in a range of cellular and nuclear receptor functional assays (100016477). The potential targets included the adrenergic receptors A2A, α1A, α1B, β2, the muscarinic receptor M3 and the serotonin receptor 5-HT2A. Neither abametapir or abametapir-COOH demonstrated any significant inhibition or stimulation of any of the receptors in this study. The lack of agonism or antagonism at levels in excess of the maximum clinical exposure of either analyte suggests the drug is unlikely to have an off target effect mediated by these receptors.

The sponsor investigated the effect of abametapir and abametapir-COOH on the activity of ECE-1 in an isolated rabbit saphenous artery assay (100017514). ECE-1 is a metallopeptidase mediating the cleavage of big endothelin-1 (big ET-1) to the vasoconstrictor endothelin-1 (ET-1), a potent mediator of smooth muscle contraction. Phosphoramidon is a metal-chelating compound known to inhibit ECE-1 activity, resulting in relaxation of vascular tone in the rabbit saphenous artery. In this assay big ET-1 elicited a concentration dependent contraction which was inhibited by phosphoramidon. However, neither abametapir or abametapir-COOH at 200 µM induced any contraction or inhibition of the contractile response to big ET-1. These results indicate that at 200 µM concentrations neither abametapir nor its primary human metabolite had an effect on ECE-1 activity.

The sponsor investigated the potential cytotoxic effects of six concentrations of abametapir or abametapir-COOH on human foreskin fibroblasts (BJ) and the human embryonic kidney (HEK-293) cell line (100015139). The results showed none to very low level toxicity in the cell lines when exposed to abametapir-COOH, while abametapir

appeared to inhibit proliferation in the BJ cell line and to be cytotoxic in the HEK-293 cells (see Figure 1 (below) abametapir on cytotoxicity profile (HEK-293), taken directly from study report).

Cerep Compound I.D.	Client Compound I.D.	IC_{50} (M)	nH	Test Concentration	% of Control Values 1st	2nd	Mean
cytotoxicity profile (HEK-293)							
100015139-1	abametapir	2.7E-05 M	n/a	2.5E-06 M	90.5	88.0	89.2
				5.0E-06 M	91.9	89.9	90.9
				1.0E-05 M	94.0	88.3	91.1
				1.5E-05 M	92.0	93.1	92.6
				3.0E-05 M	24.7	22.5	23.6
				5.0E-05 M	20.7	20.8	20.8

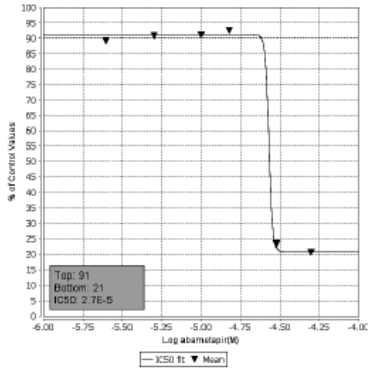


Figure 1. abametapir on cytotoxicity profile (HEK-293)

To determine if abametapir's cytotoxic effect in the HEK-293 cells was due to chelation of essential metal ions, $FeSO_4$ (60 µM) was added to see if this reduced the cytotoxicity observed after incubation with abametapir only. In the presence of $FeSO_4$ the potency of abametapir was significantly reduced (see Figure 2 abametapir + $FeSO_4$ on cytotoxicity profile (HEK-293), taken directly from study report). Abametapir's less potent cytotoxic effect observed in the presence of $FeSO_4$ is consistent with a chelating effect of the compound being responsible for the observed cytotoxicity. The lack of effect of abametapir-COOH on HEK-293 cells possibly results from the inability of the carboxyl metabolite to penetrate the cell membrane due to its polarity.

100015139-2	abametapir + FeSO4	4.3E-05 M	n/a	2.5E-06 M	103.1	103.6	103.4
				5.0E-06 M	109.3	101.7	105.5
				1.0E-05 M	108.9	100.5	104.7
				1.5E-05 M	110.9	106.0	108.5
				3.0E-05 M	89.5	74.3	81.9
				5.0E-05 M	42.0	38.7	40.4

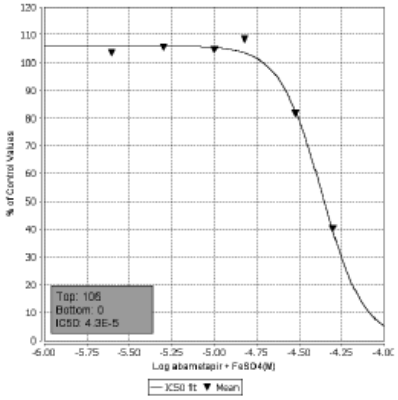


Figure 2. abametapir + FeSO4 on cytotoxicity profile (HEK-293)

These data are consistent with abametapir being characterized as a broad spectrum metalloproteinase inhibitor of low potency. The extent of metalloproteinase inhibition exhibited by abametapir is sufficient to kill lice based on the in vitro and clinical study data available for abametapir.

4.3 Safety Pharmacology

The core battery of safety pharmacology studies for abametapir have been previously reviewed under the original IND. Both the respiratory and CNS function test were acceptable and demonstrated no treatment related effects of abametapir for either parameter.

Cardiovascular safety was originally assessed in an in vitro hERG assay (b) (4) 0017/072680). Inhibitory effects on the hERG current raised concerns about QTc prolongation (IC_{50} =~56 µM). The sponsor had also conducted a study to evaluate the effects of abametapir on electrocardiographic parameters in anesthetized male rats and although it was concluded that abametapir did not appear to cause acute effects on cardiovascular variables, the study did not meet minimal standards and the sponsor was advised to conduct a cardiovascular safety study in an unanesthetized nonrodent species with a sufficient number of animals of both sexes. The sponsor subsequently conducted a cardiovascular study in minipigs using telemetry (71456) which was too flawed for regulatory use. Although the minipig study lacked acceptable dose formulation analysis, no significant changes were observed in ECG parameters with abametapir plasma concentrations as high as 329 ng/mL at 60 minutes after application of the 8.0% abametapir treatment. These studies are less than ideal, but do not present nonclinical causes for concern for potential cardiovascular effects associated with abametapir.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The in vitro metabolism of abametapir was reviewed under the original IND submission. Investigations with cryopreserved hepatocytes from rats, minipigs and humans suggest

that metabolism of abametapir in each species tested is similar, primarily consisting of rapid phase I reactions converting abametapir to hydroxylated and dihydroxylated metabolites. Abametapir-COOH was the major circulating metabolite in all three species and accounted for >97% of the exposure to total drug related material [(b) (4)]0011). Expressed as a proportion of abametapir exposure it represented >4800% in all species. These data support the use of the minipig and rat as suitable nonclinical animal models in which to assess the potential toxicity of abametapir.

The pharmacokinetics of abametapir gel have been studied in the clinic under maximal use conditions (Ha03-004). Inclusion criteria specified that all participants have active head lice infestation (at least 3 live lice) and be at least 6 months to 17 years of age. The drug product was applied as a single topical application of up to 200 mL of abametapir lotion 0.74% w/w applied to each subject, ensuring complete saturation of the scalp and hair. Exposure (as measured by both C_{max} and AUC_{0-8}) was higher in the youngest pediatric group (<12 months; see Table 1.8.1-6, taken directly from the NDA submission). Comparison of the pharmacokinetic parameters for the younger groups versus the older group showed that exposure (both C_{max} and AUC_{0-8}) was approximately 3-fold higher in the younger groups when compared to the older group. Overall, C_{max} and AUC_{0-8} were inversely correlated with age and weight.

Table 1.8.1 - 6 Mean (%CV) Ha44 Noncompartmental Parameters (Study Ha03-004)

	Age Group (# of subjects C_{max}/AUC_{0-8})	C_{max} (ng/mL) (%CV)	T_{max}[a] (hr) (range)	AUC_{0-8} (ng*h/mL) (%CV)
Ha44 (Abametapir)	<12 months (N=5/5)	227.74 (50)	0.50 (0.50-0.57)	668.24 (43)
	1 to <2 years (N=8/6)	147.33 (49)	0.59 (0.48-2.00)	405.53 (37)
	2 to <3 years (N=8/6)	160.01 (48)	0.55 (0.50-2.05)	601.79 (51)
	3 to 17 years (N=7/7)	51.61 (45)	1.00 (0.50-1.08)	193.71 (39)

%CV listed in parentheses; [a] Median (range
Reference: Ha03-004 PK report Table 4-2 (Appendix 16.2.5)

Distribution

The distribution and elimination of dermally administered radioactive abametapir was assessed in rats via wholebody autoradiography/luminography and liquid scintillation counting [(b) (4)]0012). [^{14}C]-Abametapir was administered as a single dermal unoccluded dose (20 mg/kg) formulated in a mixture of [(b) (4)] to 10% of the body surface area of male and female pigmented (Lister Hooded) rats. Lister Hooded rats were selected for this study to enable determination of distribution of drug-related material into melanin-containing tissues. The application was covered with a “saddle” (non-occlusive cover protecting the treated area) and remained in contact

with the surface of the skin until the animal's scheduled termination. Males were examined for tissue distribution and elimination over 504 hours post-dose; females were examined for tissue distribution and elimination over 168 hours post-dose. A longer time period was examined in males to assess melanin binding potential which is independent of gender.

