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RESEARCH**

*APPLICATION NUMBER:*  
**22483Orig1s000**

**MEDICAL REVIEW(S)**

## **Review of NDA 22-483 (class 1 resubmission)**

**Subject:** complete response to complete response and dispute appeal response

**SD:** 22

**Stamp Date:** 01/29/2010

**Priority Designation:** Class 1 resubmission

**PDUFA Goal Date:** 03/29/2010

**Established name:** imiquimod

**Formulation:** cream

**Trade name:** Zyclara 3.75% cream

**Applicant:** Graceway Pharmaceuticals

**Indication:** actinic keratosis

**Intended Population:** 18 years and older

**Dosing regimen:** daily application for two weeks, followed by a two-week no treatment period, (b) (4)

**Reviewer Name:** Milena Lolic, M.D.

**Team Leader:** Jill Lindstrom, M.D.

**RPM:** Kelisha Turner

**Received by reviewer:** 2/2/2010

**Review start date:** 02/08/2010

**Review completion date:** 03/01/2010

### **I Recommendation for Regulatory Action**

It is recommended that from clinical perspective NDA 22-483, Zyclara 3.75% cream for the topical treatment of actinic keratosis of the face and scalp in adults 18 years and older, be approved.

### **II Regulatory background**

This application was submitted as a “complete response” to Agency’s complete response letter dated 10/16/2009 and dispute appeal-response letter dated 1/15/2010.

Aldara (imiquimod) 5% cream was originally approved in 1997 (NDA 20-723) for the treatment of external genital warts and in 2004 for actinic keratosis and superficial basal cell carcinoma.

## **Major points from the review of NDA 22-483**

The original NDA 22-483 application for Zyclara (imiquimod) 3.75% cream was submitted on 12/19/2009. Four well-controlled Phase 3 trials (utilizing 2.5% and 3.75% cream) and one PK trial were conducted with the objective of establishing the superiority of two 2-week daily application of imiquimod cream two weeks week apart to vehicle (note different regimen then for Aldara). In all Phase 3 trials, imiquimod cream demonstrated superiority over vehicle. Applicant selected 3.75% concentration for approval. Safety data included all 5 trials. Applicant also provided summary of studies where pharmacokinetics of Aldara and Zyclara creams were evaluated. The purpose was to establish comparative systemic exposures given that dosing regimens of these two strengths of cream are different and furthermore to bridge to 13 years of safety record that exists for Aldara cream.

The safety review of NDA 22-483 revealed:

1. lack of TQT studies (communicated with sponsor in Filing letter dated 3/2/2009)
2. one case of ventricular tachycardia from pivotal trial GW 01-0702 categorized by investigator as non-serious AE (IR sent to sponsor May 14, 2009, response received May 21, 2009)
3. insufficient data to characterize comparative bioavailability of Aldara and Zyclara.

To further assess the safety profile of imiquimod cream, TQT/IRT consult as well as cardiology and OSE consults were obtained during the review.

Briefly, AERS data base revealed 3 positive rechallenge cases of tachyarrhythmia and one case of sudden death. TQT consult concluded that the applicant did not adequately address the potential of imiquimod to promote QT prolongation. Cardiac consult regarding proarrhythmic potential of imiquimod informed that no definite conclusions could be drawn from available clinical information.

(The reader is referred to the Clinical Review of the original NDA dated 09/02/2009).

## **Regulatory action**

The original NDA 22-483 received “complete response” action for the following deficiencies:

“Electrocardiographic studies were not conducted during the development of your product and the effect of imiquimod on cardiac repolarization and arrhythmias is unknown.

The comparative bioavailability of Zyclara and Aldara (used as labeled) is unknown.

In the absence of adequate information about the comparative bioavailability of Zyclara relative to Aldara and adequate data demonstrating that Zyclara does not affect cardiac repolarization, the potential risks of Zyclara are not justified by the potential benefits to patients with actinic keratoses of the face or scalp.

## Information Needed for Resolution

Conduct of a thorough QT study with Holter monitoring to demonstrate the impact of your product on cardiac repolarization and heart rate.”

(Please see attachment #1)

## **Dispute resolution**

In response, applicant requested and was granted a Type A (post-action) meeting with DDDP, held on November 17, 2009. Applicant included in the meeting package PK study R-837-009 (completed 1990, final report from 1997) in which ECG monitoring had been performed. However, that study was not included in the NDA 22-483 or in the response to filling letter, thus DDDP held its position that more ECG data were needed prior to approval. On December 16, 2009 applicant submitted request for formal dispute resolution to the director of ODE III concerning the requirement to conduct of a thorough QT study with Holter monitoring prior to approval.

After reviewing regulatory background information, cases of concern and new (post-action) information provided by QT/IRT and cardiology team, director of ODE III, in her dispute appeal –response letter, informed the applicant that:

..”Your request that the requirement for pre-approval through QT study be waived is granted” and :

.....“Graceway should, therefore, submit a complete response to its October 16, 2009 complete response letter to include the following:

- proposed product labeling;
- a safety update that includes:
  - the full study report for R-837-009, including ECG tracings; and
  - information to address the possibility that imiquimod may trigger symptomatic tachyarrhythmias, such as SVT. This information should include a) a review of the clinical trial safety database for an imbalance of adverse events such as syncope, palpitations and dizziness for imiquimod compared to placebo, and b) an assessment of available data on heart rate (e.g., change from baseline and outlier analysis by dose/concentration); and
- a draft protocol synopsis for a postmarketing controlled clinical trial designed to assess the affects of topical imiquimod on heart rhythm.

This submission will be considered a Class 1 resubmission and will be reviewed on a two-month clock.”

## **III Review of the current submission**

On January 29, 2010 the applicant submitted a Complete response containing:

- A. Safety update in response to CR. To address this issue, the sponsor submitted:
  1. significant changes or findings in the safety profile incorporated in the draft labeling proposal

2. new safety data from the ongoing studies/clinical trials for the proposed indication (actinic keratosis)
  3. adverse events occurring in clinical studies of 3.75% imiquimod cream in the treatment of EGW
  4. retabulation of the reasons for premature trial discontinuation from the newly completed trials
  5. narratives and case reports for subjects with serious adverse events, subjects who discontinued the study for adverse events during new trials
  6. overall extent of exposure for the new studies
  7. Zyclara labeling that was approved for the treatment of actinic keratosis in Canada effective December 31, 2009.
- B. Safety update in response to dispute appeal response. To address this issue, the sponsor submitted:
1. draft labeling proposal and PI
  2. full study report R-837-009 and the ECG tracings
  3. review of the clinical trial safety data base suggestive of an underlying symptomatic tachyarrhythmias
  4. assessment of available data on heart rate
- (b) (4)
- C. Other relevant information
1. additional safety information on subject 01/210 who suffered ventricular tachycardia as per information from original NDA 22-483 submission
  2. sachet and carton labels as requested by CMC reviewer

**Discussion:**

**A. Safety updates in response to CR**

1. Draft labeling proposal for Zyclara contains three terms that have been added to section 6.5 Postmarketing experience to the Aldara label: abdominal pain, hypertrophic scar, and herpes simplex.

*Reviewer's comment: Agree with new terms and would add SVT under arrhythmias.*

2. There are no completed clinical studies with Zyclara for the treatment of AK thus applicant was not able to provide new tabulated safety data. There are two ongoing studies with Zyclara cream for the treatment of actinic keratosis : GW01-0803 and GW01-0901. Applicant provided safety updates as follows:

Study **GW01-0803**- "A Follow-up Study to Evaluate Sustained Clearance Rates of Actinic Keratoses up to One Year after Completion of Studies GW01-0702, GW01-0703, GW01-0704, and GW01-0705"

Number of subjects: 179

Duration: one year

Design: open label, long term study with 2 follow-up visits (at 6 and 12 months after the Phase 3 EOS visit)

Objective: sustained clearance rate and long term safety (only local adverse events and any AE considered by investigator to be possibly or probably related to the medication)

Safety summary: there were no discontinuations from the study or related serious adverse events

*Reviewer's comment: All serious adverse events should be recorded despite obvious lack of temporal relationship with the drug application.*

Study **GW01-0901**- “A Phase 3b, Randomized, Double-blinded, Placebo-controlled, Multicenter, Efficacy and Safety Study of Imiquimod Cream Followig Cryosurgery for the Treatment of Actinic Keratoses”

Number of subjects: 247

Duration: 6 months (first subject enrolled June 2009)

Design: subjects who sufficiently healed from cryosurgery were randomized to either imiquimod 3.75% cream or placebo, treated for 6 weeks (2 two-week cycles separated by 2 week no-treatment) and followed for 20 weeks

Objective: percent change in AK lesion

Safety summary: per applicant “no reportable safety events”

