

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22483Orig1s000

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

Clinical Pharmacology Review

PRODUCT (Generic Name):	Imiquimod Cream 3.75%
PRODUCT (Proposed Brand Name):	PENDING/Marketed 5% name-ALDARA
NDA:	22-483
TYPE:	505(b)(1)
PROPOSED INDICATIONS:	actinic keratosis
SUBMISSION DATES:	1/29/10
SPONSOR:	Graceway Pharmaceuticals
REVIEWER:	CAPT E. Dennis Bashaw, Pharm.D.
OCP DIVISION:	DCP III

Background

NDA 22-483 for Zyclara (imiquimod) Cream, 3.75% was submitted to the FDA on December 19, 2008 for the topical treatment of actinic keratoses of the face or balding scalp in immunocompetent adults. On October 16, 2009 a Complete Response letter was received by Graceway, with a description of the information required to be included in a complete resubmission. Following receipt of the Complete Response letter, additional discussions were held culminating in 1) a Type A Meeting held on November 17, 2009, and 2) the submission of a Formal Dispute Resolution Request on December 16, 2009. In response to Dispute Resolution, a Dispute Appeal – Response letter was received by Graceway on January 15, 2010 from Julie Beitz MD, Director, ODEIII with a revised description of the information to be included in complete response to the October 16, 2009 letter, and clarification that this response would be considered a Class 1 resubmission.

From a Clinical Pharmacology perspective the previous data was sufficient and this was noted in the final review. For this re-submission, there are no outstanding Clinical Pharmacology issues except for the package insert.

Recommendation

Section 12.1 and 12.2 are verbatim from the approved 5% package insert. The information contained in 12.3 should be replaced with the following text as it provides some more detail as to the time course of peak concentrations and time to steady-state which is lacking in the sponsors version:

12.3 Pharmacokinetics

Following dosing with 2 packets once daily (18.75 mg imiquimod/day) for up to three weeks, systemic absorption of imiquimod was observed in all subjects when Zyclara Cream was applied to the face and/or scalp in 17 subjects with > 10 AK lesions. The mean peak serum imiquimod concentration at the end of the trial was approximately 0.323 ng/mL. The median time to maximal concentrations (T_{max}) occurred at 9 hours after dosing. Based on the plasma half-life of imiquimod observed at the end of the study, 29.3±17.0 hours, steady-state concentrations can be anticipated to occur by day 7 with once daily dosing.

12.4 Review Addendum

At the time of the original review, there was some confusion as to whether or not this application was being filed as a 505(b)(1) or (b)(2). The application is a 505(b)(1). This review acknowledges that. This finding, for this application, has no impact on the clinical pharmacology review of this application.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22483	ORIG-1	GRACEWAY PHARMACEUTICA LS LLC	IMIQUIMOD 3.75% CREAM

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/s/

EDWARD D BASHAW
03/19/2010

Clinical Pharmacology Review Addendum DSI AUDIT REPORT

PRODUCT (Generic Name):	Imiquimod Cream 3.75%
PRODUCT (Proposed Brand Name):	PENDING/Marketed 5% name-ALDARA
NDA:	22-483
TYPE:	505(b)(2)
PROPOSED INDICATIONS:	(b) (4)
SUBMISSION DATES:	8/19/09 (FDA-DSI AUDIT)
SPONSOR:	Graceway Pharmaceuticals
REVIEWER:	CAPT E. Dennis Bashaw, Pharm.D.
OCP DIVISION:	DCP III

Background

Imiquimod is an immunomodulator applied topically for a variety of dermal indications. Currently a 5% product is available in the market using a twice weekly application for 16 weeks. The product that is the subject of this NDA is a 3.75% strength cream intended for daily use for two weeks, (b) (4)

At the time of the closure of the original Clinical Pharmacology Review the Division of Scientific Investigations (DSI) report was not yet available for the pivotal in vivo clinical pharmacology study. A final report was issued by DSI on Aug 18th. This review summarizes this report and its implications for approval.

Findings

Clinical

The clinical portions of study GW01-0706 were conducted at Comprehensive Phase I, Fort Myers, Florida. A DSI audit of this facility revealed no significant findings and no FDA Form 483 (notice of inspection findings) was issued.

Analytical

the analytical portion of the study was conducted at (b) (4)
(b) (4) and all the study related documentation were transferred to (b) (4)

(b) (4) in June 2009 after (b) (4) closed down their operations. Following the analytical inspection at (b) (4) (July 13-17, 2009), a Form 483 was issued. The issues noted (along with DSI proposed action in *italics*) were:

1. Failure to report all validation experiments containing valid data. For example, a long term stability experiment conducted on August 26, 2008 was not reported.

No remedial action indicated for this study, should revise procedures for future studies.

2. Incurred sample reproducibility (ISR) was not conducted for the study.

The firm should conduct an experiment and provide data to confirm incurred samples reproducibility of the LC/MS /MS method used in study GW01-0706

3. Stock solutions of R-837 and S-26704 for making calibrators were used after the expiration date based on stability testing.

The firm needs to provide additional stock solution stability data for R-837 (analyte) and S-26704 (active metabolite) to cover the period of the study.

4. Failure to document and retain records for all aspects of study conduct. For example, QC samples (low, medium and high) were prepared in bulk, pipetted into 0.800 ml aliquots, frozen and stored at -20 degrees C until use. Although a total of 15 aliquots of QCs were prepared at each level, data audit reveals that a total of 19 aliquots of QC s were used at each level during the course of method validation and subject sample analysis. The number of QC aliquots said to have been used during the study exceeded the number prepared.

The firm should provide (1) all documentation or records concerning preparation of QCs used during method validation and in analytical runs and (2) explain why QC aliquots said to have been used during the study exceeded the number prepared.

The analytical site has agreed to respond to these issues in writing to DSI, but as of this date (Aug. 25th, 2009) no response has been received.

Discussion

Of the four issues, the first issue is one of implementation that DSI adjudged to be adequately handled by the sites procedures and was provided to the site by DSI for future projects. Of the remaining 3, item 2 has to be taken into consideration in light of the method and reported results. Although ISR was not done, examination of the analytical data does not suggest a problem with sample reproducibility and would not affect our acceptance of the assay. Likewise for item 3, while it would have been preferable for there not to be a sample stability issue raised (by simply having fresh standards or a longer stability study) this issue should be readily correctable and would not necessitate any action on our part. As for the final issue, this appears to be a record keeping issue,

and although it does demonstrate a lack of due diligence in the performance of the assay it does not, on its surface, seem to be a “show stopper”. This conclusion is supported by the DSI classification of these findings as “VAI”-Voluntary Action Indicated and thus should not be construed as an impediment to approval in and of themselves.

Conclusion

The DSI Audit of the Clinical Pharmacology study site revealed no inconsistencies in the performance of the study.

The DSI Audit of the Clinical Pharmacology analytical site revealed some inconsistencies in the performance of the study. These inconsistencies are relatively minor, in and of themselves, but taken together it does suggest a “cavalier” attitude towards their analytical procedures and SOPs. Whether or not these “issues” were related to the closure of the ^{(b) (4)} site and transfer of the materials and methods to the ^{(b) (4)} site is unknown.

While not sufficient to invalidate the study, it does highlight the importance of a DSI audit of Clinical Pharmacology study sites. No further action is indicated from OCP on this issue.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22483	----- ORIG 1	----- GRACEWAY PHARMACEUTICA LS LLC	----- IMIQUIMOD 3.75% CREAM

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/s/

EDWARD D BASHAW
08/28/2009

Clinical Pharmacology Review

PRODUCT (Generic Name): Imiquimod Cream 3.75%

PRODUCT (Proposed Brand Name): PENDING/Marketed 5% name-ALDARA

NDA: 22-483

TYPE: 505(b)(2)

PROPOSED INDICATIONS: (b) (4)

SUBMISSION DATES: 12/19/08

SPONSOR: Graceway Pharmaceuticals

REVIEWER: CAPT E. Dennis Bashaw, Pharm.D.

OCP DIVISION: DCP III

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1. EXECUTIVE SUMMARY

Currently a 5% imiquimod cream (ALDARA) is approved for topical use for the following indications and associated treatment durations:

- Clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses (AK) on the face or scalp in immunocompetent adults 2 times per week for a full 16 weeks
- Biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults; maximum tumor diameter of 2.0 cm on trunk, neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured for a period of : 5 times per week for a full 6 weeks
- External genital and perianal warts/condyloma acuminata in patients 12 years old or older for 3 times per week until total clearance or a maximum of 16 weeks

The development of different formulations/strengths of topical imiquimod has continued in order to address (according to the sponsor) physician and patient needs to treat a larger AK area in a shorter time with a simpler dosing schedule. This submission supports the use of a 3.75% imiquimod cream product applied daily for two 2-week treatment cycles separated by a 2-week no treatment period for the treatment of AK. The clinical program consisted of one pharmacokinetic study, two pivotal and two supportive studies evaluating the efficacy and safety of investigative imiquimod formulations in treatment of typical visible or palpable AKs of the full face or balding scalp.

Under maximal usage conditions, for a duration longer than that being sought by the sponsor, there was very limited systemic absorption of imiquimod following application to the face or scalp. Stratification of the data by gender or site of application did not yield any significant findings/associations. Compared to the data from a long term safety study (with pk evaluations) from the 5% marketed cream, the degree of absorption from the 3.75% cream was lower in some but not all subjects/areas of application.

1.1 Recommendation

From a Clinical Pharmacology standpoint, the sponsor has met the requirements under 21 CFR 320 and the application is acceptable.

1.2 Post-Marketing Requirements/Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Finding

The absorption of imiquimod from the to-be-marketed formulation was studied in a single was an open label, single-center, non-randomized pharmacokinetic (PK) study in adult subjects with AKs (Study GW01-0706.) The study was designed to quantify the PK profile of imiquimod and its metabolites following 3 weeks (21 days) of daily applications of 3.75% imiquimod cream in adult subjects with AKs. The study was conducted under maximal use conditions (dose, duration, disease severity, and application areas) in a population that had at least 10 AK lesions in the application area. The application area was the entire face and/or the entire balding scalp. An area estimated as approximately 200 cm². The daily dose was 2 packets of 3.75% imiquimod cream (18.75 mg of imiquimod) applied to the relevant treatment area once daily for

three continuous weeks (21 Days). Note that the proposed regimen is for two continuous weeks.

The amount of imiquimod absorbed into systemic circulation after topical application of imiquimod 3.75% cream to the face and/or scalp once daily for up to 21 days was low; Steady state was estimated to be achieved by Day 14. Maximum concentration (C_{max}) and area under the curve from 0 to 24 hours (AUC_{0-24}) on Day 21 appeared to be similar in female and male subjects and lower in male subjects who applied imiquimod 3.75% cream to balding scalp rather than to the face alone. The $T_{1/2}$ was approximately 29 hours and the median time to maximum concentration (T_{max}) ranged between 6 and 9 hours.

The in vivo pk characterization included imiquimod's primary metabolites, the isomers S-26704 and S-27700, but due to the low overall systemic absorption, the data were too sparse to assess in a meaningful manner.