Following administration of [^{14}C]-abametapir, most of the applied radioactivity was rapidly absorbed from the dose site and widely distributed throughout the animal body. The pattern of distribution was broadly similar for both sexes. The highest radioactive concentrations and areas under the curve (AUCs) were observed at the dose site, plasma, kidney (cortex and medulla), uveal tract/retina, and skin (both pigmented and non-pigmented). By 168 hours post-dose radioactive concentrations were observed only at the dose site, nasal mucosa, and skin. Blood to plasma ratios were less than 1. Approximately 45-58% of the administered dose was excreted in the urine and ~18% was excreted in the feces. Radioactivity concentrations in the expired air trap solutions were <0.1% dose, suggesting the position of the radiolabel was metabolically stable.

The in vitro binding of [^{14}C]-abametapir to proteins in plasma from rat, rabbit, minipig and human was determined ([(b) (4)]0014) for use in developing safety margins. Preliminary investigations of non-specific binding, equilibration time and radiochemical stability in plasma were conducted to confirm that equilibrium dialysis was a suitable technique for the determination of protein binding and that [^{14}C]-abametapir (100 ng/mL) was stable in rat, rabbit, minipig and human plasma at 37ºC for 2 hours (the conditions used to determine plasma protein binding by equilibrium dialysis).

The overall extent of plasma protein binding of [^{14}C]-abametapir in vitro over the concentration ranges studied for rat, rabbit, minipig and human are shown in the table below (taken directly from the study report).

Species	Concentration range	% bound
Rabbit	10 – 200 ng/mL	91.4% – 94.7%
Human	50 – 800 ng/mL	91.3% - 92.3%
Rat	100 – 4500 ng/mL	87.7% – 89.4%
Minipig	100 – 2000 ng/mL	72.6% - 75.2%

The extent of binding was greatest in the rabbit though levels were similar in the human. Lowest levels of plasma protein binding were observed in the minipig. The binding results obtained in all species suggested that the degree of binding was independent of the concentration of abametapir.

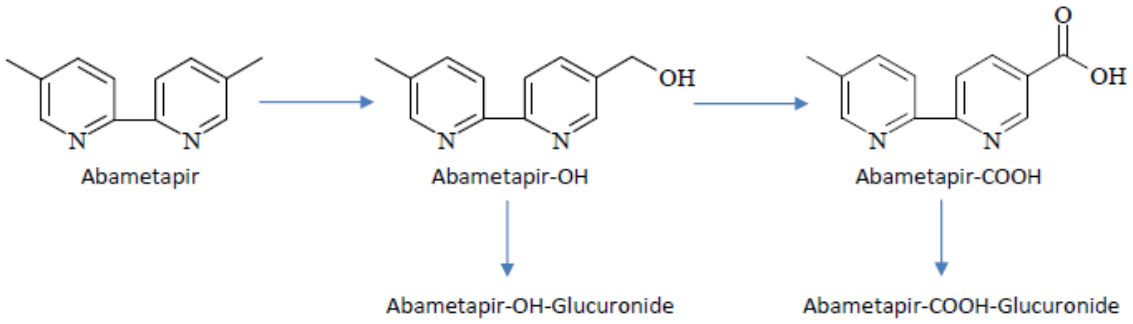
The in vitro binding of abametapir-COOH to proteins in plasma from rat, rabbit, minipig, and human was investigated ([(b) (4)]0021). The overall extent of binding was greatest in human, with slightly lower levels of binding observed in the rabbit, followed by the rat (see table below, taken directly from the study report). The lowest levels of plasma protein binding were observed in the minipig.

Species	% bound
Rat	91.0 - 91.7
Rabbit	93.9 - 94.8
Minipig	73.7 - 76.6
Human	96.0 - 97.5

Metabolism

Following incubation of abametapir with human liver microsomes, it was demonstrated that both the mono-hydroxylated metabolite (abametapir-OH) and the mono-carboxylated metabolite (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 (Htc036b, (b) (4) 0013). Given the relative rates and sequence of metabolite formation from the microsomal incubation data, 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 such as CYP1A2 with glucuronidation of both metabolites mediated by Phase II metabolism catalyzed by UDP-glucuronosyltransferase (Figure 10, taken directly from the study report).

Figure 10. The proposed metabolic pathway of abametapir



Following incubation of abametapir with human, rat or minipig liver microsomes it was demonstrated that the rate of in vitro Phase I metabolism of abametapir is similar between the three species investigated. Incubation of the Phase I metabolites did result in formation of Phase II metabolites corresponding to abametapir-OH-glucuronide and abametapir-COOH-glucuronide. It was not possible to quantify the Phase II metabolite concentrations due to lack of appropriate reference standards. However, in these Phase II metabolic reaction mixtures the concentrations of Phase I metabolites did not markedly decrease during the course of these microsomal incubations. It is therefore likely that only a small fraction of the parent compound is metabolized to the glucuronide conjugate under the conditions of study.

Both abametapir-OH and abametapir-COOH have been identified in human plasma (b) (4) 0011). Formation of these Phase I metabolites has been shown to be catalyzed predominantly by CYP1A2 (b) (4) 0013). In vitro studies have identified the potential for Phase II glucuronidation of both metabolites (HTC-036B). A retrospective analysis of frozen plasma samples from completed clinical and nonclinical studies revealed only a small amount of glucuronidated metabolites were present relative to the unconjugated forms in human and animal plasma (HTC-036A). However, the stability of these conjugates in plasma has not been established. In vivo, unconjugated abametapir-COOH accounts for the majority of the drug related plasma exposure in humans, rats, rabbits and minipigs (b) (4) 0011). Abametapir-OH was a minor metabolite in all species when considered in terms of exposure to total drug related material, accounting for <2%.

Reviewer's comment: Topically applied abametapir would first be subject to metabolism in the skin. Although not measured in vitro, abametapir skin metabolism may be both qualitatively and quantitatively different from that in the liver.

Reviewer's comment: In an advice letter (8-22-2014), the Agency agreed that due to the low contribution of abametapir-OH to the total drug-related exposure, the hydroxylated metabolite does not need to be further characterized.

Excretion

Excretion of drug-related material in the rat following dermal administration of abametapir was found to be primarily via urine (45%) and feces (18%; (b) (4) 0012).

Other pharmacokinetic studies

The ability of abametapir to inhibit human hepatic cytochrome(s) P450 (CYPs) was investigated using pooled human liver microsomes ((b) (4) 0009). A pharmacokinetic model of clinical exposure predicts the highest human C_{max} value to be ~4μM. Thus abametapir at 40 μM was selected as the maximum concentration to assess a potential 10-fold excess, allowing for possible accumulation by the liver. Abametapir (40 μM) does not notably inhibit (>30%) the following significant CYPs: CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5. It does reversibly inhibit CYP1A2 (K_i = 39 μM).

Of the CYPs investigated, CYP1A2 appeared to be the major enzyme involved in the in vitro metabolism of abametapir, with a lesser contribution by CYP2C19 ((b) (4) 0013). There also was evidence for abametapir metabolism by CYP2B6, CYP2C9, CYP2D6, and CYP3A4, but to a much lesser extent. Using cryopreserved human hepatocytes from three donors (one male, two females; (b) (4) 0010) abametapir (40 μM) caused maximal inductive effects of 3.1%, 2.3%, and 3.6% increased expression of mRNA for CYP1A2, CYP2B6 and CYP3A4, respectively. Based on regulatory guidelines (Guidance for Industry – Drug Interaction Studies), abametapir (≤40 μM) is not classed as an inducer of these enzymes. Evidence of significant abametapir suppression of

CYP3A4 mRNA expression was observed in two out of three donors, suggesting high concentrations of abametapir may downregulate this enzyme.

Abametapir-COOH, the primary human metabolite of abametapir, was tested for its ability to induce or inhibit CYP450s. Abametapir-COOH is not an inhibitor of any CYP450s investigated (*i.e.*, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) in pooled human liver microsomes ((b) (4) 0017). Nor is abametapir-COOH an inducer of the CYP450s investigated (*i.e.*, CYP1A2, CYP2B6, or CYP3A4/5) in cryopreserved human hepatocytes ((b) (4) 0018). When abametapir-COOH (5-200 µM) was incubated with pooled human liver microsomes in the presence of NADPH, essentially no test article disappeared following a 2-hour incubation ((b) (4) 0020). Thus abametapir-COOH is not considered a substrate for human hepatic CYP450 or other NADPH-dependent microsomal enzymes.

Membrane transport proteins may influence the absorption, distribution, metabolism and elimination properties of drugs. There are two main superfamilies of transport proteins, ABC (ATP-binding cassette) and SLC (solute carrier) transporters. Abametapir (40 µM) is not a substrate of ABC efflux transporters; nor is it a substrate of the common SLC uptake transporters ((b) (4) 0008). Abametapir-COOH is also not a substrate for SLC uptake or ABC efflux transporters (OPT-2014-056). Additionally, Abametapir-COOH does not notably inhibit the transport of substrates of the human ABC efflux transporters and the common human SLC uptake transporters (OPT-2014-055, OPT-2014-081).

5.2 Toxicokinetics

Two minipigs (1 male, 1 female) were administered an abametapir formulation (2.7%) once daily for at least 4 hours for 14 consecutive days for an applied dose of 18.1 mg/kg/day abametapir (1370-13220). The prototype formulation was not specified in the study report. Three male rats were administered a dose of 25 mg/kg via oral gavage once daily for 14 days ((b) (4) 0011). The vehicle was (b) (4) Toxicokinetic analysis in both species (Htc-034) indicated that the parent compound was relatively quickly absorbed after both dermal and oral administration in the corresponding species, followed by rapid metabolism to abametapir-OH and abametapir-COOH.