*Reviewer's comment: It is unclear what “reportable” means. Imiquimod 3.75 % cream has been shown to cause local and systemic AE during Phase 3 trials. Perhaps there were no new unexpected AE.*

3. Applicant has completed 2 Phase 3 trials (GW01-0801, and GW01-0805) using imiquimod 3.75% cream for the treatment of external genital warts (EGW). Summary of AE is provided:

	Imiquimod Cream		Placebo (N=202)
	3.75% (N=400)	2.5% (N=379)	
Subjects with Any AE, n (%)	144 (36.0)	134 (35.4)	56 (27.7)
Number of AEs	339	269	87
Subjects with Any Treatment-related AE *, n (%)	70 (17.5)	64 (16.9)	5 (2.5)
Subjects with Any Serious AE, n (%)	7 (1.8)	4 (1.1)	1 (0.5)
Subjects with Any Severe AE, n (%)	21 (5.3)	20 (5.3)	4 (2.0)
Subjects with Any AE Leading to Study Discontinuation, n (%)	6 (1.5)	7 (1.8)	1 (0.5)
Subjects with Any Application Site Reaction, n (%)	64 (16.0)	58 (15.3)	5 (2.5)

Source: attachment 6 Table 5.3.5.3.2.13.1

In addition, AEs from PK study GW01-0804 with 18 subjects are submitted as well.

*Reviewer's comment: The most commonly reported AEs were application site reactions (pain, irritation, pruritus) followed by infections and infestations. The type of reactions and distributions are within expected range.*

- Disposition of the subjects enrolled in the trials using imiquimod cream for the treatment of external genital warts (EGW) is presented below:

Reason for discontinuation, n (%)	Imiquimod 3.75% (400)	Imiquimod 2.5% (379)	Placebo (202)	Overall 981
Safety reasons	6 (1.5)	6 (1.5)	1 (0.5)	13 (1.3)
Investigator's request	3 (0.8)	0	1 (0.5)	4 (0.4)
Subject's request (not due to AE)	21 (5.3)	18 (4.7)	11 (5.4)	50 (5.1)
Lack of efficacy	0	1 (0.3)	0	1 (0.1)
Non-compliance	3 (0.8)	7 (1.8)	3 (1.5)	13 (1.3)
Concomitant therapy	0	1 (0.3)	0	1 (0.1)
Subject lost to follow-up	74 (18.5)	77 (20.3)	38(18.8)	189(19.3)
Other (not due to AE)	7(1.8)	10 (2.6)	5 (2.5)	22 (2.2)

Source: attachment 8 Table 5.3.5.3.1.1.1

*Reviewer's comment: High number of subjects was lost to follow-up across all arms. In the second most frequent reason for discontinuation (subject's request), there is trend towards more discontinuations in active arms suggestive of tolerance issue. However, that is not unexpected, and was observed in earlier trials.*

- Narratives for subjects who had serious adverse events or AE leading to discontinuation from the trials are provided.

Study-Site/Subject Number	SAE	Discontinued Study due to Related AEs	Discontinued Study due to Non-related AEs
<b>3.75% Imiquimod</b>			
0801-10/026		X	
0801-18/020		X	
0801-19/023	X		X
0801-31/027	X		
0805-03/014	X		
0805-06/021		X	
0805-12/005	X		
0805-22/013	X		
0805-31/005	X (Fatal)		X
0805-34/003	X		
0805-39/002	X		X
0805-40/013	X		
<b>2.5% Imiquimod</b>			
0801-01/025		X	
0801-16/013		X	
0801-26/041	X		
0801-31/004	X		
0805-03/012			X
0805-04/022		X	
0805-12/010		X	
0805-18/016		X	
0805-19/033	X		
0805-35/004	X		X
<b>Placebo</b>			
0801-26/039			X
0805-36/021	X		

Source; attachment 10 table 5.3.3.3.2-38

Deaths; there was one death; result of fatal gunshot wound considered non-related to the drug.

Serious adverse events; there were 13 SAE (12 in active arms and one in placebo arm).

*Reviewer's comment: narratives were reviewed. Eleven events are considered unrelated. One case (0801-31/004) will be further described:*

- 47 y/old AA man with h/o migraine and myopia was evaluated in ER (b) (6) for migraine and discharged on naproxen. The following day he had syncope and was hospitalized. Evaluation did not reveal cause of syncope.

*As per literature, in about 30% of the cases, the etiology of syncope remains unknown, thus the outcome of subject's evaluation is not unexpected. However, in this case there is temporal relationship to drug use, thus the role of imiquimod can not be excluded.*

Discontinued study due to related AEs revealed 9 cases. All of the cases involve severe local skin reactions (from pain to ulcerations) and in some instances flu-like symptoms.

*Reviewer's comment: Type of reactions is within those previously reported with imiquimod use. In some cases, severity of the local reaction raises additional concern and will require careful evaluation during NDA review.*

Pregnancies: There were 8 pregnancies in active groups. One healthy baby was born and for other pregnancies outcomes are to be determined.

6. Overall exposure for the new trials is provided. Mean duration of treatment was about 50 days, slightly lower in 3.75% (which also showed higher efficacy). Approximately 85% of subjects were compliant.

*Reviewer's comment: The average amount of cream was 4.7g. In PK study with 21 consecutive day application compliance was lower-78% perhaps because of more intense treatment.*

7. In response to request to provide world-wide safety experience with Zyclara and foreign labeling, the applicant submitted recently approved label in Canada. However, the product has not been placed on the market.

## **B. Safety update in response to dispute appeal response**

1. Full study report for R-837-009 entitled "Rising Dose Safety and Pharmacokinetic Study of Oral R-837 in Healthy Volunteers" with ECG tracing is included. Brief review of this study will be provided below; interested reader is referred to TQT consult that was obtained.

This study was a single blind, placebo controlled, single oral escalating dose safety trial in 40 healthy male volunteers. 30 subjects received single dose of up to 300mg of imiquimod, and 10 received placebo. Pharmacokinetic and safety parameters were followed for the next 24 hours.

Per report, there were no clinically significant changes in blood pressure, heart rate or ECGs (including intervals). The most frequent findings were elevated temperature and flu-like symptoms as expected.

C<sub>max</sub> ranges were from 120±60 ng/mL to 528 ± 128 ng/mL) following doses of 100-300mg). Half life ranged from 2-6 hours. There were measurable serum concentrations of IFN α and of metabolite S-26704.

*Reviewer's comment: This oral study in healthy volunteers did not find any significant heart rate or ECG changes. It should be noted that serum concentrations of imiquimod in this study are 100 times higher than the mean serum concentrations of topical imiquimod used as labeled*

*(0.4 ng/mL). However, this study was not designed to address the potential of imiquimod to prolong TQT (no positive control), or pro-arrhythmic potential of the drug (only 24 hour follow-up). Given the stated limitations of the study R-837-009 and, a consult from TQT/IRT team was requested.*

*In their consult QT/IRT team concluded that:*

- a) The data are reassuring that there is not a direct effect of imiquimod on QT, heart rate, and rhythm.
- b) No further study is needed to characterize imiquimod's effect on QT.
- c) It is possible that effects of imiquimod on endogenous interferons with chronic use produce increases in HR and potential arrhythmias in a vulnerable population that is not dose-dependent. However, this is best addressed by review of symptomatic arrhythmia incidence in placebo controlled clinical trial data.

*As result, TQT study is no further needed to characterize imiquimod effect on cardiac repolarization.*

2. Applicant provide review of the clinical trial safety data base suggestive of an underlying symptomatic tachyarrhythmias . Event information was pooled across completed Phase 2 and Phase 3 trials from the development program for external genital warts, actinic keratosis, superficial basal cell carcinoma, herpes genitalis, herpes labialis and non-genital warts utilizing imiquimod cream (5 %, 2.5%, and 3.75% concentrations). Applicant provided the list of placebo controlled studies that were not included in analysis.  
Pooled data have 8464 subjects exposed to imiquimod cream and 3129 to vehicle. AEs were coded using WHOART and MEDRA terms.