In terms of the ability to bridge the data from the 5% to the 3.75% cream, the degree of relative exposure of subjects to systemic imiquimod from the two formulations (5% vs. 3.75%) is unknown given their different dosing regimens in addition to strengths. Ultimately, the issue boils down from a safety point of view as to whether a short term exposure to somewhat higher levels (in certain situations) is more of a risk compared to longer exposure to levels that are lower. This is an unanswered question given the data we have now. Could such a study be performed, possibly, but assessing the long-term safety impacts of a 2week on, 1week off, 2week on regimen vs. a 16 week continuous dosing treatment arm would be challenging to say the least. Furthermore, the inability of the study to be cross-over in design will introduce the patient variability aspect into the data, ultimately making the study most likely un-interpretable for its purpose.

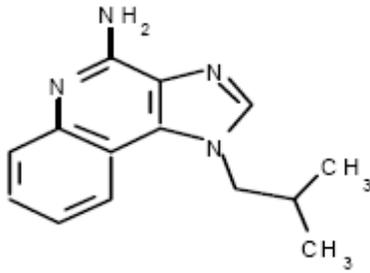
2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product

Drug Substance and Formulation

Imiquimod belongs to the chemical class of substances known as imidazoquinolinamines. Chemically, imiquimod is 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine. Imiquimod has a molecular formula of $C_{14}H_{16}N_4$ and a molecular weight of 240.3. Its structural formula is:



The drug product is a white to faintly yellow topical cream with a uniform appearance, packaged in a form, fill and seal (b) (4) (b) (4) single dose sachet. Each sachet contains 250 mg of imiquimod 3.75% topical cream (9.4mg of active drug).



The composition of imiquimod 3.75% topical cream, relative to the placebo formulation used in the clinical trials and the currently approved 5% product is presented below:

	GW030	GW030P (placebo)	Aldara 5%			
	%w/w	%w/w	%w/w			
Excipients						
Isostearic acid	(b) (4)					
Cetyl alcohol						
Stearyl alcohol						
White petrolatum						
Polysorbate 60						
Sorbitan Monostearate						
Glycerin						
Xanthan gum						
Purified water						
Benzyl alcohol						
Methylparaben						
Propylparaben						
Imiquimod				3.75	0.00	5.00

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Actinic keratoses (AKs) are regarded as precursors of squamous cell carcinoma (SCC) that appear as dry, scaly lesions on skin chronically exposed to the sun. As such AKs are associated with aging and is an indication which is unseen in the general pediatric population

Imiquimod is a toll-like receptor (TLR) agonist that stimulates the innate and adaptive immune systems. Among its actions, imiquimod induces the production of interferon alpha (IFN- α), interleukin-12 (IL-12), and tumor necrosis factor-alpha (TNF- α), with a resulting cytokine cascade that may induce and/or support a cytotoxic T-lymphocyte (Th1) immune response. Although the exact mechanism of action is not fully elucidated, imiquimod appears to mediate its effects via the activation of TLR7. This interaction stimulates effector cells such as monocytes/macrophages, and dendritic cells to produce cytokines and chemokines.

2.1.3 What are the proposed dosage and route of administration?

Currently 5% imiquimod cream (ALDARA) is approved for the treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses (AK) on the face or scalp (25 cm²) 2 times per week (2x/wk) for 16 consecutive weeks. The development of different formulations/strengths of topical imiquimod has continued in order to address what is perceived by the sponsor to be physician and patient needs to treat a larger AK area in a shorter time with a simpler dosing schedule. This submission supports the use of a 3.75% imiquimod cream product applied daily for two 2-week treatment cycles separated by a 2-week no treatment period for the treatment of AK.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical program consists of 6 studies as follows:

One Phase 1 pharmacokinetic study conducted in subjects with AKs (Study GW01-0706). The study was designed to evaluate the investigational imiquimod formulations under maximal use conditions (ie, with the highest concentration [3.75%] of the 2 investigational formulations, with the longest continuous duration of daily treatment [3 weeks], with the largest product volume [2 full packets], and in subjects with more severe disease [≥ 10 AK lesions]). In this manner the sponsor addressed the Agency's design concerns vis a vis a maximal usage trial with their product.

Four randomized, double-blind, placebo-controlled multi-center Phase 3 clinical studies, each of which included 2 active dose groups of investigational imiquimod formulations and a placebo group. The two sets of two identical studies differed only in the duration of treatment and interval cycles:

- Studies GW01-0702 & GW01-0704 (2-week treatment cycle regimen): 2 identical pivotal studies evaluating 2.5% imiquimod cream, 3.75% imiquimod cream, or placebo cream applied daily for two 2-week treatment cycles separated by a 2 weeks of no treatment period followed by an 8 week post treatment follow-up period (total study duration 14 weeks).
- Studies GW01-0703 & GW01-0705 (3-week treatment cycle regimen): 2 identical supportive studies evaluating 2.5% imiquimod cream, 3.75% imiquimod cream, or placebo cream applied daily for two 3-week treatment cycles separated by a 3-week no treatment period followed by an 8-week post treatment follow-up period (total study duration 17 weeks).
- Study GW01-0803: a long-term (1year) recurrence study that includes subjects who achieved complete AK clearance (primary efficacy endpoint) in any of the Phase 3 studies. This uncontrolled observational study is currently ongoing and will provide information on the maintenance of the treatment effect. *As agreed to during the July 27, 2007 meeting with the FDA, these data will be provided to the NDA as a post-approval submission.*

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, as part of the development of the 5% product the sponsor undertook a detailed evaluation of the metabolic schema of imiquimod. This report was re-submitted to this NDA from the original 5% application to inform the metabolic profile and the analytical section below as to the structure and relationship of two metabolites S-26704 and S-27700. These metabolites in fact isomers and represent approximately 45% of the metabolites generated in the in vitro system.

2.2.3 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

Actinic keratosis diagnosis and treatment effects are typically determined by clinical inspection of visible and/or palpable AK lesions. Actinic keratosis lesions in the defined treatment area (face/balding scalp) were counted by qualified investigators at Baseline and at each study visit to determine treatment efficacy. End of study (EOS, 8 weeks post end of treatment, Week 14 or 17 based on study design) was the time point used for evaluation of the primary (complete clearance) and 2 secondary (partial clearance, percent AK lesion reduction) efficacy endpoints. For each of the 3 efficacy endpoints in the Phase 3 studies, all AK lesions in the treatment area, including any new or subclinical lesions, were counted.

2.2.4 Exposure-Response

2.2.4.1 Does this drug prolong the QT or QTc interval?

A specific QT/QTc evaluation was not conducted for this product. A consult was submitted to the IRT/QT team. The following questions/conclusions were extracted from the IRT/QT review written by Suchitra Balakrishnan, MD.

1. Has the applicant adequately addressed the potential of their product to impact cardiac repolarization?

QT-IRT Response:

No, ECGs were not performed in the clinical development program for the Imiquimod 3.75% crème, including Studies 1520-IMIQ and 1402-IMIQ where subjects had supra-therapeutic exposures. Cardiac AEs in the studies were confounded because of co-morbidities and concomitant medications but no ECG effects are reported in the narratives.

2. Are additional data needed to address the potential for QT/QTc interval prolongation?

QT-IRT Response:

The incidence of AEs related to QT prolongation with Aldara was similar to the background rate in the general population in our MGPS data

mining analysis (see analysis for AEs related to QT prolongation under reviewer's assessments). However, if the Division is concerned about the potential of affect cardiac repolarization, then the sponsor should conduct a TQT study. Also see response to Question 1.

2. Are there any additional studies needed to address the effect of imiquimod on cardiac system?

QT-IRT Response:

We conducted an MGPS data mining analysis of the AERS database for preferred terms (PTs) related to thromboembolism and myocardial ischemia with Imiquimod. The signal scores suggested that the incidence was similar/less than the background rate in the general population (see reviewer's assessments). However, we recommend that the division also consults the Office of Surveillance and Epidemiology in this regard.

A follow-up by the OSE staff did not reveal any reports of QT prolongation beyond background levels. Reports of SVT (supraventricular tachycardias) with re-challenge have been reported and may necessitate follow-up in future development programs. Even so, for SVT detection the QT/QTc study would not be an appropriate approach to this question.

From a Clinical Pharmacology standpoint, there is no objective evidence to require additional QT evaluations at this time based on the data at hand.

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.5.1 What are the single dose (SD) and multiple dose (MD) PK parameters?

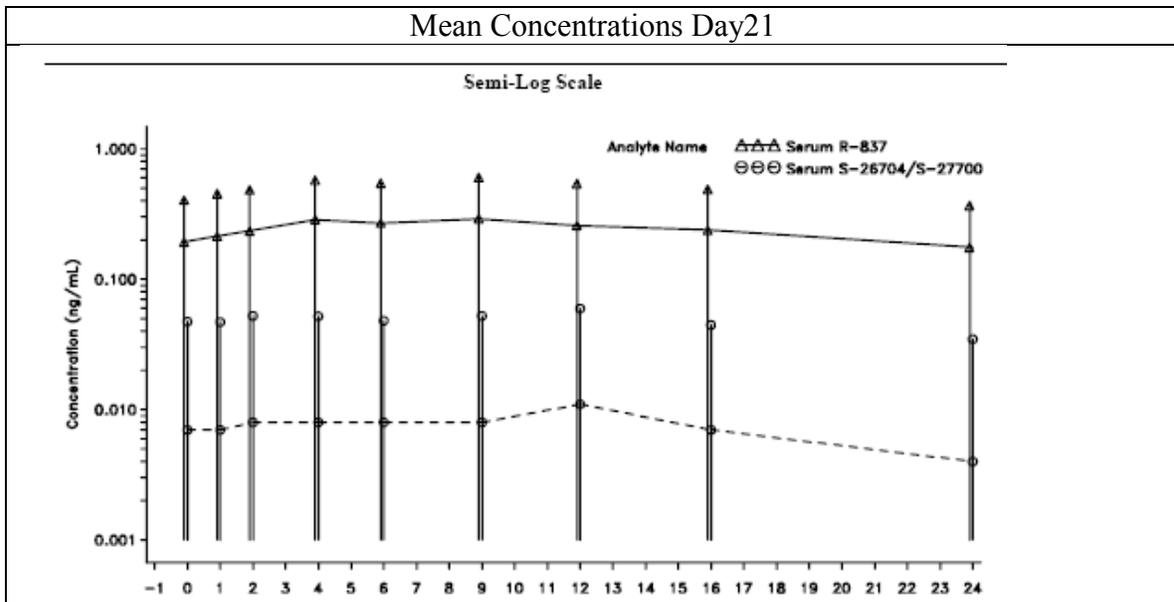
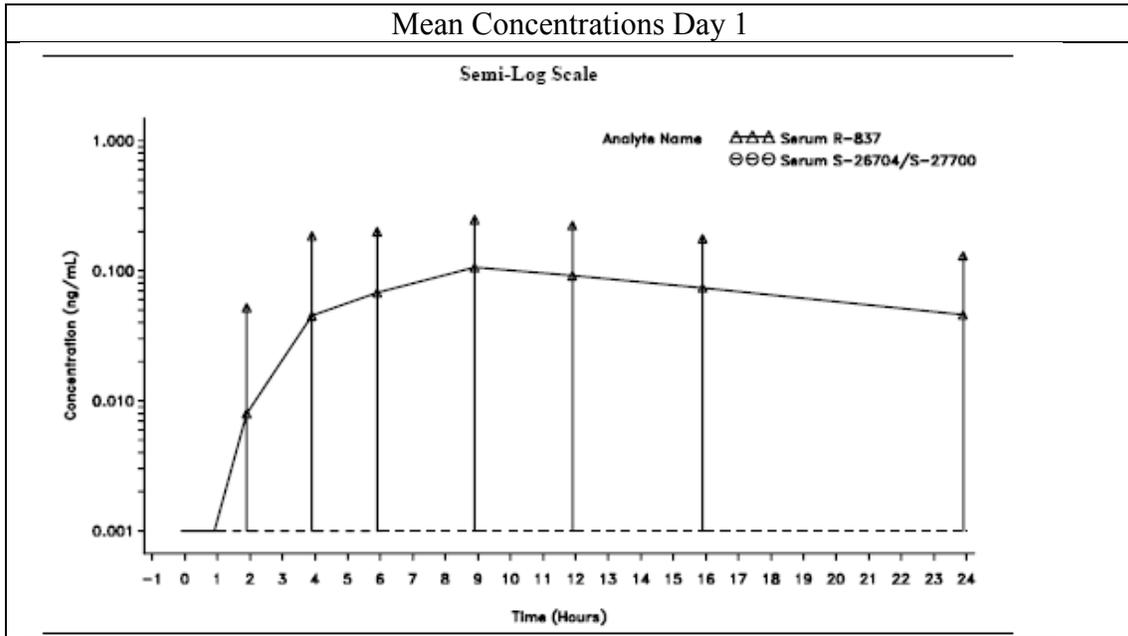
Maximal Usage Trial Study GW01-0706