In minipigs all three analytes accumulated with repeated dosing (Text Table 1, taken directly from the study report). The extent of systemic exposure varied between the analytes. On Day 14, systemic exposure to abametapir-COOH was greater than systemic exposure to abametapir, whereas systemic exposure to abametapir-OH was less than that of abametapir. The half-lives did not vary notably with repeat dosing for any of the analytes.

Text Table 1: Summary of Minipig Toxicokinetic Parameters (mean values)

Treatment	Dose	Analyte	Day	AUClast (ng.hr/mL)	Cmax (ng/mL)	Tmax (hr)	AUCinf (ng.hr/mL)	T1/2 (hr)
Abametapir	18.1 mg/kg	Abametapir	1	176	35.9	2.00	189	5.53
			14	1620	436	1.50	1640	4.50
		Abametapir-OH	1	237	45.5	2.00	258	6.88
			14	519	98.7	1.50	322	6.78
		Abametapir-COOH	1	5930	1050	4.00	6440	5.70
			14	24200	4200	4.00	24700	3.61

In the rat, systemic exposure varied between the analytes and followed a pattern similar to that in minipigs with abametapir-COOH being much greater and abametapir-OH being less than abametapir (see Text Table 2, taken directly from the study report). All three analytes were rapidly to moderately rapidly cleared, with half-lives of approximately 1 hr for the parent compound and hydroxyl metabolite and approximately 4 hr for abametapir-COOH.

Text Table 2: Summary of Rat Toxicokinetic Parameters (mean values)

Treatment	Dose	Analyte	Day	AUClast (ng.hr/mL)	Cmax (ng/mL)	Tmax (hr)	AUCinf (ng.hr/mL)	T1/2 (hr)
Abametapir	25 mg/kg	Abametapir	14	257	205	0.25	260	1.19
		Abametapir-OH	14	45.8	46.4	0.25	49.0	0.851
		Abametapir-COOH	14	74300	13000	1.00	75200	3.90

6 General Toxicology

The sponsor has conducted single-dose toxicity studies in rats and repeat-dose toxicity studies in rats and minipigs. These studies have been previously reviewed under the original IND. Summary information is provided below.

6.1 Single-Dose Toxicity

A single dose oral abametapir toxicity study was conducted in rats (0 {vehicle control; (b) (4) 150, 175, 200, 250 mg/kg; n=1/sex/dose; (b) (4) 0005). Clinical signs included body tremors at all dose levels and piloerection, fast respiration and abnormal gait or convulsions at the higher dose levels. Both males dosed at 200 and 250 mg/kg died within 4 hours of dosing.

6.2 Repeat-Dose Toxicity

The repeat-dose toxicity of abametapir was investigated in groups of Sprague-Dawley rats (3/sex/dose) at 0 (vehicle control; (b) (4) 5, or 20 mg/kg/day in a 7-day intraperitoneal toxicity study (b) (4) 612). At the end of the experimental period all animals were terminated and blood samples were taken for hematology and serum

chemistry analysis. Under the conditions of this study abametapir did not produce any toxic effects when compared with the vehicle control animals.

A 2-week repeat-dose oral toxicity study (0 {vehicle control; [redacted](b) (4)}, 8, 25, 75 or 100 mg/kg/day) was conducted in CD rats [redacted](b) (4)0006). The kidney and red blood cells were identified as target organs for toxicity. Under the conditions of this study the NOAEL for abametapir was determined to be 8 mg/kg/day.

Abametapir was administered to juvenile rats orally for 8 weeks at oral doses of 0 (vehicle control; [redacted](b) (4)), 5, 12, or 30 mg/kg/day beginning on PND 7 (70658). Body weight gain, crown-rump and tibial lengths, were unaffected by treatment. There were no adverse effects on the development or maturation of the central nervous system or reproductive organs. The primary effects noted in this study included decreased red blood cell parameters (associated with the pharmacological activity of abametapir), slightly increased creatinine (1.1 to 1.3-fold above control values at the end of the treatment and recovery periods), with no histopathological correlates at any dose. Although a dosing error during Week 4 precluded development of a NOAEL, no new target organs were identified.

Toxicokinetic analysis of abametapir-OH and abametapir-COOH concentration-time data obtained from juvenile rats administered 30 mg/kg/day (70658) indicated that the hydroxyl and carboxylic acid metabolites of abametapir are rapidly formed in vivo after oral treatment (Text Table 1, taken directly from the study report, Htc-039).

Text Table 1: Summary of Toxicokinetic Parameters

Treatment	Dose	Analyte	Day	AUClast (ng.hr/mL)	Cmax (ng/mL)	Tmax (hr)	AUCinf (ng.hr/mL)	T1/2 (hr)
Abametapir	30 mg/kg	Abametapir-OH	1	1270	450	1.00	1470	5.28
			56	108	58.2	0.50	111	1.54
		Abametapir-COOH	1	142000	16200	6.00	ND	ND
			56	171000	17900	1.00	175000	4.52

Study title: A 28-day toxicity study of Abametapir Lotion by dermal administration to minipigs with a 16-day recovery

Study no.:	20049509
Study report location:	Electronic document, SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	1-30-2014
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	Abametapir lotion , 0.74%, RD-13074, 99.9% Abametapir lotion, 3.7%, 40103-1, 96.5% Abametapir lotion vehicle, RD-13073, NA

Key Study Findings

Once daily dermal administration of abametapir lotion, 0.74% in female minipigs for 28 days was without systemic effects (correlates to a C_{max} value of 294 ng/mL and an AUC_{last} value of 622 ng●h/mL on Day 28; 14.2 mg/kg/day). Females treated twice daily with abametapir lotion, 0.74% or once daily with abametapir lotion, 3.7% had tremors and distended abdomen (≥28.2 mg/kg/day). In males, general signs of toxicity and penile prolapse were observed with once daily administration of abametapir lotion, 0.74% (correlates to a C_{max} value of 534 ng/mL and an AUC_{last} value of 1297 ng●h/mL on Day 13; 14.2 mg/kg/day). The penile prolapse observations required early termination for humane reasons and no underlying cause of the protrusion was demonstrated. Under the conditions of this study, the NOAEL in females is once daily dermal administration of abametapir lotion, 0.74% (14.2 mg/kg/day) and a NOAEL in males could not be determined.

Reviewer's comment: These treatment related effects noted after extended repeat dose testing would not be a cause for concern under the proposed clinical conditions of use which is for a one time 10-minute application and then washed off.

Methods

Doses:	0% (untreated control), 0% (vehicle control), 0.74%, 0.74% (2X/day), 3.7%; 0, 0, 14.2, 28.4, 71.0/35.5 mg/kg/day*
Frequency of dosing:	Once daily for Groups 2, 3, and 5. Animals in Group 4 were dosed twice daily, 6 hours apart.
Route of administration:	Dorsal to clipped dermal surface (~10% BSA), covered with stockinette until next dosing
Dose volume:	2 mL/kg, reduced to 1 mL/kg for Group 5 females on Day 17 when dosing started after dosing holiday
Formulation/Vehicle:	Clinical (to-be-marketed) formulation
Species/Strain:	Gottingen minipigs
Number/Sex/Group:	Main study : 4/sex/group
Age:	21 weeks
Weight:	8.1 – 12.5 kg
Satellite groups:	Recovery: 2/sex/group except no Group 4 or 5 males
Unique study design:	Group 4 animals were dosed twice daily with the same concentration as used to treated group 3 animals. It would have been a better study design to have used 3 different concentrations and a single daily treatment regimen.
Deviation from study protocol:	Treatment to Main study males ceased on Day 11 (Group 5) and on Day 14 (Groups 1 to 4). Main study males were terminated on Day 16. Recovery was not assessed in males. Group 5 females had a dosing holiday (Day 11-17) and resumed at 1 mL/kg (35.5 mg/kg/day). On Day 15, the duration of dermal contact time was reduced from 24 hours to 4 hours following each dose application for groups 2, 3, and 5 females and the stockinette was no longer used. For group 4 females, the first dose was administered for 4 hours, animals were allowed to rest for 2 hours and then the second dose was administered for 4 hours.

*dosing was based on results of a 7-day dermal minipig study (1/sex/dose; 1370-13240) in which 2 mL/kg was established as the maximum feasible volume applied to 10% BSA. Based on penile prolapse at 28.4 mg/kg, the 7-day abametapir lotion 0.74% dermal NOAEL was 14.2 mg/kg/day in males and 28.4 mg/kg/day in females.

Text Table 1
Experimental Design

Group No.	Test Material	Dose Level (mg API/kg/dose)	Dose Level (mg API/kg/day)	Dose Volume (mL formulation /kg)	Dose Concentration (mg API/mL formulation)	No. of Animals			
						Main Study		Recovery Study	
						M[a]	F	M[a]	F
1	Untreated	0	0	0	0	4	4	2	2
2	Control Article	0	0	2	0	4	4	2	2
3	Abametapir Lotion, 0.74%	14.2	14.2	2	7.1	4	4	2	2
4	Abametapir Lotion, 0.74%	14.2	28.4	2	7.1	4	4	2[c]	2
5	Abametapir Lotion, 3.7%	71.0/35.5	71.0/35.5	2/1[b]	35.5	4	4	2[c]	2

[a] Dosing was ceased for male animals in Groups 1 through 4 on Day 14. Surviving main study males were euthanized on Study Day 16 and males that were assigned to the recovery phase began recovery on Day 15.
[b] Dosing was ceased on Day 11 for the Group 5 animals. The dose volume was reduced to 1 mL/kg when the females were released from dosing holiday on Day 17.
[c] Recovery was not assessed for males due to early termination of the dose group.