AE Term	Group	Events	Sample	Rate (%)	P-value
ANGINAL PAIN [Angina pectoris, Prinzmetal Angina]	Imiquimod	3	8464	0.035	1.000
	Placebo	1	3129	0.032	
ARRHYTHMIA	Imiquimod	15	8464	0.177	0.632
	Placebo	7	3129	0.224	
ARRHYTHMIA ATRIAL	Imiquimod	0	8464	0.000	1.000
	Placebo	0	3129	0.000	
ARRHYTHMIA VENTRICULAR	Imiquimod	2	8464	0.024	1.000
	Placebo	0	3129	0.000	
CARDIAC ARREST	Imiquimod	1	8464	0.012	1.000
	Placebo	0	3129	0.000	
CARDIAC FAILURE [Cardiac failure congestive]	Imiquimod	7	8464	0.083	1.000
	Placebo	2	3129	0.064	
CHEST PAIN	Imiquimod	12	8464	0.142	0.136
	Placebo	9	3129	0.288	
DIZZINESS	Imiquimod	66	8464	0.780	0.102
	Placebo	15	3129	0.479	
DYSPNEA	Imiquimod	2	8464	0.024	1.000
	Placebo	1	3129	0.032	
FIBRILLATION ATRIAL	Imiquimod	12	8464	0.142	0.313
	Placebo	7	3129	0.224	
HYPOTENSION	Imiquimod	2	8464	0.024	0.296
	Placebo	0	3129	0.000	
MYOCARDIAL INFARCTION [Acute myocardial infarction]	Imiquimod	3	8464	0.035	1.000
	Placebo	1	3129	0.032	
MYOCARDIAL ISCHAEMIA	Imiquimod	0	8464	0.000	0.270
	Placebo	1	3129	0.032	
PAIN	Imiquimod	0	8464	0.000	0.270
	Placebo	1	3129	0.032	
PALPITATION	Imiquimod	9	8464	0.106	1.000
	Placebo	3	3129	0.096	
PULMONARY OEDEMA	Imiquimod	1	8464	0.012	1.000
	Placebo	0	3129	0.000	
SYNCOPE	Imiquimod	7	8464	0.083	1.000
	Placebo	2	3129	0.064	
TACHYCARDIA	Imiquimod	8	8464	0.095	1.000
	Placebo	2	3129	0.064	
TACHYCARDIA SUPRAVENTRICULAR	Imiquimod	0	8464	0.000	0.020
	Placebo	3	3129	0.096	
[Presyncope]	Imiquimod	1	8464	0.012	1.000
	Placebo	0	3129	0.000	
TACHYCARDIA VENTRICULAR [Ventricular tachycardia]	Imiquimod	2	8464	0.024	1.000
	Placebo	0	3129	0.000	

Source: Attachment 16, Appendix 6

Applicant did not find any imbalance between active and placebo group.

*Reviewer's comment: As acknowledged by applicant, this table does not contain all of the available data. However, with this large number of exposures, it is somewhat reassuring that events of interest are rarely occurring. It should be noted that for the most part, electrocardiographic monitoring was not included.*

3. Assessment of available data on the heart rate included reports of 2 studies where heart rate data and time matched imiquimod exposure data exist. One is already reviewed study R-837-009. Second study R-837-019 will be briefly summarized here.

That study was Phase 1 single blind, placebo-controlled, single oral dose study in 24 healthy male adults (18 received imiquimod tablet 100, 200 or 300 mg). Vital signs were recorded in 8 intervals from dosing to 48 hours later and some heart rate data are generated from periodic ECG tracings.

In both studies, some subjects had increase in heart rate was observed at 8 hours after oral administration up to 45 beats in comparison with the base line rate. There were no tachycardic (heart rate >100 beats or >25% from baseline) or bradycardic outliers.

*Reviewer's comment: Sample size is too small for any definite conclusion. Increase in the heart rate can be explained by induction of interferon  $\alpha$  which is known to cause tachycardia.*

(b) (4)

(b) (4)

**C. Other relevant information**

1. Safety information on subject 01/210

In the NDA 22-483 subject 01/210 from the trial 702 was listed as having ventricular tachycardia, not included in SAE category thus no narrative was provided.

Applicant's response on IR dated May 14, 2009 regarded this case reads as follows:

“...In May 2008 (during the follow-up observation period of study GW01-0702) the subject experienced palpitations. She reported this to her primary care physician on 28 May 2008 (day 99 of study GW01-0702). The primary care physician noted that her blood pressure was elevated and increased her lisinopril

from 5mg/day to 10 mg/day. An ECG demonstrated PVCs at about every 30 seconds and the subject was referred to a cardiologist. The subject was seen for the End of Study Visit on 29 May 2008. The cardiologist performed an outpatient cardiac ablation procedure on 9 June 2008 after which the subject was prescribed Toprol 25mg/day and was given external cardiac monitor. The subject reports that the external cardiac monitor is checked every 3 months and that she has had no further cardiac problems or symptoms...”

Per PI, event was defined as ventricular tachycardia, mild in intensity, on going, not serious and probably not related.

In the package provided for dispute resolution, applicant provided the following, up-dated explanation about the same case:

“.....On May 17, 2008-45 days after discontinuing imiquimod treatment-she experienced palpitations and syncope while driving and reported them to her primary care physician on May 28..... The follow-up information from the cardiologist indicated that the procedure was an electrophysiologic evaluation: no ablation was performed.....”

However, in the current submission, additional information related to cardiac evaluation reveals that subject did not have PVCs and cardiac ablation. Instead, she had car accident caused by syncope (date not provided). She had Holter monitoring (no dates provided) that registered one episode of non-sustained VT (date of the VT not provided). Based upon these events and family history of prolonged QT, EP study was performed on June 2008 that revealed inducible a-fib but not VT. Because of the unexplained nature of this serious event, patient received an implantable cardio-monitoring device (Reveal).

In reviewer’s opinion this case demands clear, consistent and well documented medical history evaluation. That could not be accomplished by currently available information. Thus, IR was sent to the applicant to provide dates of car accident/syncope, Holter monitoring and VT episode.

The requested information was received on February 16, 2010 (Attachment 3) and reads as follows:

“Listed below is a chronology of events regarding subject 01/210. This complete chronology is being provided as the details relayed by the subject have changed. ...The investigative site stressed that the subject refused to allow any further release of medical information from her primary care physician or cardiologist....  
...This new information from the subject suggests that the syncopal event occurred on 14 April 2008 (12 days post last application of study medication) and that the Holter monitor was in place 22-29 April 2008. The previous cardiology note mentioned that non-sustained VT was seen on a Holter monitor, presumably sometime during those dates, 20-27 days post last application of study medication. ‘

*Reviewer’s comment: It appears that exact chronology of this important event is not known (most of the latest information is based on subject’s recollection of the events). It appears that exact dates can not be determined secondary to patient’s refusal to release medical*

*documentation. The exact cause of syncope is unknown and the time relationship of imiquimod and syncope (and non-sustained VT) remains unknown because of inadequate documentation (per initial information syncope occurred on May 17, 2008; per the latest suggested date of occurrence is April 14, 2008).*

*However, objective information limitations do not provide sufficient reassurance for dismissal of this event.*

2. Applicant submitted sachet and carton labels that did not follow CMC recommended format.

#### **IV Conclusions:**

1. The applicant has provided sufficient clinical data to establish safety and efficacy of their drug product for topical treatment of actinic keratosis in adults.
2. Based on the provided report of the study R-837-009 and TQT/IRT consult, there is no need to further evaluate effect of imiquimod on cardiac repolarization.
3. The draft protocol synopsis for post marketing trial to further address potential link between imiquimod and cardiac arrhythmias needs substantial revision.
4. Draft labeling has been submitted and is under negotiation.

#### **V Recommendation on Postmarketing Actions:**

1. Risk Management activities  
There are no recommendations for a specific postmarketing risk management plan. Routine risk minimization measures such as professional labeling, prescription status, and spontaneous adverse event reporting, comprise an adequate risk management plan for this drug at this time.
2. Post Marketing Requirement  
Conduct 2-way cross-over trial in at least 100 subjects with actinic keratoses on the face to assess the effect of topical imiquimod on the cardiac rhythm. Zyclara 3.75% cream should be used as labeled, and event-monitoring (via external event recorder with loop recording capability) should be performed during all of the treatment phases (first and second 2-week treatment periods for both test articles).

## **VI References:**

1. Gibson TC, Heitzman MR. Diagnostic efficacy of 24-hour electrocardiographic monitoring for syncope. *Am J Cardiol* Apr 1;53(8):1013-7
2. Bass EB, Curtiss EI, Arena Vc et al. The duration of Holter monitoring in patients with syncope. Is 24 hours enough? *Arch Inter med* 1990 May;150(5):1073-8

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/

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MILENA M LOLIC  
03/12/2010

JILL A LINDSTROM  
03/12/2010

## Summary Review for Regulatory Action

<b>Date</b>	October 14 <sup>th</sup> , 2009
<b>From</b>	Susan J. Walker, M.D., F.A.A.D
<b>Subject</b>	Division Director Summary Review
<b>NDA #</b>	22-483
<b>Applicant Name</b>	Graceway Pharmaceuticals
<b>Date of Submission</b>	December 19 <sup>th</sup> , 2008
<b>PDUFA Goal Date</b>	October 19 <sup>th</sup> , 2009
<b>Established (USAN) Name</b>	Imiquimod
<b>Dosage Forms / Strength</b>	Cream 3.75%
<b>Proposed Indication(s)</b>	Actinic keratoses
<b>Action</b>	<i>Complete Response</i>

I concur with the review team recommendation for a “complete response” action for this submission based upon the lack of adequate information concerning the effect of the product on cardiac repolarization and heart rate. The applicant has not established that the systemic exposure to imiquimod will be less than that of the currently marketed product, therefore, I concur that the pre and post-marketing safety data for the approved product does not provide adequate information regarding the potential risk for cardiac adverse events. An adequate QT study with Holter monitoring should be completed prior to approval of this new dosing regimen for a non-lifethreatening condition for which many treatment modalities are available.