The study was designed to evaluate the investigational imiquimod formulations under maximal use conditions (ie, with the highest concentration [3.75%] of the 2 investigational formulations, with the longest continuous duration of daily treatment [3 weeks], with the largest product volume [2 full packets], over a surface area estimated as approximately 200 cm² and in subjects with more severe disease [≥ 10 AK lesions]). The 3 week duration used in this study represents a longer dosing period than is currently being sought (2 weeks)

A total of 19 subjects were enrolled (24 planned) who met the inclusion and exclusion criteria and were able to participate within the time frame of this study. Subject 001-619 discontinued the study after 14 days of treatment due to flu-like symptoms (moderate pain [body aches] and fatigue considered probably related to treatment by the investigator).

The population included in the analysis of PK data included all subjects who completed PK sampling of interest and who had sufficient concentrations to obtain reliable estimates of PK parameters. The primary analysis of steady state only included those subjects with

paired and non-zero serum concentration data on days in comparison who took all 7 doses in the preceding week and took at least 80% of the prescribed doses in all prior weeks. The secondary analysis of steady state only included those subjects with paired serum concentration data that replaced BLQ values with LLOQ/2 on days in comparison who took all 7 doses in the preceding week and took at least 80% of the prescribed doses in all prior weeks.



As shown above, imiquimod (R-837) peak exposure (Cmax) and total exposure (AUC) increased in serum over the 21 days of once daily applications. Mean Cmax increased from 0.136 ng/mL on Day 1 to 0.323 ng/mL on Day 21. Between Day 1 and Day 21, mean AUC0-24 increased from 1.831 to 5.974 ng•hr/mL. Imiquimod median Tmax was 9 hours on Days 1 and 21.

Mean accumulation ratios for imiquimod reflect the increase in peak and total exposure between Day 1 and Day 21. The ratio of peak exposure, RCmax, indicated close to a 3-fold increase (2.810), and the ratio of overall systemic exposure, RAUC, indicated a nearly 4-fold increase (3.873).

Table 11-5 Primary Analysis of Steady State for Imiquimod (R-837) Trough Serum Concentrations

Trough (Pre-Dose) Comparison	N	Geometric LS Mean ^a		Geometric Mean Ratio ^b	90% Confidence Interval
		Test	Reference		
Day 14 vs. Day 7	15	0.1391	0.1277	1.0888	0.7933-1.4946
Day 21 vs. Day 14	16	0.1791	0.1344	1.3328	0.9193-1.9325
Day 22 vs. Day 21	16	0.1671	0.1791	0.9331	0.6612-1.3169

Note: Steady-state analysis only included subjects with paired and non-zero serum concentration data on the days being compared who took all 7 doses in the preceding week and took at least 80% of the prescribed doses in all prior weeks.

^a Point estimate for geometric least-squares (LS) mean was based on an ANOVA model, including study day as a fixed effect.

^b Steady-state conditions were considered to exist during an interval if the point estimate for the geometric mean ratio was <1.43.

Data Source: [Table 14.2.3](#)

The Imiquimod mean half-lives, T_{1/2}, were 19.8±10.1 hours on Day 1 (sampling through 24 hours) and 29.3±17.0 hours on Day 21 (sampling through 72 hours). Calculations of accumulation ratio and effective half-life for accumulation were restricted to subjects who took all 7 doses during the last week of treatment and who took at least 80% of the prescribed doses during the prior weeks. The apparent increase in half-life could, according to the sponsor, be due to a better estimate of half-life on Day 21 due to the longer sampling duration. Even so, the high variability suggests it could also just be some accumulated noise in the data as even with the observed accumulation the levels are near the limit of quantification for the assay (0.05ng/ml). Based on these results, steady-state conditions should be reached on Day 6 following once daily administration.

2.2.5.1.1 Comparison to the Marketed 5% Cream

As part of the study program for this indication, there was not a direct, head to head comparison of the absorption of the 5% and 3.75% formulations. As part of the original NDA 20-723 the sponsor conducted a similar maximal usage trial 1402-IMIQ.

Study 1402-IMIQ

The objective of study 1402-IMIQ was to evaluate systemic exposure to imiquimod and its metabolites following topical applications to skin with actinic keratoses, and over surface areas greater than those previously studied. Fifty-eight subjects had 12.5 mg imiquimod (one sachet) applied to facial lesions, or 25 mg imiquimod (two sachets)

applied to scalp lesions, or 75 mg imiquimod (six sachets) applied to lesions on both hands and arms for 8-12 hours; the face and hands/arms treatments were equally divided by sex, whereas only males received the scalp treatment. Dosing continued three times per week for 16 weeks. Pharmacokinetic and pharmacodynamic serum profiles and urinary excretion data were obtained following the first dose and following the last dose on week 16. In addition, serum trough concentrations were monitored biweekly. The results of this trial are summarized in the following tables and figures.

Mean ± SD and (Median) Imiquimod Cmax and AUC(O-t) Data from Study 14024MIQ in Subjects with Actinic Keratosis given 5% Imiquimod Cream

Application Site	Dose, mg	Sex	Cmax, ng/mL		AUC, ng·h/mL	
			Day 1	Week 16	Day 1	Week 16
Face	12.5	male	0.0748±0.0718 (0.0795)	0.114±0.0756 (0.0970)	2.51±3.08 (1.11)	2.03±1.80 (1.26)
		female	0.108±0.0553 (0.118)	0.126±0.0484 (0.123)	1.57±1.75 (0.968)	2.08±1.70 (1.86)
		total	0.0907±0.0652 (0.0832)	0.120±0.0629 (0.120)	1.99±2.40 (0.997)	2.06±1.70 (1.81)
Scalp	25	male	0.139±0.0964 (0.119)	0.214±0.0968 (0.206)	3.32±4.39 (1.33)	4.89±4.41 (3.87)
Hands/Arms	75	male	0.712±0.381 (0.649)	1.39±0.946 [b] (1.40)	18.5±11.3 (18.4)	24.2±11.2 [b] (25.6)
		female	0.852±0.973 [b] (0.481)	1.32±0.803 [b] (1.63)	29.3±43.2 (17.9)	33.3±20.7 [b] (35.3)
		total	0.775±0.698 [b] (0.600)	1.35±0.841 [c] (1.63)	23.6±30.7 (17.9)	29.1±17.1 [c] (31.5)

[a] Medians also presented because of highly variable data

[b] Mean value after rejection of one outlier; see report for discussion of outlier and for unadjusted mean value

[c] Mean value after rejection of two outliers; see report for discussion of outliers and for unadjusted mean value

While not necessary for the approval of the 3.75% cream, the cross-study comparison of the two strengths shows the higher absorption of imiquimod with the 5% cream. The doses used here ranged from 12.5-75mg and “bookend” the doses used in this study.

Long Term Safety Study (Study 1520-IMIQ) 5% imiquimod cream (Aldara)

Study 1520-IMIQ was a large long-term safety trial (551 subjects enrolled), and the pharmacokinetic data comes from subset of subjects representing a cohort receiving maximal exposure to imiquimod (6 packets of 5% cream applied twice weekly). Subjects in this study could participate in up to three 16-week treatment cycles during the 18-month study. 71.9% of subjects (396 of 551) in the safety population completed the trial. Subjects in the safety population averaged 466.9 days in the study and applied an estimated average of 214.6 packets of study drug (2682.5 mg of imiquimod).

Total Cohort Surface Area Involvement

Treatment Sites		Total	Head	Torso	Extremities
	N	551	424	95	339
	% Safety population	100.0	77.0	17.2	61.5
Treatment Area Size at Baseline (cm ²)	Mean	625.3	203.2	539.5	611.0
	(SD)	(1113.53)	(171.85)	(1050.18)	(889.18)
	Median	285.00	162.00	200.00	344.00
	Min, Max	21.0, 13566	2.0, 884.0	1.0, 7776.0	1.0, 6600.0
Body Surface Area with AK (%)	Mean	7.4	3.1	6.1	6.3
	(SD)	(7.54)	(1.66)	(5.20)	(5.86)
	Median	5.00	3.0	5.0	5.00
	Min, Max	0.1, 54.0	0.1, 10.0	1.0, 32.0	0.2, 43.4

Serum concentrations of imiquimod and 2 active hydroxylated metabolites combined (S26704/S27700) were measured in a sub-population of 13 subjects with AK. These subjects were selected at 5 investigational sites so that the percutaneous absorption of imiquimod could be studied from the maximum application area that a patient would encounter during this study. The applied dose was 75 mg imiquimod as a 5% cream (6 packets) two times per week.

PK Cohort Total Surface Area Involvement-AK Data

Number of Sites Treated	One Site Only	3 (23.1%)
	Two Sites	1 (7.7%)
	Three Sites	9 (69.2%)
Baseline Lesion Sites	Head	9 (69.2%)
	Torso	10 (76.9%)
	Extremities	13 (100%)
Treatment Area Size at Baseline (cm ²)	Head	
	n	9
	Mean (SD)	304.9 (256.57)
	Median	363.00
	Min, Max	6.0, 763.0
	Torso	
	n	10
	Mean (SD)	2722.0 (2103.74)
	Median	2285.5
	Min, Max	225.0, 7776.0
	Extremities	
	n	13
	Mean (SD)	3175.2 (1555.75)
Median	3114.0	
Min, Max	440.0, 5720.0	

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Pharmacokinetics were measured following Month 1 and Month 4 of an applied dose. Most subjects had measurable predose serum concentrations of imiquimod following Month 1 (12/13 subjects) and following Month 4 (12/13 subjects), which suggests drug accumulation upon multiple dosing.

Table 11.2.2.1.A Summary of Imiquimod Pharmacokinetic Results

Statistic	Month 1			Month 4		
	Cmax ng/mL	Tmax hr	AUC(0-t) ng/mL/hr	Cmax ng/mL	Tmax hr	AUC(0-t) ng/mL/hr
Mean ± SD	0.910 ± 0.916	16 ± 13	24.2 ± 21.9	0.958 ± 1.18	13 ± 10	24.3 ± 26.9
%CV	101	80	90	123	74	111
Median	0.616	11	20.1	0.493	9	14.4
Min	0.197	6	3.20	0.144	3	4.25
Max	3.52	47.2	75.7	4.15	34.4	93.1

Data Source: Section 14, Tables 14.4.4.A and 14.4.4.B.