Observations and Results

Mortality

Animals were observed for general health/mortality and moribundity twice daily. There were 13 early terminations in abametapir lotion-treated males as a result of sustained penile prolapse. The animals euthanized early included two low dose males on Days 12 and 14, five mid-dose males on Days 13 to 17, and six high dose males on Days 10 to 14. The lone mid-dose surviving male assigned to recovery phase began recovery on Day 15 and was terminated on Day 16. The remaining Main study males (limited to the control groups and low dose group animals without penile prolapse) were terminated on Day 16 to enable group comparisons. The remaining Recovery males in the control and low dose groups began recovery on Day 15 and survived to Day 45. All females survived to their respective termination dates of either Day 29 or Day 45.

Clinical Signs

Cage side observations were performed once daily during dosing and recovery phases. Detailed clinical observations were performed weekly, beginning during Week -1. Clinical signs for males in the abametapir lotion-treated groups included partially closed eyes (high dose), decreased activity and reduced appetite (mid and high dose), protruding penis and tremors (low, mid- and high dose). Clinical signs for females in the abametapir lotion-treated groups included partially closed eyes and reduced appetite (high dose), decreased activity, distended abdomen, reduced fecal output and tremors (mid- and high dose).

Very slight (Grade 1) to moderate/severe erythema (Grade 3) with very slight (Grade 1) to slight (Grade 2) edema were noted in the animals administered abametapir lotion. Skin flaking (desquamation) was noted for all animals administered either the vehicle control or the abametapir lotion. Only very slight erythema and no edema were noted for animals during the recovery phase. As the erythema observed during dosing subsided following cessation of treatment, the irritation was considered a direct result of test article administration.

Body Weights

Each animal was weighed at least 3/week, starting Week -1. A final fasted weight was recorded at scheduled termination. There were no toxicologically meaningful abametapir lotion-related effects on mean body weight or body weight gain in males or females.

Feed Consumption

Feed consumption was measured qualitatively once daily, beginning Week -1 and continuing throughout dosing and recovery periods. There were no consistent feed consumption changes noted during the study period.

Ophthalmoscopy

Ophthalmoscopy was performed prior to in-life initiation (Day -6), on Day 13, during the last week of treatment (Day 27), and during the recovery period (Day 44). Examinations were conducted using a hand-held slit lamp and indirect ophthalmoscope. There were no test article-related differences in ophthalmic findings.

ECG

ECG measurements were obtained from all animals using leads I, II, III, vV_R, aV_L, and aV_F once prior to in-life initiation, Day 15 (all surviving males), during the last week of dosing, and during the recovery period. There were no test article-related or vehicle-related effects on ECG measurements or electrical rhythm in minipigs during the dosing and recovery phases of the study.

Hematology

Blood was collected by venipuncture from overnight fasted animals prior to initiation and at termination and analyzed for the following parameters: red blood cell count, hemoglobin concentration, hematocrit, mean corpuscular volume, red blood cell distribution width, mean corpuscular hemoglobin concentration, reticulocyte count (absolute), platelet count, white blood cell count, neutrophil count (absolute), lymphocyte count (absolute), monocyte count (absolute), eosinophil count (absolute), basophil count (absolute), large unstained cells, other cells (as appropriate). Blood samples were processed to plasma and analyzed for activated partial thromboplastin time, fibrinogen, and prothrombin time. There were no meaningful abametapir lotion-related effects on hematology and coagulation parameters.

Clinical Chemistry

Blood was collected by venipuncture from overnight fasted animals prior to initiation and at termination, processed to serum and analyzed for the following parameters: alanine

aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, creatinine kinase, total bilirubin, urea nitrogen, creatinine, calcium, phosphorus, total protein, albumin, globulin (calculated), albumin/globulin ratio, glucose, cholesterol, triglycerides, sodium, potassium, chloride, sorbitol dehydrogenase, lactate dehydrogenase. There were no meaningful abametapir lotion-related effects on clinical chemistry parameters.

Urinalysis

Urine was collected from overnight fasted animals prior to initiation (via cage pan drainage) and at termination (via cystocentesis). Samples were analyzed for: color, appearance/clarity, specific gravity, pH, protein, glucose, bilirubin, ketones, and blood. There were no abametapir lotion-related effects on urinalysis parameters.

Gross Pathology

Main study and recovery animals were subjected to a complete necropsy examination which included evaluation of the carcass and musculoskeletal system, all external surfaces and orifices, cranial cavity and external surfaces of the brain, and thoracic, abdominal and pelvic cavities with their associated organs and tissues.

Penile prolapse in two low dose males, five mid-dose males and six high dose males required unscheduled termination. Treatment-related gross necropsy observations in these males included swelling, discoloration and protrusion of the penis in the low, mid- and high dose groups and discoloration of the treated skin and scale on the treatment area in the mid- and high dose groups (see Text Table 4, taken directly from the study report).

Text Table 4
Significant Gross Findings in Early Termination (Unscheduled Euthanasia) Males[a]

Dose Group Gross Observation	14.2 mg API/kg/day Group 3	28.4 mg API/kg/day Group 4	71 mg API/kg/day Group 5
Skin, Treated	2	6	6
Discoloration; dark	0	1	1
Scale	0	1	1
Penis	2	5[b]	6
Protrusion	2	5	6
Swelling	1	3	3
Discoloration; dark	2	5	4

[a]=Gross lesions include those in #7194 (unscheduled euthanasia) and #7207 (unscheduled euthanasia) on Study Days 17 and 16, respectively.
[b]=The penis from one of the animals was not harvested at necropsy.

Reviewer's comment: The underlying cause of penile prolapse was not determined, but is likely due to an effect of abametapir on smooth muscle relaxation. This nonclinical observation noted after repeat exposure is not a cause for concern under clinical use conditions.

Treatment-related gross necropsy observations in controls and low dose males euthanized in accordance with the protocol amendment (Day 16) and all Main study

females euthanized at the end of treatment (Day 29) are summarized in the table below, taken directly from the study report. The males terminated on Day 16 did not exhibit penile protrusion, but were terminated to enable group comparisons. Observations were limited to discoloration of the treated skin and scale on the treatment area. For females terminated on Day 29 no test article-related gross findings were noted.

20049509 - Intergroup Comparison of Gross Pathology Findings

Removal Reason: TERMINAL EUTHANASIA	Male			Female				
	0 mg API/ kg/day Group 1	0 mg API/ kg/day Group 2	14.2 mg API/ kg/day Group 3	0 mg API/ kg/day Group 1	0 mg API/ kg/day Group 2	14.2 mg API/ kg/day Group 3	28.4 mg API/ kg/day Group 4	71 mg API/ kg/day Group 5
Number of Animals:	4	4	2	4	4	4	4	4
LARGE INTESTINE, RECTUM								
Submitted	4	4	2	4	4	4	4	4
No Visible Lesions	4	4	2	4	4	4	4	4
Focus; dark	0	0	0	0	0	0	0	0
GLAND, SEMINAL VESICLE								
Submitted	4	4	2	.	.	.	.	.
No Visible Lesions	4	4	2	.	.	.	.	.
Small	0	0	0	.	.	.	.	.
SKIN								
Submitted	4	4	2	4	4	4	4	4
No Visible Lesions	4	4	2	4	4	4	4	4
Scab	0	0	0	0	0	0	0	0
SKIN, TREATED								
Submitted	4	4	2	4	4	4	4	4
No Visible Lesions	4	2	0	4	4	4	4	4
Discoloration; dark	0	1	0	0	0	0	0	0
Scale	0	2	2	0	0	0	0	0
SKIN, UNTREATED								
Submitted	4	4	2	4	4	4	4	4
No Visible Lesions	4	4	2	4	4	4	4	4
Scale	0	0	0	0	0	0	0	0

The only potential test article-related gross findings in recovery animals euthanized on Day 45 was scale observed at the location of treatment in one low dose and one high dose female.

Organ Weights

The following organs were weighed at necropsy: brain, epididymis, adrenal gland, pituitary gland, prostate gland, thyroid gland, heart, kidney, liver, lung, ovary, spleen, testis, thymus, and uterus. No organ weight data was collected for animals euthanized prior to the scheduled termination, *i.e.*, abametapir treated males. No test article-related organ weight changes were noted in control males and in control, low, mid- and high dose females.

Histopathology

Representative samples of the following tissues were collected from all animals, preserved and examined microscopically: artery (aorta), biceps brachii tendon, bone marrow smear, bone (femur), bone (sternum), brain, calcanean tendon, cervix, cranial cruciate ligament, epididymis, esophagus, eye, gallbladder, adrenal gland, mammary gland, parathyroid gland, thyroid gland pituitary gland, prostate gland, salivary gland, seminal vesicle gland, gross lesions, gut-associated lymphoid tissue, heart, kidney,

large intestine (cecum, colon, rectum), liver, lung, lymph node (mandibular, mesenteric), muscle (skeletal), optic nerve, sciatic nerve, ovary, pancreas, penis, retractor penis muscle, round ligament of the uterus, skin (treated), skin (untreated), small intestine (duodenum, ileum, jejunum), spinal cord, spleen, stomach, testis, thymus, tongue, trachea, urinary bladder, uterus, vagina.