### Discussion:

The currently marketed imiquimod product labeling includes arrhythmias, reported under postmarketing experience. While the post-marketing imiquimod safety data does not raise an alarming signal, there are soft signs that indicate a direct potential effect of imiquimod on cardiac activity. These cases are detailed in the primary medical review, and include one documented case of supraventricular tachycardia with challenge, dechallenge, rechallenge effects and two cases of “self reported” tachycardia that resolved upon withdrawal of drug and recurred with rechallenge. These cases imply a temporal relationship, but no firm conclusions can be drawn from this information.

No ECG studies were performed in support of this application. The applicant did not perform a TQT study. One patient in study GW01-0702 experienced ventricular tachycardia and causal association with imiquimod therapy is indeterminate.

Consultation was obtained with the Division of Cardio-Renal Products. There is agreement that the key consideration is whether or not the new formulation will lead to an increase in systemic exposure compared to the currently available product, and that additional cardiac information may be useful if the new formulation has higher systemic exposure.

While the amount of imiquimod absorbed into systemic circulation after topical application for 3.75% cream to the face and/or scalp once daily for 21 days was low, the degree of relative

exposure of subjects to systemic imiquimod for the two formulations (3.75% and 5%) is unknown given their different dosing regimens and strengths. The current regimen proposes a lower strength dosed over a larger surface area, potentially leading to higher systemic exposure. The table below supports the concern that the 3.75% product applied daily to a large surface area will provide greater systemic exposure than the currently approved dosing regimen (5% applied 2x wkly).

Study	Strength	Dose regimen	Number of subjects	Site	Area	C <sub>max</sub> (ng/mL) Mean (SD)	AUC (ng-hr/mL) Mean (SD)
GW01-0706	3.75%	2pkt 7x/wk	17	Face or scalp	200cm <sup>2</sup>	0.323 (0.159)	5.974 (3.088)
1402-IMIQ	5%	1pkt 3x/wk	23	Face	25cm <sup>2</sup>	<b>0.120</b> <b>(0.063)</b>	<b>2.06 (1.70)</b>
		2pkt 3x/wk	11	Scalp	>25cm <sup>2</sup>	<b>0.214</b> <b>(0.097)</b>	<b>4.89 (4.41)</b>
		6pkt 3x/wi	24	UE	~300-400cm <sup>2</sup>	1.35 (0.841)	29.1 (17.1)
1520-IMIQ	5%	6pkt 2x/wk	13		>25%BSA	0.958 (1.18)	24.3 (26.9)

Source: adapted from NDA 22-483 2.7.2.3.2 pp10-11.

Source: (CDTL Review)

The risk-benefit assessment prior to approval of this application includes consideration of the benefits of therapy and the potential risks. The current submission does not propose treatment of a new indication and does not propose treatment of a new population. The application proposes a new dosing regimen for the same indication (actinic keratoses) and same population (adults). Actinic keratosis is not a serious or life-threatening condition and many treatment modalities are available. The proposed product does not answer an unmet medical need. The risks of this product have not been fully characterized, especially as related to cardiac function. I concur with the assessment of the clinical team that there is a need for additional data to inform the potential of the product to affect cardiac function. Although this study could be completed post-approval, based upon the clinical concerns it seems unwise to take an approval action prior to obtaining and reviewing this cardiac repolarization information. The information obtained from this study will inform the final agency decision and also product labeling.

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/s/  
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SUSAN J WALKER  
10/14/2009

## Cross-Discipline Team Leader Review

<b>Date</b>	9.23.2009
<b>From</b>	Jill Lindstrom, MD
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	22-483
<b>Applicant</b>	Graceway Pharmaceuticals, LLC
<b>Date of Submission</b>	12.19.2008
<b>PDUFA Goal Date</b>	10.19.2009
<b>Medical Officer</b>	Milena Lolic, MD
<b>Project Manager</b>	Kelisha Turner
<b>Proprietary Name / Established (USAN) names</b>	ZYCLARA/imiquimod
<b>Dosage forms / Strength</b>	Cream/3.75%
<b>Proposed Indication(s)</b>	Topical treatment of clinically typical, non-hyperkeratotic, non-hypertrophic actinic keratoses (AK) on the face or scalp in immunocompetent adults
<b>Recommended:</b>	<i>Complete Response</i>

### 1. Introduction

ZYCLARA (imiquimod) Cream, 3.75%, is a topical drug product for which the applicant seeks approval under Section 505 (b) (1) of the Federal Food Drug and Cosmetic Act for the topical treatment of clinically typical, non-hyperkeratotic, non-hypertrophic actinic keratoses (AK) on the face or scalp in immunocompetent adults. This memo will summarize the findings of the multi-disciplinary review team and provide the rationale for my recommended action.

### 2. Background

Imiquimod, an imidazoquinolinamine, is thought to be a toll-like receptor agonist that acts on TLR7 and induces the production of various cytokines including interferon alpha, interleukin-12, and tumor necrosis factor-alpha. Imiquimod is currently marketed in the US as a 5% cream under the tradename ALDARA. ALDARA received approval for the treatment of external genital warts (EGW) in 1997, and subsequently received approvals for the treatment of AKs in March 2004 and superficial basal cell carcinoma (sBCC) in July 2004.

The dosage regimen for ALDARA for the treatment of AKs is application of one packet to a treatment field of 25cm<sup>2</sup> on the face or balding scalp twice weekly for sixteen weeks. In the current application, the applicant seeks approval for a 3.75% cream (ZYCLARA) for the treatment of a larger field (entire face or balding scalp) using a dosage regimen of application of one or two packets to the treatment area once daily for two 2-week treatment cycles separated by a 2-week rest period.

AKs are dysplastic lesions of the epidermis that are thought to be induced by chronic ultraviolet radiation exposure. They are commonly found on the sun-exposed skin of fair-

complicated older adults. Clinically-typical AK lesions are yellow-to-red papules with a rough surface which may be more easily palpated than visualized. They may be tender or asymptomatic. Although AKs can progress to squamous cell carcinoma, the rate of malignant transformation is low. AKs may also resolve spontaneously.

### 3. CMC/Device

Dr. Agarwal found that the NDA contained sufficient information to assure the identity, strength, purity, and quality of the drug product. The components of the drug product are the same as those for the marketed product (5% cream), differing (b) (4) in the concentrations of imiquimod (from 5% to 3.75%) and isostearic acid (b) (4) and resultant (b) (4) in water content (b) (4).

Dr. Agarwal recommended a *Complete Response* from a CMC perspective as inspections by the Office of Compliance were not complete. Pending satisfactory completion of inspections by the Office of Compliance, there are no CMC issues which would preclude *Approval* of the NDA.

### 4. Nonclinical Pharmacology/Toxicology

At the 7.27.2007 Guidance meeting, the Agency confirmed with the sponsor that no new non-clinical studies would be needed beyond what were provided in NDA 20-723 for the approved ALDARA (imiquimod) Cream, 5%.

In the pharmacology studies reviewed under NDA 20-723, imiquimod was found to inhibit the autonomic nervous system and cause cardiac stimulation in beagle dogs (respiratory stimulation, analeptic activity, mild hypertension, moderate tachycardia, moderate to marked respiratory stimulation and increased pulse pressure). In ex vivo studies of isolated guinea pig myocardium, imiquimod caused a positive inotropic response and increased contractility at lower doses, with tachyphylaxis with repeat exposures and decreased response at high dose exposures. In 28 day and 6 month oral toxicity studies in cynomolgus monkeys (maximum dose 100mg/kg/d and 20mg/kg/d, respectively), no QTc prolongation was observed.

(b) (4) a related compound in development, (b) (4) another related compound in development, had a (b) (4)

In his review, Dr. Wang highlighted nonclinical findings that long-term systemic exposure to imiquimod results in immune system exhaustion leading to immunosuppressive effects, and the vehicle caused skin papillomas at the treatment site and enhanced UVR-induced skin tumor formation.

Drs. Wang and Hill did not recommend further nonclinical studies or phase 4 commitments, and recommended an *Approval* action from a pharmacological/toxicological perspective.