Since the PK parameters were measured following Month 1 and Month 4, an accumulation ratio comparing Month 4 with Month 1 were calculated for Cmax and for AUC(O-t).

Table 11.2.2.1.B Summary of Imiquimod Accumulation Ratios (Month 4/Month 1) for Cmax and AUC(0-t)

Statistic	Cmax, ng/mL			AUC(0-t), ng/mL/hr		
	Month 1	Month 4	Ratio	Month 1	Month 4	Ratio
Mean ± SD	0.910 ± 0.916	0.958 ± 1.18	1.22 ± 0.786	24.2 ± 21.9	24.3 ± 26.9	1.14 ± 0.555
%CV	101	123	64	90	111	49
Median	0.616	0.493	0.973	20.1	14.4	1.22
Min	0.197	0.144	0.175	3.20	4.25	0.195
Max	3.52	4.15	2.66	75.7	93.1	2.09

Data Source: Section 14, Table 14.4.4.C.

These accumulation ratios were found to be close to unity, which is consistent with the interpretation that steady-state was achieved by the end of Month 1 and that no further accumulation occurred at Month 4.

2.2.5.1.2 Cross-Study Direct Comparison to the Marketed 5% Cream

One outstanding issue is the degree of relative exposure of subjects to systemic imiquimod from the two formulations (5% vs. 3.75%) given their different dosing regimens. This is of some concern due to the potential for systemic toxicity. For the purposes of this discussion we will limit our comparison to data from the associated AK indications for application to the scalp and face.

Mean (median)					
Daily Dose/Site	5% Cream Applied 3x weekly		3.75% Applied Daily		
	12.5mg Face Only	25mg Scalp Only	18.8mg Face and Scalp	18.8mg Face Only	18.8mg Scalp Only
	Week 16 Data		Day 21 Data		
AUC	2.06 (1.7)	4.89 (3.87)	5.974 (3.088)	6.553 (2.534)	1.770 (0.723)
Cmax	0.0907 (0.0832)	0.214 (0.206)	0.323 (0.159)	0.354 (0.126)	0.096 (0.038)
Total Dose/Wk	37.5mg	75mg	131.6mg	131.6mg	131.6mg

Although this represents a cross-study comparison, the information is informative. The easiest comparison is between the 25mg scalp treatment groups between the two studies. In this case although the mean and median data for the 3.75% cream represent a dosing level ~1.8x that of the 5% product, the resulting exposure is markedly lower. The data for “face only” use does show an increased exposure for the 3.75% cream but now in a roughly proportional manner, i.e. the dose multiple is 3.5 while the observed AUC

multiple is 3.2. This is probably more than anything indicative of the high degree of variability induced by the disease state, the nature of drug absorption and the cross-study nature of the data. While this is only a relative comparison, and NO attempt has been made to correct for sample sizes, etc., it is instructive in that it shows that the more frequent administration of the 3.75% cream, while it does produce higher levels in some situations (face), does not do so exclusively (scalp). This comparison has also excluded the 75mg dose (225mg/wk) used in the 5% study and in the long term safety trial presented immediately above.

Ultimately, the issue boils down from a safety point of view as to whether a short term exposure to somewhat higher levels (in certain situations) is more of a risk compared to longer exposure to levels that are lower. This is an unanswered question given the data we have now. Could such a study be performed, possibly, but assessing the long-term safety impacts of a 2week on, 1week off, 2week on regimen vs. a 16 week continuous dosing treatment arm would be challenging to say the least. Furthermore, the inability of the study to be cross-over in design will introduce the patient variability aspect into the data, ultimately making the study most like un-interpretable for its purpose.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The dermal absorption of a topical product is dependent upon the interplay of drug substance, formulation, and disease state. Given this, dermal absorption in normal volunteers is a poor predictor of absorption in diseased skin and it thus not relevant.

2.2.5.3 What are the characteristics of drug absorption?

3.75% imiquimod cream

Bioavailability was not estimated for the 3.75% imiquimod cream product.

5% imiquimod cream

The relative extents of absorption of the topical imiquimod doses were estimated by two different methods in study 1402-IMIQ. One method used the urinary recovery of imiquimod and metabolites to give an estimated bioavailability of less than 0.6% in any individual. A second method compared the topical systemic AVC data with that obtained in a previous study with a subcutaneous dose. The AUC method gave estimated topical imiquimod bioavailabilities (median values) of approximately 0.4 to 1% in the face and scalp groups, and between 2% and 3.5% in the hands/arms group. The differences in topical bioavailability values between the methods are not unreasonable for the reasons given in the preceding section.

2.2.5.4 What are the characteristics of drug distribution?

The binding of [¹⁴C]imiquimod and [¹⁴C]R-842 (S-26704) to human plasma proteins was assessed in vitro with heparinized plasma from healthy adult donors using the Amicon

Centrifree Micropartition System (Study No. R-837-DM-60). The extent of binding of both compounds of interest to plasma protein was independent of the concentration of drug over the concentration ranges studied. [¹⁴C]Imiquimod was bound more extensively (90-95%) than [¹⁴C]R-842 (60-67%). The extent of binding to isolated plasma proteins, high and low density lipoproteins, albumin, and α 1-acid glycoprotein was also assessed. The rank order of binding to these proteins was the same for the 2 compounds. The extent of binding to the isolated proteins was greater for imiquimod than for R-842.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

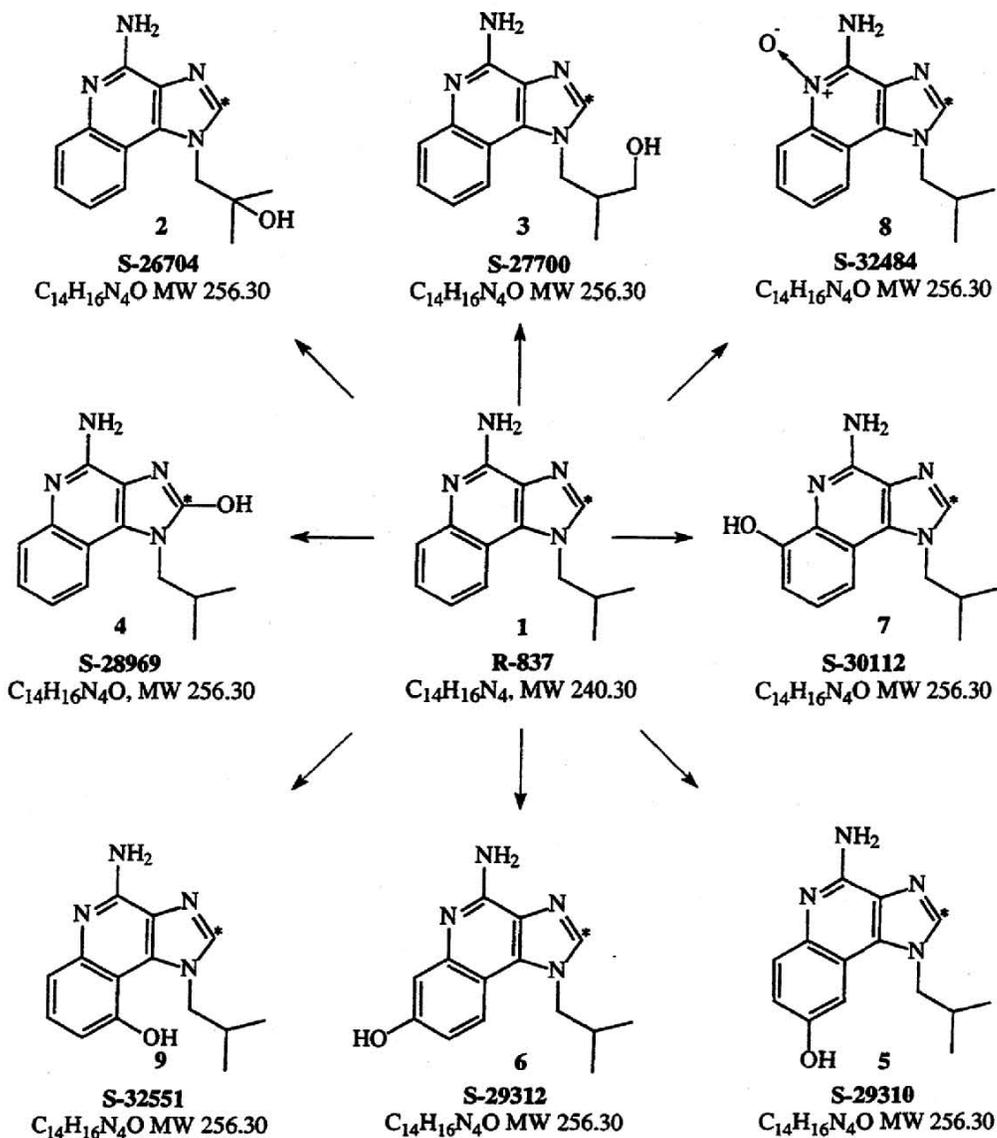
The primary excretion route for imiquimod is the urine.

2.2.5.6 What are the characteristics of drug metabolism?

As part of the development of the original 5% imiquimod gel formulation, the human urinary metabolites of imiquimod were identified by LC/MS and H NMR analysis. The in vitro metabolism of imiquimod performed previously in the presence of human liver microsomes, yielded seven metabolites that were identified by LC/MS analysis with a thermospray interface. The objective of this study (R-837-DM-79) by 3M was to confirm, and possibly enhance, the identification of the in vitro metabolites of imiquimod using newer MS techniques, atmospheric pressure chemical ionization (APCI) and electrospray (ES). This report describes the new HPLC-UV-radiometric and LC/MS methods and the identification of the chemical structures of imiquimod metabolites formed in the presence of human liver microsomes as determined by the new LC/MS methods.

Imiquimod Metabolic Profile

(* = Position of C-14 label)



2.2.5.7 What are the characteristics of drug excretion?

Median total urinary recoveries of unchanged drug plus five metabolites (S-26704, S-27700, S-29310, S-29312 and S-30112) were less than 0.25% of the applied dose (5% imiquimod cream) for all treatment groups in study 1402-IMIQ.

**Mean ± SD and (Median) Total % Dose Excreted in the Urine from Study 1402.-
IMIQ in Subjects with Actinic Keratosis given 5% Imiquimod Cream**

Application Site	Dose, mg	Sex	Total % Dose in Urine [b]	
			Day 1	Week 16
Face	12.5	male	0.12 ± 0.09 (0.09)	0.19 ± 0.13 (0.14)
		female	0.12 ± 0.07 (0.10)	0.17 ± 0.14 (0.14)
		total	0.12 ± 0.08 (0.10)	0.18 ± 0.13 (0.14)
Scalp	25	male	0.08 ± 0.05 (0.07)	0.24 ± 0.17 (0.24)
Hands/Arms	75	male	0.04 ± 0.01 (0.04)	0.08 ± 0.05 (0.07)
		female	0.05 ± 0.06 (0.03)	0.15 ± 0.13 (0.10)
		total	0.05 ± 0.05 (0.04)	0.12 ± 0.11 (0.09)

[a] Medians also presented because of highly variable data

[b] Imiquimod, S-26704, S-27700, S-29310, S-29312, and S-30112

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.3.1.2 Effect of Gender

Male vs. Female (facial application only)

Using subjects with facial application only, there were only small relative differences between male and female subjects in either C_{max} or AUC (<15%).