Adequate Battery - yes

Peer Review- not indicated

Histological Findings
Microscopic findings were limited to the penis, bone marrow, and application site skin. Observations in the penis (hemorrhage, neutrophilic infiltration, edema, congestion, ulceration, increased exudates, and necrosis) and bone marrow (increased hematopoietic proliferation) were determined to be the result, not the cause, of the penile protrusion for an extended period of time. No drug-related penile or bone marrow findings were apparent at the end of the recovery period, but all males observed with penile protrusion were terminated early for ethical reasons and thus recovery of penile protrusion was not assessed. A single observation of penile hemorrhage involved one low dose male and was considered a background lesion unrelated to treatment. Microscopic observations in the application site skin consisted of minimal or mild dermal mixed cell infiltration, epidermal hyperplasia, hyperkeratosis, parakeratosis, erosion and/or ulceration. The dermal signs were considered non-adverse in all dose groups. The severity of these dermal findings was considered minimal to mild and not dose-related in male or female animals.

Toxicokinetics

Blood samples for toxicokinetics were collected on Days 1, 13 (males and females), 24 (females only), and 28 (females only) utilizing a sparse sampling technique (2 to 6 animals/sex/timepoint). Plasma samples were assayed to determine the concentration of abametapir, abametapir-OH and abametapir-COOH. Toxicokinetic parameters were determined using non-compartmental analysis. Mean toxicokinetic parameters for abametapir, abametapir-COOH and abametapir-OH are presented in the table below (taken directly from the NDA submission).

Reviewer's comment: Although minipigs were treated with abametapir on the dorsal area which is relatively inaccessible to a singly housed minipig and the treatment area was covered for the first 15 days of treatment, it is not known to what extent these measures prevented the animals from ingesting the drug product. Thus the resulting toxicokinetic data may reflect both topical and oral administration.

Abametapir was present in the systemic circulation within 0.5 hour after dosing and formation of both the abametapir-COOH and abametapir-OH metabolites occurred without any major delay. All three analytes were identified at all timepoints in both sexes of all dose groups during the dosing periods. The extent of exposure (AUC_{0-24}) to all three analytes increased with increasing dose in both sexes. Repeated dosing resulted in accumulation (2 to 3-fold) of abametapir and abametapir-COOH, but not

abametapir-OH. Reduction of dermal contact time on Day 15 was associated with lower systemic exposures in females on Day 28 relative to Day 13. Males exhibited higher (~2-fold) exposure to abametapir than females on Day 13, but no consistent sex-based differences were apparent in abametapir-COOH or abametapir-OH exposure. Systemic exposure to abametapir-COOH was greater (Day 13: 6 to 16-fold) than systemic exposure to abametapir, and systemic exposure to abametapir-OH was less (Day 13: 0.1 to 0.4-fold) than systemic exposure to abametapir.

Abametapir, abametapir-OH and abametapir-COOH systemic exposure in minipigs treated topically with abametapir lotion for up to 28 days

Daily Dose:	**0 mg API/kg/day (Untreated)**		**0 mg API/kg/day (Vehicle)**		**14.2 mg API/kg/day**		**28.4 mg API/kg/day**		**71.0/35.5[3] API/kg/day**	
Sex:	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Toxicokinetics: AUC_{last} (h•ng/mL)										
Abametapir										
Day 1[5]	NA	NA	NA	NA	533	232	1016	446	1087	1004
Day 13[6]	NA	NA	NA	NA	1297	1134	4391	2688	NA[4]	NA[4]
Day 28[5]	NA	NA	NA	NA	NA	622	NA	2120	NA	2216
Abametapir carboxyl										
Day 1[5]	NA	NA	NA	NA	4954	5415	13407	16300	11838	32584
Day 13[6]	NA	NA	NA	NA	18081	13252	26812	42754	NA[4]	NA[4]
Day 28[5]	NA	NA	NA	NA	NA	8919	NA	32969	NA	31916
Abametapir hydroxyl										
Day 1[5]	NA	NA	NA	NA	302	182	409	428	847	785
Day 13[6]	NA	NA	NA	NA	478	274	354	571	NA[4]	NA[4]
Day 28[5]	NA	NA	NA	NA	NA	206	NA	523	NA	556

[3] Dosing was ceased for all females in the 71.0 mg API/kg/day group from Day 11 until Day 17. On Day 17, dosing was reinstated at a lower level (35.5 mg/kg/day).

[4] Only a single time point toxicokinetic sample taken.

[5] N = 6 for males and females.

[6] N = 5 for males and 6 for females.

Reviewer's comments: Refer to experimental design table above for a description of when dosing was stopped in treated males in this study.

There were no detectable concentrations of abametapir or its metabolites in recovery animals on Day 45 (with the exception of one low dose male animal with abametapir-COOH detected at 1.2 ng/mL) indicating the majority of each compound was cleared from recovering animals in all dose groups.

Dosing Solution Analysis

All study samples analyzed were within or equal to the acceptability criterion of ± 10% of their theoretical concentrations. No abametapir was detected in the vehicle lotion. The mean concentrations of abametapir were all within ± 10% of nominal concentrations confirming stability and homogeneity of the formulation throughout the study.

7 Genetic Toxicology

The sponsor has performed the complete ICH genotoxicity battery for abametapir. These genotoxicity studies were reviewed under the IND submission and briefly described below.

Abametapir (≤500 µg/plate) with or without metabolic activation was not mutagenic in the bacterial reverse mutation test. Higher concentrations were limited by toxicity. In the in vitro chromosomal aberration test in Human lymphocytes, chromosomal aberrations were observed, but only at cytotoxic concentrations (230.3 µg/mL). This result was considered equivocal. Abametapir (<160 mg/kg/day) did not induce micronucleus formation in the in vivo rat micronucleus assay. Abametapir is considered to be negative for genotoxic potential.

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Evaluation of the genotoxicity of abametapir-COOH in a bacterial reverse mutation (AMES) test with five *Salmonella typhimurium* strains with and without metabolic activation (±S9) at five concentrations

Study no.:	HTCH0001-002-2130
Study report location:	Electronic document, SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 12, 2014
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	Abametapir-COOH, 666-199-4, 99.85%

Key Study Findings

The mutagenic effect of abametapir-COOH was tested in the Ames test using the plate incorporation method in TA98, TA100, TA102, TA1535, and TA1537 *Salmonella typhimurium* tester strains with 5 dose concentrations (7.9, 25, 79, 250, and 790 µg/plate) in both the presence and absence of metabolic activation. Abametapir-COOH elicited cytotoxicity at 2500 µg/plate in a dose range finding study. Abametapir-COOH was negative for both cytotoxicity and mutagenicity at dose concentrations of 7.9-790 µg/plate for each of the five tester strains both with and without metabolic activation (±S9).

Methods

Strains:	*Salmonella typhimurium* TA98, TA100, TA102, TA1535, TA1537
Concentrations in definitive study:	7.9, 25, 79, 250, and 790, µg/plate
Basis of concentration selection:	The maximum soluble dose of 2,500 µg/plate was serially diluted to obtain 8 concentrations for the initial cytotoxicity test. Preliminary data indicated the test article was cytotoxic at 2,500 µg/plate. The highest non-cytotoxic dose (790 µg/plate) and 4 additional concentrations were chosen for the mutagenicity test.
Negative control:	DMSO
Positive control:	See table below (taken directly from study report)
Vehicle:	DMSO
Incubation & sampling time:	37± 2º C, 48± 1 hours

The positive conditions applicable to each positive control are summarised in the following table:

Positive Control Compound	Dose (µg/plate)	Strain(s)	Metabolic Condition
9-Aminoacridine	50	TA1537	-S9
Benzo(α)pyrene	5	TA98, TA100, TA1537	+S9
	10	TA102	+S9
Cumene hydroperoxide	100	TA102	-S9
Cyclophosphamide monohydrate	100	TA1535	+S9
2-Nitrofluorene	1	TA98	-S9
Sodium Azide	0.5	TA100, TA1535	-S9

Study Validity

The acceptability of results was assessed by comparing the concurrent negative and positive results with the criteria defined in the table below:

Tester Strain	Acceptable negative control results (spontaneous revert colonies per plate)	Acceptable positive control results (ratio of colonies per plate: positive vs. negative)
TA98	10 - 70	≥ 3
TA100	50- 200	≥ 2
TA102	300 - 600	≥ 2
TA1535	3 - 40	≥ 3
A1537	1 - 25	≥ 3

The number of colonies in concurrent negative/vehicle controls and positive controls were within the acceptable ranges in the current test. The test is considered to be valid.

Criteria for positive results: Positive test results are defined as ≥ 3-fold increase in revertant colonies in the tester strain TA98, TA1535, and TA1537, or a ≥2-fold increase in the tester strain TA100 and TA102.

Results

Triplicate cultures were tested and revertant colonies were counted with an automated colony counter. The mean number of revertants in each test article-treated culture was compared to that of the spontaneous revertant colonies in the negative control.

Treatment with the test article in TA98, TA1535, and TA1537 at all concentrations tested with and without S9 produced a group colony ratio (test article versus vehicle) of <3 (see Tables 2 and 3, taken directly from the study report).

Treatment in TA100 and TA102 at all concentrations tested with and without S9 produced a group colony ratio of <2 (see Tables 2 and 3, taken directly from the study report).