## 5. Clinical Pharmacology/Biopharmaceutics

ZYCLARA is a topical cream containing 3.75% imiquimod and intended for topical administration daily for two 2-week treatment cycles separated by a two week rest period for the treatment of clinically typical, non-hypertrophic, non-hyperkeratotic actinic keratoses.

The applicant conducted a pharmacokinetic study (GW01-0706) under maximal use conditions (two packets applied once daily to the entire face or balding scalp, an area of  $\sim 200\text{cm}^2$ ) in 19 subjects (17 evaluable) with at least 10 actinic keratoses in the treatment field; treatment was applied for three weeks. The median time to reach the maximum serum concentration ( $t_{\text{max}}$ ) in subjects with AKs was 9 hours. The median half-life ( $t_{1/2}$ ) of imiquimod was  $19.8 \pm 10.1$  hrs on Day 1 and  $29.3 \pm 17.0$  hrs on Day 21. Steady-state was reached between Day 7 and Day 14. The mean peak serum imiquimod concentration ( $C_{\text{max}}$ ) at the end of week 3 was 0.323 ng/mL, and  $\text{AUC}_{0-24}$  was 5.974 ng-hr/mL. Absorption was notably higher on the face ( $C_{\text{max}}$  0.354 ng/mL) than on the scalp ( $C_{\text{max}}$  0.096 ng/mL).

The applicant did not conduct a direct comparative bioavailability study of ALDARA and ZYCLARA. However, the applicant previously conducted a PK study (Study 1402-IMI) with ALDARA, which was dosed above labeled conditions, and obtained PK data in a long term safety study (1520-IMI), in which ALDARA was also dosed above the labeled dose. The results from Studies GW01-0706, 1402-IMI and 1520-IMI are summarized in the following table.

Study	Strength	Dose regimen	Number of subjects	Site	Area	$C_{\text{max}}$ (ng/mL) Mean (SD)	AUC (ng-hr/mL) Mean (SD)
GW01-0706	3.75%	2pkt 7x/wk	17	Face or scalp	200cm <sup>2</sup>	0.323 (0.159)	5.974 (3.088)
1402-IMI	5%	1pkt 3x/wk	23	Face	25cm <sup>2</sup>	<b>0.120 (0.063)</b>	<b>2.06 (1.70)</b>
		2pkt 3x/wk	11	Scalp	>25cm <sup>2</sup>	<b>0.214 (0.097)</b>	<b>4.89 (4.41)</b>
		6pkt 3x/wi	24	UE	$\sim 300\text{-}400\text{cm}^2$	<i>1.35 (0.841)</i>	<i>29.1 (17.1)</i>
1520-IMI	5%	6pkt 2x/wk	13		>25%BSA	<i>0.958 (1.18)</i>	<i>24.3 (26.9)</i>

Source: adapted from NDA 22-483 2.7.2.3.2 pp10-11.

All of the dose regimens for the 5% cream (in 1402-IMI and 1520 IMI) represent increases over the labeled dose regimen (increased frequency of application, increased area of application, increased amount applied per application, or combination). The first two dose regimens in Study 1402 (1pk 3x/wk to 25cm<sup>2</sup> facial skin, and 2pk 3x/wk to >25cm<sup>2</sup> scalp) resulted in lower  $C_{\text{max}}$  and AUC values (bolded in table above) when compared (cross-study) to the values for the 3.75% cream, even though these dose regimens represent increases over the labeled regimen for the 5% cream for treatment of actinic keratoses (1 pk 2x/wk to 25cm<sup>2</sup> face or scalp). Although based on cross-study comparison, the data suggest that the 3.75% cream applied per proposed labeling may result in greater systemic exposure than the 5% cream when used as labeled (1pk 2x/wk to 25cm<sup>2</sup> face or scalp). The most extreme dose regimen in study 1402-IMI, as well as the regimen in 1520-IMI, showed greater  $C_{\text{max}}$  and AUC values (italicized in the Table above) than those seen in study GW01-0706, but these dose regimens for the 5% cream represent marked increases (6-fold increase in amount per

application, 9 to 25 fold increase in area of application, 0 to 50% increase in application frequency) over the labeled dose. No ECGs were performed during these studies.

In the minutes for the PreNDA meeting, no agreement is documented regarding the applicant's assertion that there was no need for additional data to address the potential for QT interval prolongation. The applicant was referred to the ICH E14 guidance document, as well as to a previous answer regarding systemic exposure of the 3.75% versus 5% formulations.

No QT study or other assessment of the impact of the drug on cardiac repolarization was provided. The applicant did not perform ECGs in any of the studies in their development program. The applicant's rationale for not conducting a TQT study is that the systemic exposure from the 3.75% cream is less than that which was seen with the 5% cream (at suprathreshold doses) in studies IMIQ-1402 and IMIQ-1520, and that there is not a postmarketing signal for ventricular arrhythmia with ALDARA cream. Although the systemic exposure achieved in IMIQ-1520 with the 5% product used at suprathreshold doses may be higher (by cross-study comparison) than that seen with the 3.75% product, this does not address the concern regarding the impact of the moiety on cardiac repolarization because a) no cardiac monitoring was performed, b) the number of subjects is small, c) safety of the suprathreshold regimen has not been established, and d) comparative bioavailability is based on cross-study comparison. Additionally, as the applicant has not established that the 3.75% cream will result in lower systemic exposure than the 5% product used according to approved labeling, it is not possible to bridge to the postmarketing safety database to support the cardiac safety of this product.

Consultation was obtained from the QT Interdisciplinary Review Team. The QT-IRT consultant found that the applicant has not adequately addressed the potential of their product to impact cardiac repolarization and noted that the proposed dosing regimen for the 3.75% cream "will provide greater exposure compared to the approved dosing regimen of ALDARA 5% cream for actinic keratoses." The consultant recommended that OSE be consulted to review the postmarketing AE database, and that a TQT study be conducted if the Division had concern about the potential for the product to affect repolarization. Consultation was obtained from the Office of Surveillance and Epidemiology regarding cardiac adverse events in the postmarketing database; three cases of arrhythmia, including one case of supraventricular tachycardia with positive de- and re-challenge, were identified. Based on these cases, the OSE consultant concluded that "it is possible that imiquimod is associated with a risk of arrhythmia." Consultation was obtained from the Division of Cardiovascular and Renal Products regarding the proarrhythmic potential of imiquimod. The consultant advised that if there was potential for higher exposure from the new formulation, a TQT study should be performed.

Dr. Bashaw concluded that, "From a Clinical Pharmacology standpoint, the sponsor has met the requirements under 21 CFR 320 and the application is acceptable." I agree that the applicant has provided adequate information about the pharmacokinetics of their 3.75% product to inform labeling. I concur with Dr. Bashaw's conclusion that, "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.” As the applicant sought to rely on a bridge to the postmarketing safety database for ALDARA to support the safety of ZYCLARA with regard to cardiac repolarization, I do not find that the applicant has addressed the potential of ZYCLARA to cause cardiac repolarization. In addition to the lack of adequate comparative bioavailability data to bridge between the two products, I do not find that the studies conducted with suprathreshold dosing of ALDARA (IMIQ-1402, IMIQ-1520) are adequate to address the risk of cardiac repolarization from ZYCLARA, as no cardiac monitoring was performed in these studies.

I concur with the recommendation of Dr. Lolic, supported by the consults from the QT Interdisciplinary Review Team and the Division of Cardiovascular and Renal Products, that a thorough QT study should be obtained prior to approval to evaluate the impact of ZYCLARA on cardiac repolarization.

## **6. Clinical Microbiology**

Not applicable.

## **7. Clinical/Statistical- Efficacy**

During the development program, the applicant interacted with the Agency at four meetings:

- Guidance meeting, July 27, 2007
- Guidance meeting, October 31, 2007
- Guidance teleconference, November 7, 2007
- PreNDA meeting, November 26, 2008

No End-of-Phase 2 (EOP2) meeting was conducted for the indication of actinic keratoses, although an EOP2 meeting was held [REDACTED] <sup>(b) (4)</sup>. No Special Protocol Assessment was performed, and no agreement letter was issued.

The Agency consistently recommended that the applicant conduct phase 2 dose-range finding studies (see meeting minutes from 7.27.07, 10.31.07, and 11.7.07). The applicant declined to do so, and chose to study two different strengths (2.5% and 3.75%) and two different dosing regimens (two 2-week treatment cycles separated by a 2-week rest period, and two 3-week treatment cycles separated by a 3-week rest period) in Phase 3. In their briefing document for the 10.31.07 meeting, the applicant stated their intent to submit only, “one formulation (either 2.5% or 3.75%) at one dose regimen (either 2-week cycles or 3-week cycles)...in [the] NDA.”