Table 11-3 Comparison of Female and Male Subject Face Application Serum Pharmacokinetics for Imiquimod (R-837) on Day 21

Parameter	Mean (SD)			
	Day 21			
	N	Female	N	Male
C _{max} (ng/mL)	4	0.415 (0.140)	10	0.354 (0.126)
C _{min} (ng/mL) ^a	4	0.222 (0.071)	10	0.230 (0.110)
T _{max} (hr) ^b	4	6.5 (4.0-9.0)	10	9.0 (4.0-16.0)
AUC ₀₋₂₄ (ng•hr/mL)	4	7.678 (2.928)	10	6.553 (2.534)

^a Pre-dose concentration (t=0)

^b Median (minimum-maximum)

The differences are not thought to be clinically relevant and may be due to the smaller body weight of the female subjects (relative to their male counterparts) resulting in a smaller volume with correspondingly high plasma concentrations.

2.3.1.3 Effect of Site of Application

Site of Application-facial vs. scalp application (*Male Subjects only*)

Absorption of imiquimod from the scalp was markedly lower than that following facial application. T_{max} was achieved earlier, but both AUC and C_{max} were only ~25% of facial values. By nature of the rates of and degree of balding, this portion of the trial was conducted in men only.

Table 11-4 Comparison of Male Subject Scalp and Face Application Serum Pharmacokinetics for Imiquimod (R-837) on Day 21

Parameter	Mean (SD)			
	Male Subjects, Day 21			
	N	Balding Scalp	N	Face
C _{max} (ng/mL)	3	0.096 (0.038)	10	0.354 (0.126)
C _{min} (ng/mL) ^a	3	0.066 (0.005)	10	0.230 (0.110)
T _{max} (hr) ^b	3	6.0 (4.0-9.0)	10	9.0 (4.0-16.0)
AUC ₀₋₂₄ (ng•hr/mL)	3	1.770 (0.723)	10	6.553 (2.534)

^b Pre-dose concentration (t=0)

^c Median (minimum-maximum)

The differences seen here are quite striking but are most likely due to the different structure of the stratum corneum between these two anatomically linked but structurally different areas of skin. Even should these differences should not result in a clinically meaningful safety difference given the experience with the 5% marketed product.

2.3.2.1 Pediatric patients

A pediatric indication is not being sought at this time, and a pediatric waiver has been requested and was given as the indication essentially does not exist in the pediatric population to any meaningful extent.

2.3.2.2 Renal impairment

No clinical studies have been conducted to evaluate the effect of renal impairment on the PK of imiquimod, nor are they required given the low level of absorption and the indication.

2.3.2.3 Hepatic impairment

No clinical studies have been conducted to evaluate the effect of hepatic impairment on the PK of imiquimod, nor are they required given the low level of absorption and the indication.

2.3.2.4 What pregnancy and lactation use information is there in the application?

No information is provided; the currently marketed 5% product is labeled as a Pregnancy Class C. Its use in pregnant or lactating women should be done only if the potential benefit justifies the potential risk to the fetus.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The extrinsic factor influence on dose-exposure and/or –response was not explored

2.4.2 Drug-drug interactions

Drug-drug interactions were not and are normally not evaluated for topically applied products.

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Not Applicable

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The proposed-to-be-marketed formulation is the same as the formulation used in pivotal Phase 3 trials.

2.5.2.1 What data support or do not support a waiver of in vivo BE data?

A waiver of in vivo BE data is not necessary, as the proposed-to-be-marketed formulation is the same as the formulation used in pivotal Phase 3 trials.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Not Applicable

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Imiquimod (R-837) and its two metabolites combined (S-26704 and S-27700) were extracted by protein precipitation from human serum using a validated analytical method. The samples were injected into a liquid chromatography with tandem mass spectrometer detection (LC/MS/MS) system of analysis. The lower limit of quantitation (LLOQ) was 0.05 ng/mL, and the upper limit of quantitation (ULOQ) was 10 ng/mL for R-837 in human serum. For S-26704/S-27700 in human serum, the LLOQ was 0.05 ng/mL and the ULOQ was 20 ng/mL. A detailed discussion of the analytical methods including its performance characteristics is presented in the study appendix. As performed the assay method may be considered to be adequately validated for the purposes of this study.

2.6.2 Which metabolites have been selected for analysis and why?

In vitro metabolism studies were performed by incubating [¹⁴C]imiquimod in the presence of human liver microsomes. The chemical structures of the metabolites produced in the incubations were determined by analyzing the incubation samples using LC-MS methods. All in vitro metabolite formation was microsome- and NADPH-dependent. Eight metabolites were identified. The primary imiquimod metabolites from these incubations were the 8-hydroxy derivative, representing 45% of all metabolites; and the 5-N-oxide derivative, representing 25% of all metabolites.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Imiquimod and its two primary metabolites (S-26704/S-27700) were appropriately measured as total (i.e., unbound and bound) drug.

2.6.4 What bioanalytical methods are used to assess concentrations?

The liquid chromatography (LC) system employed a reversed-phase gradient method with triple-quadrupole mass spectrometric (MS/MS) detection. Sample preparation involved organic solvent precipitation of serum proteins.

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies?

The linear range of the method was 0.0500 to 10.0 ng/mL for R-837 and S-26704/S-27700 using 0.100 mL of human serum. Given the experience gained in the development of the 5% cream, the working range was adequate.

2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

The lower limit of quantitation (LLOQ) was 0.05 ng/mL, and the upper limit of quantitation (ULOQ) was 10 ng/mL for R-837 in human serum. For S-26704/S-27700 in human serum, the LLOQ was 0.05 ng/mL and the ULOQ was 20 ng/mL.

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

The precision (%CV) ranged from 3.39% to 7.35%, and the accuracy (%RE) at all concentrations ranged from -9.33% to 6.89% for R-837. The precision (%CV) ranged

from 5.21% to 7.89%, and the accuracy (%RE) at all concentrations ranged from -4.80% to 3.00% for S-26704/27700.

2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

The analytical report contained sufficient information to demonstrate that the samples were stable at room temperature for >24hrs and that the samples were stable for a minimum of 2 freeze thaw samples. All samples were shipped express on dry ice and were reported to have reached the analytical site (b) (4) in a frozen manner.

As of August 1, 2009 the Biopharm-DSI inspection is still pending.

2.7 Labeling

Aldara Cream (5%) is currently indicated for the topical treatment of:

- Clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses (AK) on the face or scalp in immunocompetent adults
- Biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults; maximum tumor diameter of 2.0 cm on trunk, neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured
- External genital and perianal warts/condyloma acuminata in patients 12 years old or older

The 3.75% product is seeking the following more limited set of indications:

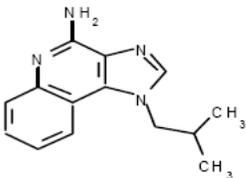
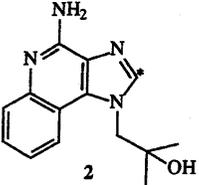
- The topical treatment of clinically typical visible or palpable actinic keratoses of the face or balding scalp in immunocompetent adults

Indicative of the lack of systemic availability of the 3.75% product the proposed package insert contains minimal Clinical Pharmacology information. At this time it is unclear if this will be a separate label or a combined label. If the labels ultimately are combined then there would need to be a separation of the information such that the lack of systemic absorption with the 3.75% material does not inform the 5% product which, while low, does have systemic availability.

(b) (4)

“LC/MS/MS Quantitation of R-837 and S-26704/S-27700 in Human Serum.”

The liquid chromatography (LC) system employed a reversed-phase gradient method with triple-quadrupole mass spectrometric (MS/MS) detection. Sample preparation involved organic solvent precipitation of serum proteins.

	<p>Imiquimod, code #R-837</p>
	<p>Metabolites S-26704 and S-27700 are isomers and elute from the column as one completely merged peak as the column is not stereospecific. Thus, as isomers, the two metabolites have the same exact mass, fragmentation pattern and product ion, they can be analyzed as a combined peak. To assess the technical merit of this approach, the two metabolites were assayed separately and the measured concentrations were compared to theoretical values at levels of 100 pg/mL and 1000 pg/mL. The measured concentrations of each individual metabolite were within -8.0 to 6.0% of the theoretical values, indicating that S-26704 and S-27700 can be measured as one combined peak.</p>

A total of 814 (407 from Set 1 and 407 duplicate samples from Set 2) human serum samples were received in four shipments on July 22 and 29, August 19 and 26, 2008 from Comprehensive PhaseOne. Eleven samples from Subject 19, Day 21, all timepoints, were not received. Samples were received frozen and in good condition, and were stored at -20°C at 1 page of clinpharm has been withheld in

Results of Quality Control Samples

The precision (%CV) ranged from 3.39% to 7.35%, and the accuracy (%RE) at all concentrations ranged from -9.33% to 6.89% for R-837. The precision (%CV) ranged from 5.21% to 7.89%, and the accuracy (%RE) at all concentrations ranged from -4.80% to 3.00% for S-26704/27700.

Precision and Accuracy of R-837 and S-26704/S-27700 QC Samples in Human Serum

Batch Number	R-837 Quality Control Samples in Human Serum, ng/mL			
	0.075	0.15	1.5	7.5
1	0.064	*0.174	1.579	7.825
	0.064	0.155	1.551	8.397
2	0.066	0.162	1.497	7.930
	0.073	0.148	1.591	8.525
3	0.067	0.170	1.533	8.132
	0.068	0.159	1.560	8.398
4	0.071	0.166	1.563	8.201
	0.077	0.159	1.571	8.078
5	0.074	0.171	1.410	6.899
	0.069	0.166	1.546	7.973
6	0.065	0.140	1.474	7.798
	*0.060	0.143	1.506	8.050
Mean	0.068	0.159	1.532	8.017
S.D.	0.005	0.011	0.052	0.420
%CV	7.35	6.92	3.39	5.24
%RE	-9.33	6.00	2.13	6.89
n	12	12	12	12

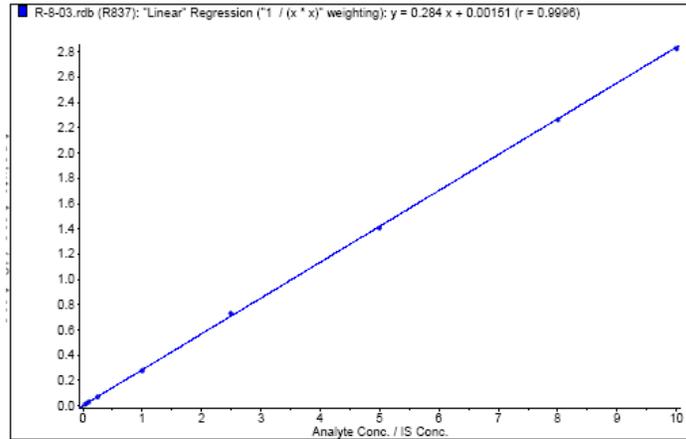
Batch Number	S-26704/S-27700 Quality Control Samples in Human Serum, ng/mL			
	0.15	0.3	3	15
1	0.144	0.293	2.717	13.581
	0.151	0.297	2.758	14.367
2	0.147	0.283	2.697	13.805
	0.154	0.299	2.787	14.290
3	0.138	0.293	2.754	14.194
	0.161	0.291	2.795	14.510
4	0.130	0.300	2.796	14.115
	0.143	0.293	2.745	14.340
5	0.161	*0.347	3.022	14.095
	0.167	0.344	3.029	15.720
6	0.166	0.342	3.064	15.583
	0.166	0.324	3.102	15.859
Mean	0.152	0.309	2.856	14.538
S.D.	0.012	0.024	0.151	0.757
%CV	7.89	7.77	5.29	5.21
%RE	1.33	3.00	-4.80	-3.08
n	12	12	12	12