Table 2: Mutagenicity Test Results (-S9) - Pour Plate Method

Test Article	Dose (µg/plate)	Number of Colonies per Plate (Mean ±SD)				
		TA98	TA100	TA102	TA1535	TA1537
		-S9				
Negative Control		23 ± 5	175 ± 22	614 ± 44	17 ± 4	21 ± 2
Abametapir-COOH	790	34 ± 17	133 ± 9	165 ± 20	19 ± 3	14 ± 6
	250	13 ± 0	140 ± 10	499 ± 106	12 ± 2	19 ± 7
	79	14 ± 1	128 ± 28	587 ± 52	19 ± 2	14 ± 1
	25	20 ± 8	139 ± 45	664 ± 29	15 ± 2	14 ± 2
	7.9	28 ± 12	140 ± 17	640 ± 14	16 ± 4	12 ± 4
Positive Control Vehicle		23 ± 5	211 ± 21	614 ± 44	17 ± 7	21 ± 2
Positive Control		274 ± 31	467 ± 40	2334 ± 121	261 ± 27	344 ± 65

a. DMSO, the vehicle for the test article

b. For TA98: 2- Nitrofluorene 1.0 µg/plate (-S9) or Benzo(a)pyrene 5 µg/plate (+S9); TA100: Sodium azide 0.5 µg plate (-S9) or Benzo(a)pyrene 5 µg/plate (+S9); TA102: Cumene Hydroperoxide 100 µg/plate (-S9) or Benzo(a)pyrene 10 µg/plate (+S9); TA1535: Sodium Azide 0.5 µg /plate (-S9) or Cyclophosphamide 100 µg/plate (+S9); TA1537: 9-Aminoacridine 50 µg/plate (-S9) or Benzo(a)pyrene 5 µg/plate (+S9).

c.DMSO is positive control vehicle for 2- Nitrofluorene, Cumeme Hydroperoxide, Benzo(a)pyrene and 9-Aminoacridine. Water is positive control vehicle for Sodium Azide and Cyclophosphamide

Table 3: Mutagenicity Test Results (+S9) - Pour Plate Method

Test Article	Dose (µg/plate)	Number of Colonies per Plate (Mean ±SD)				
		TA98	TA100	TA102	TA1535	TA1537
		+S9				
Negative Control		29 ± 7	156 ± 15	506 ± 12	27 ± 4	15 ± 5
Abametapir-COOH	790	14 ± 6	146 ± 18	131 ± 13	10 ± 3	9 ± 1
	250	32 ± 10	147 ± 20	505 ± 37	20 ± 3	15 ± 7
	79	23 ± 3	170 ± 27	640 ± 30	20 ± 1	21 ± 10
	25	30 ± 4	198 ± 63	436 ± 25	22 ± 8	22 ± 5
	7.9	38 ± 11	201 ± 27	537 ± 19	32 ± 10	28 ± 4
Positive Control Vehicle		29 ± 7	156 ± 15	506 ± 12	23 ± 5	15 ± 5
Positive Control		619 ± 37	912 ± 25	1202 ± 76	183 ± 16	131 ± 3

a. DMSO, the vehicle of test article

b. For TA98: 2- Nitrofluorene 1.0 µg/plate (-S9) or Benzo(a)pyrene 5 µg/plate (+S9); TA100: Sodium azide 0.5 µg plate (-S9) or Benzo(a)pyrene 5 µg/plate (+S9); TA102: Cumene Hydroperoxide 100 µg/plate (-S9) or Benzo(a)pyrene 10 µg/plate (+S9); TA1535: Sodium Azide 0.5 µg /plate (-S9) or Cyclophosphamide 100 µg/plate (+S9); TA1537: 9-Aminoacridine 50 µg/plate (-S9) or Benzo(a)pyrene 5 µg/plate (+S9).

c.DMSO is positive control vehicle for 2- Nitrofluorene, Cumeme Hydroperoxide, Benzo(a)pyrene and 9-Aminoacridine. Water is positive control vehicle for Sodium Azide and Cyclophosphamide

A rat micronucleus assay was conducted with abametapir [(b) (4)]0015) and included with the original IND submission. No toxicokinetics were assessed in the original study. The sponsor conducted a toxicokinetic bridging study to match the mid-dose evaluated in the rat micronucleus assay (120 mg/kg/day) and characterized the associated plasma toxicokinetics of abametapir, abametapir-COOH and abametapir-OH (HTCH0001-001-2107). The high dose of 160 mg/kg/day used in the rat micronucleus assay [(b) (4)]0015) could not be assessed in the bridging study due to the predicted level of toxicity and ethics policies of the animal facility. Toxicokinetic analysis of abametapir, abametapir-OH and abametapir-COOH concentration-time data obtained from rats orally administered 120 mg/kg/day abametapir indicated that the parent compound was quickly absorbed after administration with rapid formation of hydroxyl and carboxylic acid metabolites in vivo. The toxicokinetic bridging study confirms that the in vivo rat micronucleus assay of abametapir [(b) (4)]0015) also characterizes the clastogenic potential of abametapir-COOH at up to 120 mg/kg/dose abametapir.

8 Carcinogenicity

No carcinogenicity studies were included in this NDA submission. Abametapir lotion is intended as a single use drug product. Re-infestation would require a second application, but the product is not intended for chronic use.

9 Reproductive and Developmental Toxicology

The sponsor has performed the complete reproductive and developmental toxicology battery for abametapir. These studies were reviewed under the IND submission. Summaries of the reproductive and developmental toxicology studies performed with abametapir are provided below.

9.1 Fertility and Early Embryonic Development

Oral doses of abametapir (0 {vehicle; (b) (4)}, 10, 25, 75 mg/kg/day) were evaulated for effects on fertility and early embryonic development in the CD rat ((b) (4) 0006). Treatment-related findings were observed at all dose levels, but at 10 and 25 mg/kg/day none of the changes were considered to be of toxicological importance. The NOAEL for parental toxicity was 25 mg/kg/day abametapir and the NOAEL for fertility and early embryonic development was 75 mg/kg/day abametapir in CD rats.

Toxicokinetic data were not collected during this study. In order to develop approximate multiples of human exposure, data from the systemic rat embryofetal study ((b) (4) 0003) conducted with abametapir (0 {vehicle control; (b) (4)}, 10, 25, or 75 mg/kg/day) are provided below (table taken directly from the study report).

Reviewer's comment: Toxicokinetic data from this study were chosen because it provided blood levels of abametapir after a single exposure which most closely approximates the clinical dosing regimen.

Dose level (mg/kg/day)	C_{max} (ng/mL)		AUC_{24} (ng.h/mL)	
	Day 6	Day 17	Day 6	Day 17
10	33.9	40.5	64.3	134
25	146	139	345	590
75	2050	1890	4760	3130

9.2 Embryonic Fetal Development

Rodent

Oral doses of abametapir (0 {vehicle control; (b) (4)}, 10, 25, 75 mg/kg/day) were evaluated for embryofetal development in the CD rat ((b) (4) 0003). The NOAEL for maternal toxicity of abametapir was 25 mg/kg/day, based on reduced bodyweight gain (-15%) and feed consumption (-7%) at 75 mg/kg/day relative to vehicle control animals. The NOAEL for developmental toxicity was 25 mg/kg/day based on lower fetal bodyweights (-7%) and delayed ossification at 75 mg/kg/day relative to

control values. The effects on ossification corresponded with reduced maternal body weight gains and fetal body weights and were only observed in the subset of bones commonly affected by maternal toxicity (Carney and Kimmel, 2007), suggesting they are secondary effects of maternal toxicity and not primary effects on F_1 animals. Abametapir was not teratogenic at the highest dose, 75 mg/kg/day.

Maximum mean plasma concentrations (C_{max}) of abametapir and areas under the mean plasma abametapir concentration-time curves estimated up to 24 hours postdose (AUC_{24}) on GD 6 and 17 are summarized below (table taken directly from the study report):

Dose level (mg/kg/day)	C_{max} (ng/mL)		AUC_{24} (ng.h/mL)	
	Day 6	Day 17	Day 6	Day 17
10	33.9	40.5	64.3	134
25	146	139	345	590
75	2050	1890	4760	3130

On day 17 after mating, absorption was rapid with T_{max} occurring 30 minutes postdose in the low and mid-dose groups, and 1 hour postdose in the high dose group. The mean plasma concentrations of abametapir at 24 hours postdose (C_{24}) were below the limit of quantitation (<1.00 ng/mL) in all dose groups on GD 6 and 17, suggesting animals were not continuously exposed to quantifiable concentrations of abametapir during a dosing interval.

Toxicokinetic data for abametapir-OH and abametapir-COOH are summarized in the text table below (taken directly from the study report Htc-040). Systemic absorption of abametapir was rapid followed by rapid hydroxylation and moderately rapid carboxylation, with T_{max} values of 0.5 – 1 hr for abametapir-OH and 2- 4 hr for abametapir-COOH.

Text Table: Summary of Toxicokinetic Parameters

Treatment	Analyte	Dose mg/kg/day	Day	AUClast (ng.hr/mL)	Cmax (ng/mL)	Tmax (hr)	AUCinf (ng.hr/mL)	T1/2 (hr)
Abametapir	Abametapir-OH	25	6	111	45.0	0.50	112	1.13
			17	94.8	23.3	0.50	118	3.31
		75	6	451	160	0.50	479	1.97
			17	321	148	1.00	ND	ND
	Abametapir-COOH	25	6	132,000	20,500	2.00	133,000	3.09
			17	235,000	21,700	2.00	237,000	3.18
		75	6	689,000	65,400	4.00	ND	ND
			17	1,120,000	81,500	4.00	ND	ND

Nonrodent
Oral administration of abametapir in [redacted] (0 {vehicle control},10, 20, or 40 mg/kg/day) to New Zealand White rabbits during the organogenesis phase of gestation (gestation days 6 - 19) did not produce any statistically significant adverse effects when compared with vehicle control animals ([redacted]0004). However, the vehicle itself caused reduced maternal weight gain and the NOAEL for maternal toxicity is considered to be 10 mg/kg/day based on a reduced maternal weight gain at the end of treatment (Day 20) of 23% and 46% at 20 and 40 mg/kg/day, respectively. Although there were no differences in maternal body weight at termination (Day 29), does in the high dose group took longer to catch up with the control group body weight during the post treatment period. No treatment-related effects were observed on the mean number of corpora lutea, implantation sites, resorptions (early, late), dead fetuses, viable fetuses, fetal sex ratio, fetal and placental weights, and external, visceral and skeletal morphology. The NOAEL for developmental toxicity was 40 mg/kg/day, the highest dose tested.