At the Guidance meeting on 7.27.07, the Agency stated the need for recurrence data, and agreed to the applicant’s request to submit such data in Phase 4.

At the Guidance meeting on 10.31.07, the Agency recommended that primary endpoint be, “100% clearance of AK at efficacy assessment.”

At the teleconference on 11.7.07, the Agency advised that the study population be sufficiently “distinct from that for which the 5% product is indicated, such that labeling could describe the population for whom the new product and regimen would be intended.”

The applicant submitted data from two pivotal trials, Study GW01-0702 and Study GW01-0704 (hereafter 702 and 704, respectively), to establish the effectiveness of their product applied daily for two 2-week treatment cycles separated by a 2-week rest period in the treatment of actinic keratoses. Both trials were multi-center, prospective, randomized, double-blind, parallel-group studies with three arms: 2.5% imiquimod, 3.75% imiquimod and vehicle. The population enrolled were subjects 18 years of age and older with 5 to 20 non-hyperkeratotic, non-hypertrophic, AKs involving an area greater than 25cm<sup>2</sup> on either the face or balding scalp. In addition to the two pivotal trials, the applicant also submitted data from two supportive trials (703 and 705) which evaluated the same dosage strengths using two 3-week treatment cycles separated by a 3-week rest period.

The primary efficacy measure was AK lesion counts. The primary timepoint was 8 weeks after completion of treatment, which was week 14 in the pivotal trials and week 17 in the supportive trials due to the differing regimens. The primary efficacy endpoint was the complete clearance rate, defined as the proportion of subjects with no clinically visible or palpable AK lesions in the treatment area. The efficacy results, from Dr. Kathleen Fritsch’s review, are presented in the table below.

Complete Clearance Rates 8 Weeks Post-Treatment (ITT)

	ZYCLARA 2.5% cream	ZYCLARA 3.75% cream	Vehicle cream
Study 702	23.5% (19/81)	25.9% (21/81)	2.5% (2/80)
Study 704	38.0% (30/79)	45.6% (36/79)	10.1% (8/79)
Study 703	23.2% (12/82)	32.5% (26/80)	5.1% (4/78)
Study 705	26.8% (22/82)	35.4% (29/82)	5.8% (29/82)

Both concentrations at both dosing regimens were superior to vehicle in the proportion of subjects that achieved complete clearance of their AKs. The complete clearance rate was slightly higher for the 3.75% than the 2.5% strength. The data from the pivotal and supportive trials, detailed in the reviews by Drs. Lolic and Fritsch, allow a determination of efficacy.

## 8. Safety

The safety database is derived from five studies (two pivotal phase 3 studies, two supportive phase 3 studies, and a PK study), and includes 665 subjects exposed to imiquimod, 341 of whom received 3.75% cream (160 for 2-week cycles and 181 for 3-week cycles) and 324 of whom received 2.5% cream (160 for 2-week cycles and 164 for 3-week cycles). The safety database is adequate.

There were no deaths in the development program. There were 33 serious adverse events in 25 subjects, 12 in the 3.75% group, 9 in the 2.5% group, and 4 in the placebo group. Two SAEs, diarrhea and pancytopenia, were considered by the investigator to be probably related to study drug treatment. In her review, Dr. Lolic found the pancytopenia case to be confounded by the subject’s prior medical history and concomitant medication use (colchicine), but could not exclude an association with study drug.

The most common AEs were headache, local site reactions, fatigue and nausea. Local site reactions were more frequent and more severe in the 3.75% group vs the 2.5% group, and in the 3-week cycle group vs the 2-week cycle group. Collection of adverse event data and assessment of local tolerance did not reveal unexpected safety signals.

As discussed in Section 5 of this review, the applicant did not obtain ECGs in their development program. The applicant did not conduct a TQT study to assess the impact of their product on cardiac repolarization.

## **9. Advisory Committee Meeting**

The application was not presented at an Advisory Committee meeting. Imiquimod is not a new molecular entity; a 5% concentration of the drug product is approved for a similar indication. Review of the application did not identify novel issues which would merit Advisory Committee input.

## **10. Pediatrics**

Actinic keratoses are caused by chronic ultraviolet radiation exposure and occur almost exclusively in adults. Actinic keratoses are seen in children with xeroderma pigmentosa, a condition caused by defective DNA repair mechanisms, but this genodermatosis is rare. The applicant requested a waiver for all pediatric age groups on the grounds that pediatric studies would be impossible or highly impracticable because there are too few children with the disease/condition to study. The application was presented to the Pediatric Review Committee (PeRC) on June 24, 2009; PeRC agreed with the Division's recommendation to grant a complete pediatric waiver.

## **11. Other Relevant Regulatory Issues**

DSI audits were conducted but did not find deficiencies that would preclude reliance upon the data that was submitted.

## **12. Labeling**

The applicant requested a unique trade name, ZYCLARA, and a separate package insert for this new strength (3.75%) of imiquimod cream; the applicant already markets ALDARA (imiquimod) cream, 5%, for treatment of AKs (as well as EGW and sBCC). The Division of Medication Error and Prevention Analysis initially found this tradename unacceptable because of the potential risk for inadvertent concomitant use in patients being treated by different providers for different dermatologic conditions, which could result in increased adverse events. Specifically, concerns existed that patients could be independently prescribed ZYCLARA and ALDARA and use both products concomitantly on the same area, resulting in increased local adverse events, or use both products concomitantly on different areas resulting in increased systemic exposure and systemic adverse events. In a letter dated June 12, 2009, the Agency informed the applicant was informed their proposed tradename, ZYCLARA, was unacceptable because of this risk for medication errors. The applicant requested reconsideration of the tradename ZYCLARA, making the argument that the risks of

inadvertent concomitant use would be present with identical tradenames. DMEPA subsequently determined that the risks for inadvertent concomitant use could be addressed with labeling, and the tradename ZYCLARA was found acceptable. The letter communicating the acceptability of the tradename ZYCLARA was in clearance at the time of closure of this review, and had not been conveyed to the applicant.

Draft labeling had not been shared with the applicant at the time of close of this review. In addition to the carton and container labels, labeling includes professional (package insert) and patient (patient package insert) components. Review of the patient package insert by DRISK was pending at the time of close of this review.

### **13. Recommendations/Risk Benefit Assessment**

Recommended Regulatory Action: *Complete Response*

Risk Benefit Assessment: Actinic keratoses are not a serious or life-threatening condition. Treatment of actinic keratoses does not represent an unmet medical need, as there are multiple drug products approved for the indication. A new product for the treatment of actinic keratoses therefore can only provide a modest contribution to public health; and justifies only proportionately limited risk.

The comparative bioavailability of ZYCLARA (used per proposed labeling) and ALDARA (used as labeled) is unknown. The applicant has not adequately investigated the potential risk of ZYCLARA to cause cardiac adverse events. Therefore, in the absence of adequate information about the comparative bioavailability of ZYCLARA relative to ALDARA, or adequate data demonstrating that ZYCLARA does not affect cardiac repolarization, the potential risks of ZYCLARA are not justified by the potential benefits to patients with actinic keratoses of the face or scalp.

Recommended Comments to Applicant: The applicant should demonstrate the impact of their product on cardiac repolarization and heart rate through conduct of a thorough QT study with Holter monitoring.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22483

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ORIG-1

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GRACEWAY  
PHARMACEUTICA  
LS LLC

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IMIQUIMOD 3.75% CREAM

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JILL A LINDSTROM  
09/23/2009

## CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-483
Priority or Standard	Standard
Submit Date(s)	19 December, 2008
Received Date(s)	8 January, 2009
PDUFA Goal Date	19 October, 2009
Reviewer Name(s)	Milena M. Lolic, M.D.,M.S.
Review Completion Date	17 August, 2009
Review Revision Date	02 September, 2009
Established Name	Imiquimod 3.75% cream
(Proposed) Trade Name	Zyclara
Therapeutic Class	Immune response modifier
Applicant	Graceway
Formulation(s)	Topical cream
Dosing Regimen	Once daily for two 2- week cycles
Indication(s)	Actinic keratosis
Intended Population(s)	Adults older then 18 years

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

The recommendation on regulatory action is a COMPLETE RESPONSE. The lack of electrocardiographic studies precludes recommendation for approval of imiquimod 3.75% cream at this time.

Basis for “Complete Response” recommendation is as follows.

During a pre-NDA meeting that was held on October 28, 2008, it was concluded that a determination of the need to address the potential for QT/QTc interval prolongation for the new imiquimod cream concentration will be based on systemic exposure data and E14 guidance document.