*: Value out of $\pm 15\%$ of acceptance, but retained in the calculations

Calibration/Standard Curve

The linear range of the method was 0.0500 to 10.0 ng/mL for R-837 and S-26704/S-27700 using 0.100 mL of human serum. The lower limit of quantitation (LLOQ) is defined as the lowest calibration standard that meets the validation criteria for linearity, as well as precision and accuracy. The upper limit of quantitation (ULOQ) is the highest calibration standard that meets the validation criteria for linearity, as well as precision

and accuracy. The precision (%CV) ranged from 1.15% to 10.68% and the accuracy of the back-calculated values of the calibration standards (%RE, percent difference) ranged from -2.10% to 3.00% for R-837. The precision (%CV) ranged from 0.84% to 3.00% and the accuracy of the back-calculated values of the calibration standards (%RE, percent difference) ranged from -2.60% to 3.00% for S-26704/S-27700. The mean coefficients of determination (r^2) for R-837 and S-26704/S-27700 were 0.997 and 0.999, respectively.



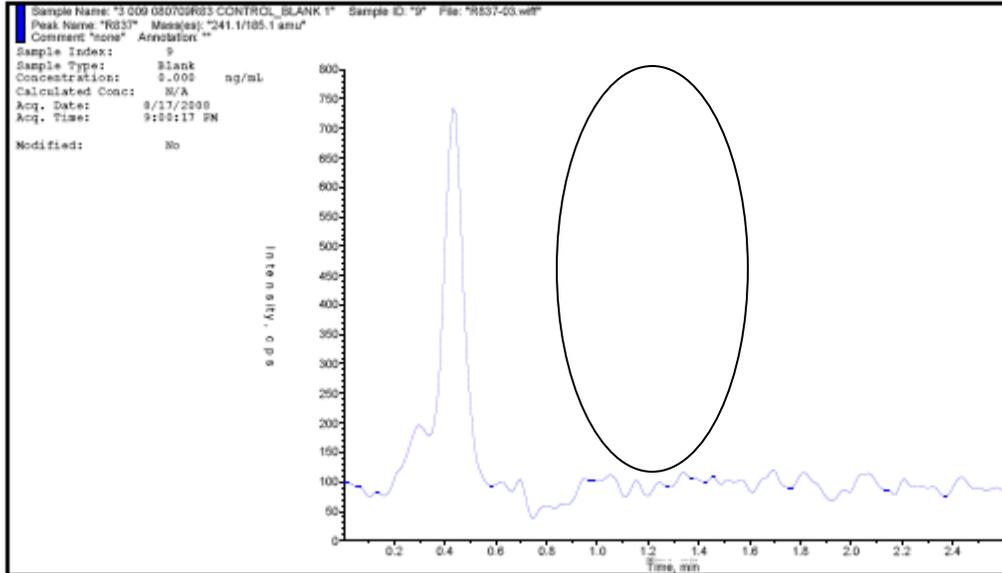
Batch Number	Calibration Curve Parameters for R-837 Calibration Standards in Human Serum		
	Slope	Intercept	r^2
1	0.297679835	0.001924556	0.998
2	0.289033388	0.001466004	0.994
3	0.283605894	0.001508564	0.999
4	0.281662300	0.000804179	0.999
5	0.372276550	-0.001044647	0.999
6	0.369114354	0.003656895	0.995
Mean	0.315562054	0.001385925	0.997
S.D.	0.043077410	0.001530685	0.002
%CV	13.65	110.45	0.20
n	6	6	6

Batch Number	Calibration Curve Parameters for S-26704/S-27700 Calibration Standards in Human Serum		
	Slope	Intercept	r^2
1	0.257941637	0.002473254	0.999
2	0.256317775	0.002092269	0.998
3	0.249679133	0.004479924	0.999
4	0.250546420	0.004921309	0.999
5	0.271747203	0.006735775	0.999
6	0.274078691	0.002349057	1.000
Mean	0.260051810	0.003841932	0.999
S.D.	0.010486909	0.001849848	0.001
n	6	6	6

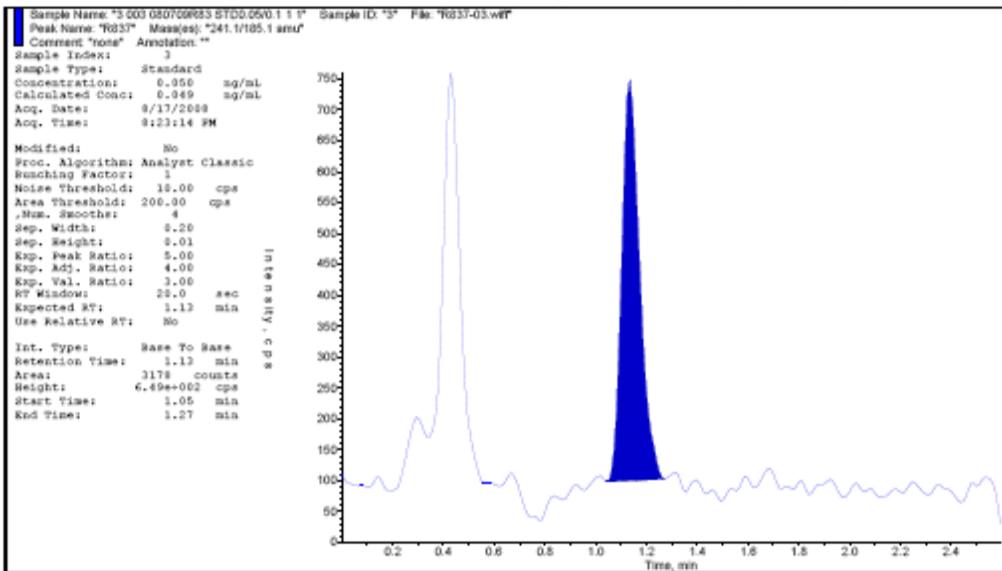
Analytical Specificity

Specificity was demonstrated by analyzing six different lots of blank human serum with and without the addition of IS and LLOQ concentrations of R-837 and S-26704/S-27700. The figures below display the LC/MS/MS chromatographic profile of R-837 spiked at the LLOQ level, as well as for unspiked human serum, respectively.

Chromatogram of R-837 Human Serum Blank



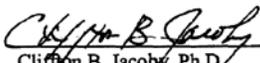
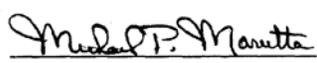
Chromatogram of R-837 Lower Limit of Quantitation Sample (0.05 ng/mL)



As can be seen the blank matrices tested did not have significant interference in the chromatographic regions of interest for R-837 (nor for S-26704/S-27700 (>25% of the LLOQ response)) or the internal standard (>5% of internal standard response). Thus, the blank matrices were determined to be free of interference that would adversely affect quantitation of R-837 or S-26704/S-27700.

Data Integrity

Although not a particular issue to the data associated with the study results of GW01-0706, as part of the review the following notation was located in the bio-analytical study report. Namely that the original developer of the assay (3M Pharmaceuticals) “lost”/”destroyed”/”purged” the original assay development reports for the imiquimod assay procedure!

3M Pharmaceuticals – Pharmacokinetics/Drug Metabolism Department Method Validation Report Addendum	
<p>Issue: The original method validation report for this Bioanalytical Method was inadvertently disposed of by 3M Maintenance Engineering personnel sometime during the first two weeks of June, 2000. Despite all reasonable efforts, the original validation report for this study was not recovered.</p>	
<p>Resolution: A complete copy of the “lost” method validation report for Method 9196.38, titled “LC/MS/MS Method for the Quantitation of Imiquimod, S-26704/S-27700 in Human Serum” was obtained from a study report on file within 3M Pharmaceuticals Division or Pharmacokinetics/Drug Metabolism Department archives.</p>	
<p>The signatures given below signify that the attached copy of the Bioanalytical Method Validation Report is an exact copy, obtained from the study report located in the archives.</p>	
 Clifford B. Jacoby, Ph.D. Section Head Bioanalytical Group Pharmacokinetics/Drug Metabolism Department	<u>15 Jun 2003</u> Date
 Michael P. Marietta, Ph.D. Department Manager Pharmacokinetics/Drug Metabolism Department	<u>15 January 2003</u> Date

As noted, they were able to locate a copy of said development report, and while it has no particular bearing on the results of this study, it does show a weakness in the data retention strategy used by this sponsor. Going forward this area should be of some concern with 3M related projects.

Analytical Conclusion

The assay as performed was adequately validated over the working range and no meaningful problems with regards to either accuracy, specificity, linearity, etc were noted.

Title: An Open Label, Single Center, Non-Randomized
Pharmacokinetic Study to Evaluate Safety of and Systemic
Exposure to Multiple Applications of Imiquimod Cream in
Subjects with Actinic Keratoses of the Face and/or Balding
Scalp

Sponsor: Graceway Pharmaceuticals, LLC

Study Number: GW01-0706

Name of Study Drug: Imiquimod

Phase I

Study Initiation Date: 15 May 2008 (first subject screened)

**Study Completion Date:
(Last Subject Completed)** 09 Sep 2008 (last subject contact)

Principal Investigator: Melanie C. Fein, MD
Comprehensive Phase One TM
3745 Broadway, Suite 100
Fort Myers, FL 33901

Sponsor Signatory: Sharon Levy, MD
Vice President, Product Development
Graceway Pharmaceuticals, LLC

Date of Report: 18 November 2008

Objectives:

The objective of this study was to quantify the pharmacokinetics of imiquimod and its metabolites during 3 weeks of daily applications of 3.75% imiquimod cream in subjects with actinic keratoses under maximal use conditions. Secondary objectives included subject tolerability and safety assessments.

Methodology:

This study was designed to quantify the pharmacokinetic (PK) profile of imiquimod and its metabolites following 3 weeks (21 days) of once daily applications of 3.75% imiquimod cream in adult subjects with actinic keratoses (AKs). The study was conducted under maximal use conditions (dose, duration, disease severity, and application areas) anticipated in Phase III studies. The daily dose was 2 packets of 3.75% imiquimod cream for 3 continuous weeks. The application area was either the entire face (exclusive of nares, vermillion, periocular areas, and ears) and/or the entire balding scalp; areas estimated as approximately 200 cm². If the area of the entire balding scalp was less than 200 cm², the forehead area was to be included for the entire application area to be approximately 200 cm². The study was an open label, single center, non-randomized PK study in approximately 24 subjects with at least 10 actinic keratosis lesions in the application area.