Oral gavage dosing resulted in measurable plasma concentrations of abametapir on GD6 (dosing day 1) and GD 19 (dosing day 14) in all dose groups, except in control animals. Maximum mean plasma concentrations (C_{max}) of abametapir and the areas under the mean plasma abametapir concentration-time curves estimated up to 24 hours postdose (AUC_{24}) on GDs 6 and 19 are summarized below.

Dose level (mg/kg/day)	C_{max} (ng/mL) GD6	C_{max} (ng/mL) GD19	AUC_{24} (ng.h/mL) GD6	AUC_{24} (ng.h/mL) GD19
10	11.2	11.4	10.8	13.2
20	18.8	37.2	36.4	24.5
40	48.3	36.8	156	60.7

The rate (C_{max}) and extent (AUC_{24}) of systemic exposure of pregnant female rabbits to abametapir generally appeared to be characterized by linear (dose-dependent) kinetics over the dose range 10 to 40 mg/kg/day on Day 6 and Day 19 after mating. Abametapir did not accumulate in plasma. Analysis did not include measures of abametapir-COOH levels.

9.3 Prenatal and Postnatal Development

Abametapir (0 {vehicle control; [redacted]}, 10, 25, 75 mg/kg/day) was evaluated for effects on pre- and post-natal development in the CD rat by oral gavage administration [redacted]0005). The NOAEL for the F_0 females was 25 mg/kg/day based on severe maternal toxicity (12/22 deaths) at 75 mg/kg/day. Of these 12 maternal deaths, one was found dead on gestation day 22 , four others were terminated for welfare reasons prior to littering and the seven remaining were terminated for welfare reasons on days 1-3 after giving birth. All seven animals terminated after giving birth were found to have inactive mammary glands after macroscopic examination at necropsy. The 12 decedent females showed clinical signs including piloerection, hunched posture, reduced body temperature and pallor, but these signs were not observed during gestation for those females terminated after littering. Only one of the 10 surviving high dose females showed signs of hunched posture, pallor and piloerection prior to parturition, but this female successfully littered with no other signs noted. The NOAEL

for pre- and postnatal survival of the F_1 offspring was 25 mg/kg/day, the highest non-maternally toxic dose tested, based on a reduced number of live litters (-23%) at 75 mg/kg/day and a 12-14% reduced body weight at postnatal day 1. Although reproductive capacity of all F_1 offspring was unaffected by maternal treatment, F_1 males of dams receiving 75 mg/kg/day had low sperm count estimates derived from vaginal smears at mating. The NOAEL for growth, development, maturation, and reproductive performance of the F_1 offspring was 75 mg/kg/day.

Maximum mean plasma concentrations (C_{max}) of abametapir and areas under the mean plasma abametapir concentration-time curves estimated up to 24 hours postdose (AUC_{24}) on Day 11 of lactation are summarized below (table devised by reviewer based on the study report):

Dose Level	Cmax (ng/mL)	AUC24 (ng●h/mL)
mg/kg/day	Day 11	Day 11
10	46.4	47.0
25	155	214
75	1940	2230

The mean plasma concentrations of abametapir were below the limit of quantification (<1.00 ng/mL) at 4 hours postdose at the lowest dose level (10 mg/kg/day) and at 24 hours postdose at the 25 and 75 mg/kg/day dose levels on Day 11 of lactation, indicating that the animals were not continuously exposed to quantifiable concentrations of abametapir during a dosing interval and that abametapir does not accumulate after repeated oral dosing.

10 Special Toxicology Studies

The EpiOcular™ Human Cell Construct was used to assess the potential ocular irritation of abametapir lotion, 0.74% (Study # 14AB04-AB05.015001). The MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) conversion assay, which measures the NAD(P)H-dependent microsomal enzyme reduction of MTT (and to a lesser extent, the succinate dehydrogenase reduction of MTT) to a blue formazan precipitate, was used to assess the cellular metabolism after exposure to each test article for six exposure times (0.33, 1, 2, 4, 8, and 24 hours). One hundred microliters of the test article was applied to each EpiOcular™ human cell construct. Duplicate cultures of the negative control (exposure time control), 100 µL of sterile deionized water, were exposed for 0.25, 4, 8 and 24 hours. Duplicate cultures of the positive control, 100 µL of 0.3% Triton®-X-100, were exposed for 15 and 45 minutes. The exposed cultures were then incubated for the appropriate amount of time at standard culture conditions. The duration of exposure resulting in a 50% decrease in MTT conversion in test article-treated EpiOcular™ human cell constructs, relative to control cultures, was determined (ET_{50}). Table 1 (taken directly from the study report) summarizes the ET_{50} results of the screening assay of abametapir lotion using the EpiOcular™ assay. Since the positive control fell within two standard deviations of the historical mean (18.5 – 35.4 minutes), and the corrected mean OD_{550} value for the negative control exposure time (1.448) was within 20% of the corrected mean OD_{550} value for the maximum negative control exposure time (up to 4 hours) (1.333), the

assay was accepted.

Table 1

Assay Date	IIVS Test Article Number	Sponsor's Designation	Conc.	ET_{50} (hours)	pH
29 January 2014	14AB04	Abametapir Lotion, 0.74%	Neat	1.1	5.5
	14AB05	Abametapir Lotion, Vehicle	Neat	8.2	5.0
	Positive Control	0.3% Triton®-X-100	NA	18.6 minutes	NA

NA - Not Applicable

The test articles were determined to directly reduce MTT. Therefore, a killed-control experiment was performed. The results of the killed-control experiment showed that there was little or no direct reduction in the test article-treated killed control compared to the negative control treated killed control. Therefore, the MTT reduction in the test article treated viable tissue was totally ascribed to the viable cells.

The ET_{50} values of both of these test articles represent mild ocular irritation potential (Stern *et al*., 1998). Although both test articles were considered mild, the abametapir 0.74% lotion demonstrated a greater cytotoxic response (ET_{50} of 1.1 hours) than the abametapir lotion vehicle (ET_{50} of 8.2 hours).

Reviewer's comment: In a previously conducted/reviewed in vivo acute ocular irritation study conducted in rabbits as per OECD 405, a prototype 0.90% abametapir lotion (formulated in (b) (4) *batch RD-09041) was not corrosive to the eye, but was classified as slightly irritating to the eyes of rabbits (0421LH27.001).*

Abametapir (diluted to 3%, 1.5% or 0.75% w/v in acetone:olive oil (4:1 v/v)) was tested in a murine local lymph node assay (LLNA; (b) (4) 0012/063738). These concentrations are equivalent to dosages of 93.8, 46.9, or 23.4 mg/kg/day. Female CBA/Ca mice (5/group) were exposed to 25 µL of either the vehicle control, one of the treatments or the positive control (25% hexyl cinnamic aldehyde in acetone:olive oil) by application to the dorsum of each ear on three consecutive days. Five days following the first topical application of test substance (Study Day 6), mice were injected with 20 µCi of ^{3}H-methyl thymidine (^{3}HTdR) via the tail vein. Five hours following ^{3}HTdR administration mice were terminated via carbon dioxide asphyxiation and the draining auricular lymph node was excised from each experimental animal. Skin sensitization potential was then assessed by measurement of ^{3}THdR incorporation, expressed as disintegrations per minute (dpm) in the lymph nodes. A stimulation index (SI) was calculated as the total dpm detected in each test treatment group, divided by the total dpm in the matched

vehicle control group. A SI of ≥3.0 was defined as a positive result for skin sensitization potential.

A SI of less than 3 was recorded for all treatment groups and the individual values for all treated animals receiving 0.75 or 3% abametapir were within the control range (Table 1, taken directly from the study report). The individual dpm values for most treated animals being within the control range provide robust evidence that topical administration of abametapir does not cause a proliferative response which may lead to skin sensitization. A few low dpm values were recorded for animals receiving 1.5% abametapir, resulting in this value being less than control, but this was considered to be a chance occurrence due to normal biological variation. A SI of 3.8 was recorded for the positive control group and verifies the validity of the conclusion that abametapir is considered as negative for skin sensitization potential under the conditions used in the assay. The SI for the positive control group failed to achieve a statistically significant difference from the control group because of a particularly low individual value which increased the standard deviation for the data set.

TABLE 1

Group dpm/node and test/control ratios

Group	Concentration % w/v	dpm	Number of lymph nodes per animal	dpm/node	Test/control ratio†	Result + = positive - = negative
1	Control/vehicle	196.85	2.0	98.43	n/a	n/a
2	0.75	151.65	2.0	75.83	0.8	-
3	1.5	101.35	2.0	50.68	0.5*	-
4	3	219.05	2.0	109.53	1.1	-
5	HCA 25% v/v (Positive control)	750.85	2.0	375.43	3.8	+

Control/vehicle = Acetone:olive oil (4:1 v/v)

HCA Hexyl cinnamic aldehyde
† Test/control ratio of 3 or greater indicates a positive result
n/a Not applicable
dpm Disintegrations per minute (less background count of 38.25 dpm)
* $p \leq 0.05$

11 Integrated Summary and Safety Evaluation

Repeat-dose nonclinical studies have been conducted in both rodent and nonrodent species. In both the rodent and nonrodent models target organs of toxicity after repeat dosing were consistently limited to smooth muscle, kidney and red blood cells. Effects in smooth muscle (penile prolapse, decreased gastrointestinal motility, difficult parturition, disruption of lactation) were consistent with relaxation. No clinical signs consistent with gastrointestinal targets or smooth muscle function were observed in the clinical program.