The response from the sponsor to the Agency’s request from 74 Day Letter about the lack of TQT study in this submission was received on April 1, 2009. Sponsor’s explanation was that systemic exposure with imiquimod 3.75% cream is significantly lower than with Aldara® cream and that safety data of Aldara® cream provides enough reassurance about any effect on ventricular repolarization. However, safety data from post marketing Aldara® reports may not fully support the safety of imiquimod 3.75% cream for the following reasons:

- The comparison of systemic levels of imiquimod cream 3.75% to the levels produced by the 5% cream reveal a high degree of variability, with insufficient data to support sponsor’s argument about consistently lower systemic exposure to 3.75% cream therefore safety data from Aldara® use may not be applicable ([4.4 Clinical Pharmacology](#)).
- Post-approval AERS database for Aldara® contains 3 cases of supraventricular tachycardia with positive rechallenge and one case of unexplained sudden death raising the question about imiquimod’s pro-arrhythmic effect ([2.6 Other Relevant Background Information](#)) both, supraventricular and ventricular.

The need for EKG studies is further supported by:

-one case from this submission that involves poorly defined ventricular tachycardia where the causal relationship to imiquimod could not be excluded ([5.3.4 Review of Safety for Pivotal Trials GW01-0702 and GW01-0702](#)),and

-proven cardiac effect of related immunomodulators that was discovered in pre-clinical development ([2.4 Important Safety Issues with Consideration to Related Drugs](#)).

E14 document (Guidance for Industry Clinical Evaluation of QT/QTc Interval Prolongation and proarrhythmic Potential for Non-Antiarrhythmic Drugs) states that “evaluation of the effect of a drug on the QT interval would also be considered important if the drug or members of its

chemical or pharmacological class have been associated with QT/QTc interval prolongation, TdP, or sudden cardiac death during post marketing surveillance”.

Electrocardiographic studies were not done during the imiquimod development program, and the effect of imiquimod on cardiac repolarization and arrhythmias is unknown. Furthermore, there is one case of sudden cardiac death during post marketing surveillance of imiquimod.

In conclusion, in order to fully assess the safety profile of imiquimod 3.75% cream, the TQT studies with submission of interval and waveform data should be conducted prior to approval.

## 1.2 Risk Benefit Assessment

This assessment is provided solely on the basis of the data provided in this submission, regardless of recommendation on regulatory action.

The primary rationale for treatment of actinic keratosis is that actinic keratosis is considered premalignant lesion of squamous cell carcinoma.

Risk benefit assessment was based on analysis of pooled data from four randomized trials that utilized two different concentrations of the cream and two different dosing regimens.

Selection of the optimal dosing regimen, 2-week treatment cycles, was based on statistical comparisons of results of the pivotal studies (two 2-week treatment cycles) with the results of the supportive studies (two 3-week treatment cycles). The analyses showed that the longer treatment cycle did not provide significant improvement in efficacy and was associated with more adverse events. Thus, the dose regimen consisting of two 2-week treatment cycles provides a better choice compared to the regimen consisting of two 3-week treatment cycles.

In regard to two different concentrations, trials have shown that both concentrations were statistically superior to placebo when primary, secondary, or tertiary end points were analyzed.

The 3.75% cream had slightly higher observed clearance rates (on average about 5%) than the 2.5% cream but the results do not provide convincing evidence that 3.75% cream is clinically superior to 2.5% cream. Furthermore, number and intensity of adverse events tend to increase at the same rate for 3.75% cream, thus added efficacy does not outweigh the risk.

A once-daily dosing of 2.5% imiquimod cream is recommended in order to avoid additional exposure to active ingredient that is associated with increase in adverse events, both systemic and local.

## 1.3 Recommendations for Postmarketing Risk Management Activities

Potential approval of this product will result in the presence of two marketed products (Aldara and Zyclara) containing the same active ingredient in different concentrations. Inadvertent concomitant administration of both products is possible, increasing the frequency and possibly the severity of adverse events. Furthermore, erroneous application of one cream concentration for indication of another cream concentration may cause the same problem. In order to minimize medication errors, the Agency is considering appropriate labeling changes and REMS. Neither of recommendations was finalized before this review was completed.

#### 1.4 Recommendations for Postmarketing Studies/Clinical Trials

It is recommendation that the sponsor submits the data from the ongoing long term efficacy study reflecting AK recurrence rate.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

Imiquimod is the first topical imidazoquinoline. Imidazoquinolines are small molecules that have antiviral and anti-tumor activity that appears to be related to immune activation and modulation. Although the exact mechanism of action is not fully understood, imiquimod appears to mediate its effects via the activation of Toll like receptor 7 (Gibson, 2002) that is present on immune cells of different species including humans. This interaction induces a number of different cytokines including interferon  $\alpha$ , TNF  $\alpha$ , and interleukins 1, 6, 8 (Imbertson, 1998). Imiquimod has been found to be effective antiviral and antitumor agent in animal models (Testerman, 1995) presumably through this biologic activity.

Imiquimod was developed for the treatment of several skin disorders where activation of immune system was expected to be beneficial. First approval of imiquimod 5% cream in USA was in 1997 for the treatment of genital warts. Two more indications that were added in 2004: basal cell carcinoma and actinic keratosis.

### 2.2 Currently Available Treatments for Proposed Indications

Currently available treatment options for actinic keratosis (AK) include:

- lesion-directed-e.g., cryosurgery with liquid nitrogen, curettage (with or without electrodesiccation), resurfacing procedures (e.g., chemical peels, dermabrasion, laser resurfacing), photodynamic therapy (LevulanKerastick ). This therapy is suitable for treating solitary or few lesions,
- field directed therapy -e.g., topical 5-fluorouracil (5-FU) formulations, (e.g., Efidex, Carac), sodium diclofenac (Solaraze) gel, imiquimod 5% (Aldara). This therapy is suitable for more widespread lesions. Imiquimod 5% (Aldara) indication is limited to area of less than 25cm<sup>2</sup>.

In the U.S., cryosurgery with liquid nitrogen is probably the most widely used treatment for actinic keratoses (Dinehart SM, 2000). By some authors it is considered standard treatment for isolated AK lesions (Stockfleth, 2002). However it is less optimal for treatment of large surfaces. Topical therapy, such as 5-FU, is preferred approach to treatment of multiple actinic keratoses and generally involves treatment of fairly circumscribed regions rather than individual lesions. The advantage of field therapy is that it may also treat subclinical lesions and that is patient administered.

The sponsor's product would potentially add to the field directed therapy of actinic keratoses, extending the treatment area for imiquimod to > 25cm<sup>2</sup>.

### 2.3 Availability of Proposed Active Ingredient in the United States

Imiquimod cream 5% (Aldara®) is approved for three indications:

1. Treatment of external genital and perianal warts/condyloma acuminata in individuals 12 years old and above (February 27, 1997).
2. Topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp within surface area of <25cm<sup>2</sup> in immunocompetent adults (March 2, 2004).
3. Topical treatment of biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in adults with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured. (July 14, 2004).

### 2.4 Important Safety Issues with Consideration to Related Drugs

Imiquimod is the first generation imidazoquinoline. This class of drugs is referred to as immune response modifiers. Imiquimod's mechanism of action is not fully understood, however it up regulates the local production of cytokines, mostly interferon  $\alpha$ , tumor necrosis factor  $\alpha$ , and interleukin 6 (Tyring 2002), thus causing a pro-inflammatory response.

- Safety data from Aldara® label (when used for AK treatment) show that application site reactions are common. The most common local skin reaction is erythema (occurring in 97% of treated patients) and it is usually of moderate intensity. Severe forms of erythema occur in 18% of subjects. The next most common local skin reaction is combined category of flaking/scaling/dryness occurring in 93% of patients (severe form in 7% of patients). Systemic exposure as the result of the topically applied imiquimod is documented (Smith 2003). More frequent systemic reactions included in Aldara® label are: upper respiratory infections (15%), sinusitis (7%), and headache (5%). Flu-like signs and symptoms have been noted and may develop independently of local skin reactions.
- Systemically administered interferon  $\alpha$  (Roferon®-A) can cause: flu-like symptoms (e.g., fatigue, fever, and chills), nervous system effects (e.g., headache, dizziness), gastrointestinal effects (e.g., nausea/vomiting), and psychiatric effects (e.g., depression).