Subjects stayed at the study center overnight at treatment initiation (Day 1, 1st dose) and end-of-treatment (Day 21, last dose) visits for collection of a 24-hour serum PK profile. During the domiciled periods of initiation (Day 1) and end-of-treatment (Day 21) visits, serum PK samples were collected pre-dose and at planned time points through 24 hours post dose. At the end of treatment (Day 21), additional PK samples were taken at approximately 48 and 72 hours post application. Single blood draws for PK analysis of trough concentrations were obtained on Day 7 and Day 14 (in the morning prior to dosing).

Adverse events (AEs), study medication accountability, and subject compliance were reviewed at each visit. Routine clinical laboratory assessments (serum chemistry, hematology, and urinalysis) were performed at screening, Day 1 (pre-dose), and the end-of-study visits.

Duration of Treatment: 21-day treatment period with 3-day follow-up; 4-week screening period

Criteria for Evaluation:**Pharmacokinetics:**

Blood samples to determine the concentrations of imiquimod and its two metabolites combined (S-26704 and S-27700) were obtained at 9 time points on Day 1 and Day 21 and once at 48 and 72 hours after the last dose. In addition, single blood draws for PK analysis of trough concentrations were obtained on Day 7 and Day 14. The following parameters were calculated: maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), time C_{max} was observed (T_{max}), area under the concentration versus time curve (AUC_{0-24} and AUC_{0-4}), accumulation ratios ($R_{C_{max}}$ and R_{AUC}), effective elimination rate constant ($\lambda_{z,eff}$), and effective half-life for accumulation ($T_{1/2,eff}$). If sufficient data were available, apparent elimination rate constant (λ_z), apparent half-life ($T_{1/2}$), and AUC_{0-inf} were also calculated.

Safety and Tolerability:

Safety and tolerability were evaluated through the recording and monitoring of AEs, assessment of local skin reactions (LSRs), clinical laboratory results, vital signs, and physical examination results.

Conclusions:

The amount of imiquimod (R-837) absorbed into systemic circulation after topical application of imiquimod 3.75% cream to the face and/or scalp once daily for up to 21 days was low; peak and total serum imiquimod concentrations increased 3- to 4-fold between Day 1 and Day 21. Steady state was achieved by Day 14. C_{max} and AUC_{0-24} on Day 21 appeared to be similar in female and male subjects and lower in male subjects who applied imiquimod 3.75% cream to balding scalp rather than the face.

Imiquimod 3.75% cream applied to the face and/or scalp once daily for up to 21 days was generally well-tolerated. Treatment-related adverse events occurred in less than half of the subjects and were nearly all mild. Expected local skin reactions, if they occurred, were generally mild to moderate and were observed primarily on or after Day 14. Severe reactions were only observed for erythema and occurred in 5 of the 19 subjects.

Demographic or Baseline Characteristic	Parameter	Imiquimod 3.75% Cream QD (N=19)
Gender	Male - n (%)	14 (73.7)
	Female - n (%)	5 (26.3)
Race	Caucasian - n (%)	19 (100.0)
Ethnicity	Hispanic or Latino - n (%)	1 (5.3)
	Not Hispanic or Latino - n (%)	18 (94.7)
Age (years)	Mean (SD)	75.74 (7.901)
	Median (minimum-maximum)	78 (52-86)
Height (in)	Mean (SD)	66.37 (2.912)
	Median (minimum-maximum)	66 (60.4-74)
Weight (kg)	Mean (SD)	182.53 (36.889)
	Median (minimum-maximum)	178 (128-264)
Fitzpatrick Skin Type	n (%)	
	Type I: Burns easily, never tans	1 (5.3)
	Type II: Burns easily, tans minimally with difficulty	2 (10.5)
	Type III: Burns moderately, tans moderately and uniformly	11 (57.9)
	Type IV: Burns minimally, tans moderately and easily	5 (26.3)
	Type V: Rarely burns, tans profusely	0 (0.0)
	Type VI: Never burns, tans profusely	0 (0.0)

Application Area

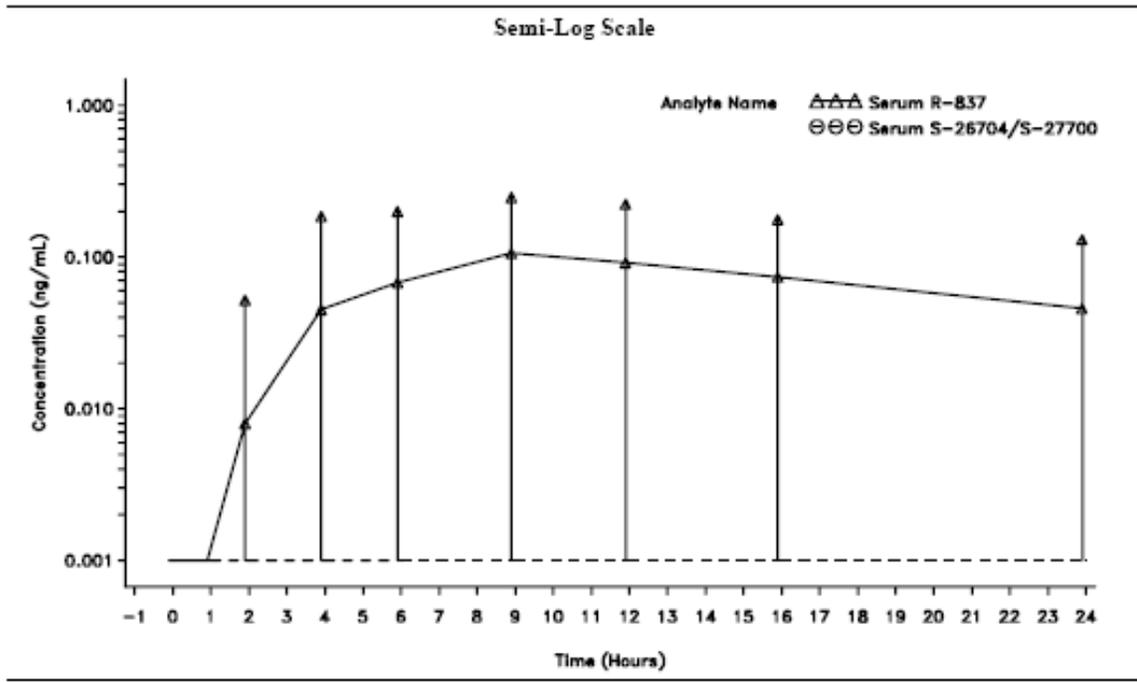
Application area	Balding scalp only - n (%)	3 (15.8)
	Balding scalp and upper face - n (%)	1 (5.3)
	Entire face (upper and lower face) - n (%)	15 (78.9)
Number of lesions in application area ^a	Balding scalp (n=4) - mean (SD)	15.25 (3.948)
	- median (minimum-maximum)	14.5 (12-20)
	Entire face (n=15) - mean (SD)	14.53 (5.153)
	- median (minimum-maximum)	12 (10-29)

^a Subjects were required to have at least 10 typical visible or palpable AK lesions located in the application area on the face and/or balding scalp to participate in the study.

Number of Packets Used

		IMIQUIMOD 3.75% CREAM QD (N=19)
TOTAL NUMBER OF PACKETS APPLIED PER SUBJECT	N	19
	MEAN	41.16
	STD	3.219
	MIN	28.0
	MEDIAN	42.00
	MAX	42.0

DAY 1 Mean Plasma Concentrations



Day 21 Mean Plasma Concentrations

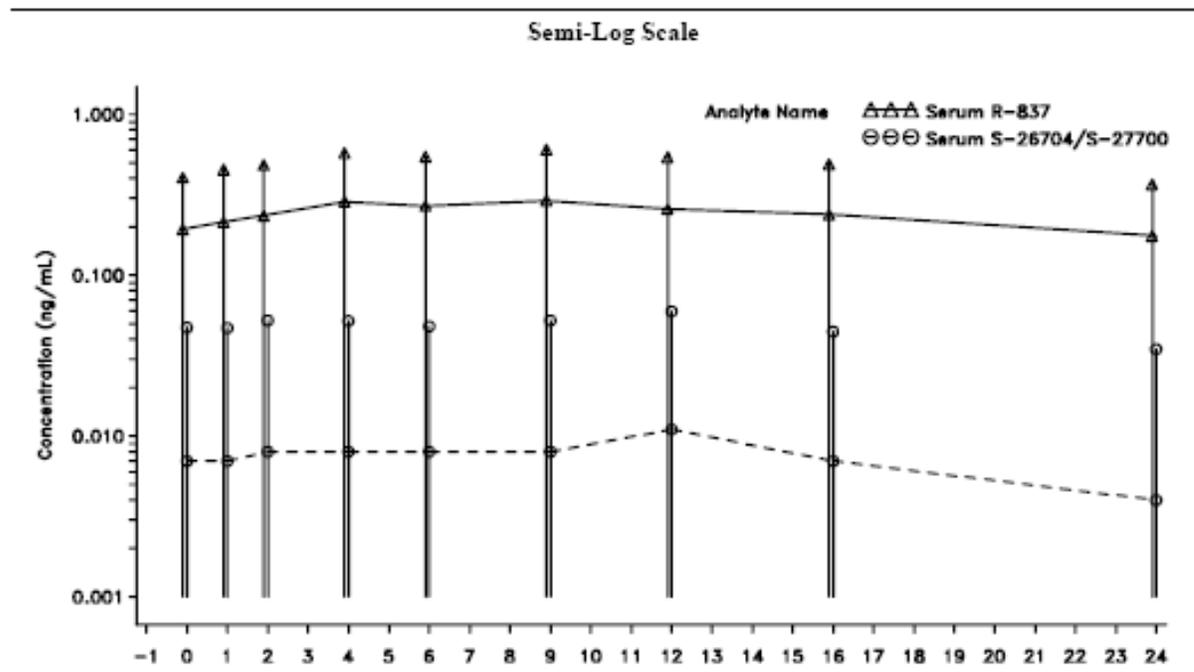


Table 11-2 Summary of Serum Pharmacokinetics for Imiquimod (R-837) on Day 1 and Day 21

Parameter	Mean (SD)			
	N	Day 1 ^a	N	Day 21 ^b
C _{max} (ng/mL)	17	0.136 (0.059)	17	0.323 (0.159)
C _{min} (ng/mL) ^c	–	NA	17	0.199 (0.109)
T _{max} (hr) ^d	17	9.0 (4.0-24.03)	17	9.0 (4.0-16.0)
AUC ₀₋₂₄ (ng•hr/mL)	17	1.831 (0.889)	17	5.974 (3.088)
AUC _{0-t} (ng•hr/mL)	17	1.679 (1.056)	–	NA
AUC _{0-inf} (ng•hr/mL)	11	4.443 (1.309)	–	NA
λ _z (1/hr)	11	0.0450 (0.0219)	15	0.0294 (0.0142)
T _{1/2} (hr)	10	19.818 (10.125)	15	29.260 (16.979)
R _{AUC}	–	NA	15	3.873 (2.153)
R _{Cmax}	–	NA	15	2.810 (1.514)
λ _{z, EFF} (hr ⁻¹)	–	NA	15	0.0235 (0.0229)
T _{1/2, EFF} (hr)	–	NA	15	55.339 (36.380)

NA=Not applicable

^a Serum concentrations for Subjects 001-601 and 001-618 were BLQ; consequently, PK parameters could not be calculated.

^b Subject 001-619 did not have concentration data on Day 21; Subject 001-608 was excluded for missing the dose on Day 20.