Abametapir was administered by oral gavage to the rat in order to ensure adequate systemic exposure was achieved to identify target organs of toxicity. Oral doses of 8, 25, 75, and 100 mg/kg/day abametapir were administered daily for 14 days in rats. The kidney and red blood cells were identified as target organs of toxicity. Within the context of this study 8 mg/kg/day was determined to be the NOAEL. In a 28-day repeat-dose dermal study in minipigs with abametapir lotion (0%, 0.74%, 0.74% (administered twice/day), 3.7%), dermal effects associated with topical administration included erythema and flaking with histological observations of epidermal hyperplasia, hyperkeratosis, erosion and/or ulceration. These effects were dependent on dosing parameters (*i.e.*, strength, frequency and contact time) and were reversible. Systemic effects included tremors, decreased activity and decreased feed consumption in both males and females. In males, extended dosing (>10 days) was associated with penile protrusion and related secondary microscopic findings in the penis and bone marrow. Reversibility of these systemic effects could not be assessed in males due to early termination in affected animals based on ethical considerations. Reversibility of clinical signs was demonstrated in females.

Apametapir was administered by oral gavage to juvenile rats to compare the toxicity profile noted in adult rats to juvenile rats. Oral doses of 5, 12, or 30 mg/kg/day abametapir were administered to juvenile rats beginning on PND 7 for 8 weeks. Body weight gain, crown-rump and tibial lengths were unaffected by treatment. There were no adverse effects on the development or maturation of the central nervous system or reproductive organs. The primary effects noted in this study included decreased red blood cell parameters (associated with the pharmacological activity of abametapir), slightly increased creatinine (1.1 to 1.3-fold above control values at the end of the treatment and recovery periods) with no histopathological correlates at any dose. In summary, no effects on growth or maturation and no unique target organ toxicities were observed in the oral juvenile rat toxicity study.

The systemic effects noted in the oral rat or the dermal minipig studies are not a cause for concern for the clinical single topical application of abametapir lotion which is subsequently washed off after 10 minutes. The systemic exposure achieved in the oral rat and dermal minipig studies is greater than obtained under clinical conditions of single application use. Also the duration of treatment is much greater in the oral rat and dermal minipig studies (i.e., 14 to 28 days) compared to clinical conditions of use (single 10 minute application that is washed off). The assertion that the systemic effects noted

in the oral rat and dermal minipig studies are not a cause for concern for the clinical use of abametapir is supported by no observed clinical signs consistent with gastrointestinal targets or smooth muscle function in the clinical program.

The sponsor has performed the complete ICH genotoxicity battery. Abametapir and abametapir-COOH, the major human metabolite, were not mutagenic in the Ames test. Abametapir caused increases in chromosome aberrations in Human lymphocytes but only at cytotoxic concentrations and was negative in the in vivo rat micronucleus assay when administered orally at doses up to 160 mg/kg/day.

Abametapir has been tested for reproductive and developmental toxicology with no significant findings independent of maternal toxicity.

Xeglyze is approvable for the treatment of head lice infestation in children six months of age and older from a Pharmacology/Toxicology perspective.

12 Appendix/Attachments

Appendix #1 Multiple of human exposure calculations

Calculations

Multiples of human exposure have been derived based on C_{max} values for abametapir. Multiples of human exposure based on C_{max} values are appropriate for the reproductive toxicity data provided in the label since abametapir lotion is a single 10 minute application drug product. Although abametapir-COOH was the major clinical metabolite, both the clinical and rodent data for this metabolite were highly variable. Additionally, no analysis for abametapir-COOH was performed in the rabbit.

C_{max} of adult clinical cohort age group (≥18 years) = 41 ng /mL

Multiples of clinical dose based on C_{max} values

Rat Embryofetal development study

NOAEL for developmental effects = 75 mg/kg

C_{max} 75 mg/kg = 2050 ng /mL

Clinical C_{max} = 41 ng /mL
Exposure comparison = 2050 ÷ 41 = 50

Rabbit Embryofetal development study

NOAEL for developmental effects = 40 mg/kg

C_{max} 40 mg/kg = 48.3 ng /mL

Clinical C_{max} = 41 ng /mL
Exposure comparison = 48.3 ÷ 41 = 1

Rat Peri- Postnatal Development Study

NOAEL for developmental effects = 75 mg/kg

C_{max} 75 mg/kg = 1940 ng /mL

Clinical C_{max}= 41 ng /mL
Exposure comparison = 1940 ÷ 41 = 47

Rat Fertility Study

NOAEL for effects on fertility = 75 mg/kg

C_{max} 75 mg/kg = 2050 ng /mL

Clinical C_{max} = 41 ng /mL
Exposure comparison = 2050 ÷ 41 = 50

Appendix #2 Clean version of recommended label

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Xeglyze Lotion is a pediculicide indicated for the topical treatment of head lice infestation in patients 6 months of age and older.

9 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
There are no available data on Xeglyze Lotion use in pregnant women to inform a drug associated risk. In embryofetal development studies conducted with oral administration of abametapir during organogenesis no evidence of fetal harm or malformations, independent of maternal toxicity, were observed in pregnant rats and rabbits at doses that produced exposures up to 50 times and equivalent to the maximum recommended human dose (MRHD) in rats and rabbits, respectively. The highest dose evaluated in

rabbits was limited due to maternal toxicity associated with the vehicle used in the study *[see Data]*.

Data

Animal Data

Systemic embryofetal development studies were performed in rats and rabbits. Oral doses of 10, 25, and 75 mg/kg/day abametapir were administered during the period of organogenesis (gestational days 6 – 17) to pregnant rats. In the presence of maternal toxicity, embryofetal toxicity (lower fetal body weights and delayed ossification) was noted at 75 mg/kg/day. No treatment related effects on malformations were noted at 75 mg/kg/day (50 times the MRHD based on C_{max} comparisons).

Oral doses of 4, 16 and 40 mg/kg/day abametapir were administered during the period of organogenesis (gestational days 6 – 19) to pregnant rabbits. No treatment related effects on embryofetal toxicity or malformations were noted at 40 mg/kg/day (~1 times the MRHD based on C_{max} comparisons). Maternal toxicity related to the vehicle limited the maximum dose in pregnant rabbits.

In a perinatal and postnatal development study in rats, oral doses of 10, 25, and 75 mg/kg/day were administered from the beginning of organogenesis (gestation day 6) through the end of lactation (lactation day 20). In the presence of maternal toxicity, embryofetal lethality and decreased fetal body weight gain were noted at 75 mg/kg/day. No treatment related effects on postnatal development were noted at 75 mg/kg/day (47 times the MRHD based on C_{max} comparisons).

Lactation

Risk Summary

No data are available regarding the presence of abametapir in human milk, or the effects of abametapir on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Xeglyze (b) (4) and any potential adverse effects on the breastfed child from Xeglyze (b) (4) or from the underlying maternal condition.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

Excretion

Excretion of abametapir and its human metabolites was not examined in patients.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been conducted to evaluate the carcinogenic potential of Xeglyze (b) (4) or abametapir.

Abametapir was not mutagenic or clastogenic based on the results of two in vitro genotoxicity tests (Ames test and human lymphocyte chromosomal aberration assay) and one in vivo genotoxicity test (rat micronucleus assay).

No effects on fertility have been observed in rats following repeated oral doses of up to 75 mg/kg/day abametapir (50 times the MRHD based on C_{max} comparisons).

Appendix #3 References

Bowles VM, Young AR, Barker SC. 2008. Proteases and egg-hatching in *Pediculus humanus humanus*, the body (clothes) louse of humans (Phthiraptera: Insecta). *Parasitology* **135**: 125-130.

Carney EW, Kimmel CA. 2007. Interpretation of skeletal variations for human risk assessment: delayed ossification and wavy ribs. Birth Defects Res B Dev Reprod Toxicol 80(6):473-96.

Gershanik J, Boecler B, Ensley H, McCloskey S, George W. 1982. The gasping syndrome and benzyl alcohol poisoning. N Engl J Med 307(22):1384-1388.

Sakai T, Takahashi M, Mitsumori K, Yasuhara K, Kawashima K, Mayahara H *et al*. 2000. Collaborative work to evaluate toxicity on male reproductive organs by 2-week repeated dose toxicity studies in rats. Overview of the studies. J Toxicol Sci 25:1-21.

Stern M, Klausner M, Alvardo R, Renskers K, Dickens M. 1998. Evaluation of the EpiOcular™ tissue model as an alternative to the Draize eye irritation test. Toxicol In Vitro 12(4):455-461.

Sui YP, Liu XB, Chai LQ, Wang JX and Zhao XF. 2009. Characterisation and influences of classical insect hormones on the expression profiles of a molting carboxypeptidase A from the cotton bollworm (*Helicoverpa armigera*). *Insect. Mol. Biol.* **18**: 353-63.

Williamson AL, Brindley PJ, Knox DP, Hotez PJ and Loukas A. 2003. Digestive proteases of blood-feeding nematodes (review). *Trends in Parasitol* **19**: 417-423.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JILL C MERRILL
04/12/2016

BARBARA A HILL
04/13/2016