^c Pre-dose concentration (t=0)

^d Median (minimum-maximum)

Pharmacokinetic Results:

Serum concentrations of imiquimod (R-837) were relatively low in subjects treated with once daily applications of imiquimod 3.75% cream for 21 days. The concentration-time profile on Day 21 was relatively flat, with mean C_{max} values less than two times the mean C_{min} values. Serum concentrations of two imiquimod metabolites (S-26704 and S-27700 combined) were measured, but the data were too sparse to assess (only 3 subjects had any concentrations above the LLOQ on Day 21).

In the total pharmacokinetic population, imiquimod (R-837) mean peak (C_{max}) and total exposure (AUC₀₋₂₄) increased during once daily administration of imiquimod 3.75% cream. The accumulation ratio based on peak exposure, R_{Cmax}, indicated close to a 3-fold accumulation (2.810), and the accumulation ratio based on overall systemic exposure, R_{AUC}, indicated a nearly 4-fold accumulation (3.873). T_{1/2, EFF} was 55.339 hours. The imiquimod mean half-life, T_{1/2}, was 29.3±17.0 hours on Day 21; this was a better estimate of T_{1/2} than Day 1 as it represented sampling through 72 hours rather than 24 hours and fewer BLQ concentrations. Analysis of trough concentrations over time indicated that steady-state conditions were achieved between Day 7 and Day 14, which was consistent with the time to steady state predicted from the observed elimination half-life (approximately 6 days) and the effective half-life for accumulation (approximately 12 days).

Attainment of Steady-State

The imiquimod mean half-lives, T_{1/2}, were 19.8±10.1 hours on Day 1 (sampling through 24 hours) and 29.3±17.0 hours on Day 21 (sampling through 72 hours). This apparent increase in half-life most likely represented a better estimate on Day 21 due to the longer sampling duration. Steady-state conditions should be reached on Day 6 following once daily administration.

Table 11-5 Primary Analysis of Steady State for Imiquimod (R-837) Trough Serum Concentrations

Trough (Pre-Dose) Comparison	N	Geometric LS Mean ^a		Geometric Mean Ratio ^b	90% Confidence Interval
		Test	Reference		
Day 14 vs. Day 7	15	0.1391	0.1277	1.0888	0.7933-1.4946
Day 21 vs. Day 14	16	0.1791	0.1344	1.3328	0.9193-1.9325
Day 22 vs. Day 21	16	0.1671	0.1791	0.9331	0.6612-1.3169

Note: Steady-state analysis only included subjects with paired and non-zero serum concentration data on the days being compared who took all 7 doses in the preceding week and took at least 80% of the prescribed doses in all prior weeks.

^a Point estimate for geometric least-squares (LS) mean was based on an ANOVA model, including study day as a fixed effect.

^b Steady-state conditions were considered to exist during an interval if the point estimate for the geometric mean ratio was <1.43.

Data Source: [Table 14.2.3](#)

Male vs. Female (facial application only)

Using subjects with facial application only, there were only small relative differences between male and female subjects in either C_{max} or AUC (<15%)

Table 11-3 Comparison of Female and Male Subject Face Application Serum Pharmacokinetics for Imiquimod (R-837) on Day 21

Parameter	Mean (SD)			
	Day 21			
	N	Female	N	Male
C _{max} (ng/mL)	4	0.415 (0.140)	10	0.354 (0.126)
C _{min} (ng/mL) ^a	4	0.222 (0.071)	10	0.230 (0.110)
T _{max} (hr) ^b	4	6.5 (4.0-9.0)	10	9.0 (4.0-16.0)
AUC ₀₋₂₄ (ng•hr/mL)	4	7.678 (2.928)	10	6.553 (2.534)

^a Pre-dose concentration (t=0)

^b Median (minimum-maximum)

Male Subjects (facial vs. scalp application)

Absorption of imiquimod from the scalp was markedly lower than that following facial application. T_{max} was achieved earlier, but both AUC and C_{max} were only ~25% of facial values.

Table 11-4 Comparison of Male Subject Scalp and Face Application Serum Pharmacokinetics for Imiquimod (R-837) on Day 21

Parameter	Mean (SD)			
	Male Subjects, Day 21			
	N	Balding Scalp	N	Face
C _{max} (ng/mL)	3	0.096 (0.038)	10	0.354 (0.126)
C _{min} (ng/mL) ^a	3	0.066 (0.005)	10	0.230 (0.110)
T _{max} (hr) ^b	3	6.0 (4.0-9.0)	10	9.0 (4.0-16.0)
AUC ₀₋₂₄ (ng•hr/mL)	3	1.770 (0.723)	10	6.553 (2.534)

^b Pre-dose concentration (t=0)

^c Median (minimum-maximum)

12 pages of draft labeling has been withheld in full immediately following this page as B4 CCI/TS

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22483	ORIG 1		IMIQUIMOD 3.75% CREAM
NDA 22483	ORIG 1		IMIQUIMOD 3.75% CREAM
NDA 22483	ORIG 1		IMIQUIMOD 3.75% CREAM
NDA 22483	ORIG 1		IMIQUIMOD 3.75% CREAM
NDA 22483	ORIG 1		IMIQUIMOD 3.75% CREAM

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

/s/

EDWARD D BASHAW
08/16/2009

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-483	Brand Name	Aldara
OCP Division	DCP-3	Generic Name	Imiquimod
Medical Division	Derm/Dental	Drug Class	Immunomodulator
OCP Reviewer	Bashaw	Indication(s)	Actinic Keratosis of face
OCP Team Leader	Bashaw (acting)	Dosage Form	Topical Cream
		Dosing Regimen	QD at Bedtime x 2 weeks
Date of Submission	12/19/2008	Route of Administration	topical
Estimated Due Date of OCP Review	June 15 th , 2009	Sponsor	Graceway
PDUFA Due Date	Oct. 2009	Priority Classification	Standard
Division Due Date	June 30th		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology		1		
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>		N/A		
single dose:				
multiple dose:				
<i>Patients-</i>				
single dose:				
multiple dose:		1		
Dose proportionality -		N/A		Topical product
fasting / non-fasting single dose:		N/A		
fasting / non-fasting multiple dose:		N/A		
Drug-drug interaction studies -		N/A		
In-vivo effects on primary drug:		N/A		
In-vivo effects of primary drug:		N/A		
In-vitro:		N/A		
Subpopulation studies -				
ethnicity:		N/A		
gender:		N/A		
pediatrics:		N/A		
geriatrics:		N/A		
renal impairment:		N/A		
hepatic impairment:		N/A		
PD:				
Phase 2:	1	1		Dose Ranging Trial
Phase 3:	2	2		Clinical Trials in patients
PK/PD:				
Phase 1 and/or 2, proof of concept:		1		
Phase 3 clinical trial:		N/A		

Population Analyses -				
Data rich:		N/A		
Data sparse:		N/A		
II. Biopharmaceutics				
Absolute bioavailability:		N/A		
Relative bioavailability -		N/A		
solution as reference:		N/A		
alternate formulation as reference:		N/A		
Bioequivalence studies -				
traditional design; single / multi dose:		N/A		
replicate design; single / multi dose:		N/A		
Food-drug interaction studies:		N/A		
Dissolution:				
(IVIVC):		N/A		
Bio-wavier request based on BCS		N/A		
BCS class		N/A		
III. Other CPB Studies				
Genotype/phenotype studies:		N/A		
Chronopharmacokinetics		N/A		
Pediatric development plan		N/A		
Literature References		N/A		
Total Number of Studies	1	1		With PK data
	4	4		Clinical Studies with no pk data but with clearance as endpoint
Filability and QBR comments:				
	"X" if yes	Comments		
Application filable ?	X			
Comments sent to firm ?		In regards to the metabolism of imiquimod and the identification of metabolites, please submit the following study report, and supporting materials, for Drug Metabolism Experiment No. R-837-DM-79 which contains information on the identification of metabolites for imiquimod which you refer to in your drug metabolism/identification subsection of your application.		
QBR questions (key issues to be considered)	<ol style="list-style-type: none"> 1.) What is the degree of systemic exposure to imiquimod? 2.) How does it compare to the exposure from the 5% product? 3.) Does lesion count/surface area correlate with absorption? 4.) Is there a safety signal with regards to cardiac? OSE to adjucate, based on the 5% data. 5.) Formulation viscosity issue to be discussed with CMC at their request. 			
Other comments or information not included above	<p>This product is basically a line extension. Aldara is currently available for different (but related) indications as a 5% product. This product is currently intended for us on the face and balding area of the scalp only. The issue of its appropriateness as a supplement or a standalone NDA is still under consideration.</p> <p>There is a safety issue with regards to a potential cardiac signal that needs to be incorporated into this application. No TQT study has been done to date.</p>			
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

Filing Memo

Clinical Pharmacology and Biopharmaceutics Review

NDA: 22-483
Compound: Imiquimod 3.75% Topical Cream
Sponsor: Graceway Pharmaceuticals
Date: 4/17/09
Reviewer: E. Dennis Bashaw, Pharm.D.

Background:

Aldara® (imiquimod) Cream, 5% is currently approved under NDA 20-723 for the treatment of actinic keratoses (AK), superficial basal cell carcinoma (sBCC), and external genital warts (EGW). The treatment regimens for these indications are 2 times a week for 16 weeks, 5 times a week for 6 weeks, and 3 times a week for up to 16 weeks, respectively. Graceway Pharmaceuticals has developed a lower-strength formulation for AK with a dosing regimen that would be more convenient for patient use (once daily at bedtime for 2 weeks). As such it is proposed that the dosing be limited to the face and any exposed balding portion of the scalp. It should be noted that there are ongoing studies that are not a part of this NDA for other indications at the 3.75% strength.

The container closure system is a (b) (4) single dose sachet (packet) consisting of a (b) (4) material which uses (b) (4) (b) (4). The cream (250 mg) is retained in the bottle shaped (b) (4) area of the sachet.

Application Overview:

The Clinical Pharmacology portion of the NDA consists of 1 clin pharm study in 20 subjects (19 completers and 1 drop-out) with facial and scalp actinic keratosis consistent with the proposed indication (location and severity). In addition the sponsor has submitted a phase 2 “dose-ranging” clinical study with the approved 5% and a 2.5% and 3.75% cream. The 3.75% cream was chosen by the sponsor for development on the basis of a slight superiority of response over the 2.5% product. The sponsor also makes extensive reference to the approved 5% NDA 20-723.

Recommendation:

This memo memorializes the clinical pharmacology filing decision that was transmitted via e-mail previously The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 find that the Human Pharmacokinetics and Bioavailability section for

NDA 22-483 is fileable.

74-Day Letter Comments:

As part of the filing review of this application the following report (submitted with the original NDA application for the 5% product) was found to be missing from this submission. The following request was contained in 74 day letter:

- In regards to the metabolism of imiquimod and the identification of metabolites, please submit the following study report, and supporting materials, for Drug Metabolism Experiment No. R-837-DM-79 which contains information on the identification of metabolites for imiquimod which you refer to in your drug metabolism/identification subsection of your application.

Dennis Bashaw , Division Dir.

Date

Dennis Bashaw, ACTING TL

Date

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

/s/

Dennis Bashaw

4/17/2009 05:24:27 PM

BIOPHARMACEUTICS

This filing memo memorializes the filing decision of OCP
that was previously communicated to the division via
e-mail on 2/20/09