- (b) (4) is a second generation imidazoquinoline that is 100 times more potent cytokine inducer than imiquimod (Smith, 2003) (b) (4)
- (b) (4) (b) (4)

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Relevant pre-submission regulatory activity for imiquimod 3.75% for treatment of actinic keratosis was notable for the following:

- On July 27, 2007 a Guidance Meeting was held to provide general guidance for development of new strength of imiquimod cream for actinic keratosis, (b) (4) under 21 CFR 312. Agency comments in regard to treatment of AK included:
  - No additional nonclinical studies are required to support new strength of cream.
  - Additional Phase 2 dose ranging studies are recommended before proceeding to Phase 3. If the sponsor elects to follow multiple dosing regimens to Phase 3 (such as 2 week and 3 week periods) these should be evaluated within the same study rather than in separate studies so that the benefits and risks of different regimens can be directly compared. If different concentrations of the product are considered for the same indication (e.g. 2.5% and 3.75%) the one that shows the best efficacy and no worse safety than the comparators is the one that might be most appropriate for further development. Further, the sponsor will need to demonstrate how the 2.5% and 3.75% products compare to the approved 5% in the treatment of AK.
  - The primary endpoint should be the proportion of subjects with complete clearance of all AK (baseline and new) at efficacy assessment.
  - The development program should provide for the assessment of recurrence.
  - A full pediatric waiver may be acceptable provided a formal request with rationale.
  - For the new concentrations (2.5% and/or 3.75%) the sponsor requested a separate NDA and package insert from that of Aldara (5%). Agency recommended one NDA and one PI for one product and requested a rationale for sponsor's proposal.
- On October 1, 2007 a second Guidance Meeting was held to further assist in development program for lower strength and different dosing regimen for the treatment of actinic keartosis only. The sponsor proposed to conduct seven clinical studies to support marketing application:
  - a pharmacokinetic study under conditions of maximal use

- a study in which the approved dosing regimen for Aldara would be compared to the proposed new formulations and dosing regimens (the sponsor intends that this trial would be “supportive” and conducted in parallel with the Phase 3 trials)
- four randomized, double-blind, placebo-controlled Phase 3 studies identical in design except for duration of treatment and interval cycles
- a Phase 4 observational recurrence study in subjects who completely clear in Phase 3

Discussion included:

- PK maximal use study for the 3.75% imiquimod formulation is acceptable.
  - Agency does not concur with the sponsor’s plan to proceed directly to Phase 3 and acknowledges that the sponsor has accepted the risk of so doing.
  - The need to conduct dermal safety studies is under consideration.
  - The sponsor may be able to incorporate the assessment of long-term safety into the recurrence study.
  - A follow-up meeting (or teleconference) is recommended for continued discussion about the challenge to design the study in which the approved dosing regimen for Aldara would be compared to the proposed new formulations and dosing regimens.
- A teleconference was held on November 28, 2007. Agency comments included:
    - The population proposed for study with the new formulations should have disease of an extent to clearly warrant full face or scalp treatment and it should be distinct from that for which the 5% product is indicated.
    - Alternative to conducting a recommended Phase 2 studies might be to conduct one Phase 3 study with all four treatment arms ( 2.5%, 3.75%, 5% and placebo) and use this information to design a smaller second study with a reduced number of arms.
    - List of criteria for excluding subjects from per protocol population.
    - Limit the number of secondary endpoints
    - Dermal safety studies are not required for development of the lower-strength imiquimod cream formulation
- On October 29, 2008 a Pre-NDA Meeting was held. Discussion included:
    - The Agency agrees that sponsor could submit a new NDA. However, the proposed submission will be for a different strength of the active ingredient in a previously approved and marketed product and thus supplement is more appropriate.
    - Sponsor will submit with the sNDA/NDA full justification for different trade name. Agency’s position is that single label is most appropriate for this product and would most likely reduce the rate of medication errors. Agency will seek other consultation before making a final decision on this matter.
    - Agency agrees that study GW01-0803 will provide adequate information regarding recurrence.

- A determination of the need to address the potential for QT/QTc interval prolongation will be based on systemic exposure data and E14 guidance document.

## 2.6 Other Relevant Background Information

A post-marketing safety review completed in 2004 by the Office of Drug Safety described 12 cases of cardiac events and six cases of death in which an association between imiquimod and the events could not be ruled out. (b) (4)

. Total data base contained 1366 cases. Per report:

“Twelve cases reported cardiac events, including 4 cases of possible ischemia (chest pain-2, angina-1, myocardial infarction-1), 7 cases of arrhythmia (tachycardia-2, syncope-2, palpitation-1, sudden death-1, a fib-1), and 1 case of cardiomyopathy. This disparate set of cases included two cases of tachycardia with a positive rechallenge. The use of imiquimod could have contributed to these events”.

In the 6 cases of death, one subject was previously healthy 71 years old man who had a sudden death (found dead at home) and the remaining 5 cases were confounded due to co-morbidities and advanced age (CLL, malignant lymphoma, acute myeloid leukemia, 98 yr old with hemolytic anemia, an 83-year-old man with a history of Parkinson’s disease).

There were no labeling recommendations at that time.

During this review, a DVP consult was requested to review lymphoma, pancytopenia and cardiovascular adverse events of interest (ischemic heart disease, thromboembolic events and arrhythmias) with serious outcomes associated with imiquimod 5% cream. The AERS search retrieved 1630 total adverse events and did not suggest a compelling post-marketing safety signal for pancytopenia, lymphoma or ischemic CV disease. In regard to arrhythmias, the search identified one case (from 2006) that involves healthy 44 years old man with supraventricular tachycardia and positive rechallenge.

DVP reviewer concluded that “based on the case describing a positive rechallenge of a supraventricular tachycardia, it is possible that imiquimod is associated with a risk of arrhythmia; however, arrhythmias are currently listed in the imiquimod label...”

Since this review did not identify new post-marketing safety signals, DPV did not recommend labeling enhancements at this time.

### 3 Ethics and Good Clinical Practice

#### 3.1 Submission Quality and Integrity

The overall quality of the clinical information contained in this submission was acceptable.

#### 3.2 Compliance with Good Clinical Practices

The Sponsor states that all the trials were carried out in accordance with Good Clinical Practice (GCP) guidelines.

DSI inspections of selected clinical sites were requested, and included the inspection of Site 34 (Michael Jarratt, M.D., TX) and Site 30 (Zoe Draelos, M.D., High Point, NC).

Site 34 was selected by the Division based on high number of patients enrolled and the high number of treatment responders. Deficiencies found at this site, per DSI report, were: inadequate drug accountability (04) and inadequate and inaccurate records (06). A Form FDA 483 was issued to the investigator who responded adequately. The conclusion from the report was that “although regulatory violations were noted, they are not expected to have a significant adverse effect on study outcome. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.”

Site 30 was selected because of randomization problem. Dr. Zoe Draelos’ site did not use the IVRS (ClinPhone) to randomize 5 subjects and ‘self-randomized’ these subjects instead. The site also had large efficacy and no reported adverse reactions. Randomization deficiencies were confirmed during DSI inspection of the site and the conclusion was that “the subjects were randomized appropriately and received drugs to which they were randomized. No significant other issues were noted during the inspection and a Form FDA 483 was not issued. These studies appear to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.”

#### 3.3 Financial Disclosures

Financial disclosure forms were reviewed, and all but one Investigator reported no financial interests.

(b) (6), who participated in GW01-0704 study and enrolled (b) (6) disclosed more than \$25,000 as a consultant and speaker for Graceway.

In the opinion of this Reviewer, the results from 6 patients were not critical in determining efficacy or safety of imiquimod 3.75%, thus, any financial interests of the investigator would not affect the overall study results.

## 4 Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

From the CMC Review by Rajiv Agarwal, Ph.D :

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

The components of the drug product are the same as those for the approved product Aldara Cream, 5% (imiquimod). The imiquimod cream 3.75% differs only in the reduction of the concentrations of the active ingredient (imiquimod) from 5% to 3.75%, the (b) (4) of isostearic acid from (b) (4) and the concomitant (b) (4) in water content from (b) (4).

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. However, the final recommendation from the Office of Compliance involving all facilities pertaining to the cGMP inspections of drug substance and drug product manufacturing and testing operations is pending. Until a final recommendation is made by the Office of Compliance, the recommendation from a CMC perspective is a COMPLETE RESPONSE. If the Office of Compliance issues an ACCEPTABLE recommendation, then the NDA would be recommended for APPROVAL from a CMC standpoint.

### 4.2 Clinical Microbiology

There were no clinical microbiology data in this submission.

### 4.3 Preclinical Pharmacology/Toxicology

At the pre-NDA meeting, sponsor was advised that it may cross-reference nonclinical studies contained in NDA 20-723 (Aldara®) to support this submission. Consequently, no additional non-clinical toxicology studies were conducted. Please see the Pharmacology/Toxicology Review (by Jianyuong Wang, Ph.D.) for more detailed information on the non clinical data relevant to this NDA submission.

### 4.4 Clinical Pharmacology

The reader is referred to the Clinical Pharmacology review (by E. Dennis Bashaw, Pharm. D) for detailed review.

#### 4.4.1 Mechanism of Action

Although not fully understood, it appears that imiquimod mediates its effects via the activation of Toll receptor (TLR7). The primary mechanism of action appears to be through the induction of the cytokine INF- $\alpha$  at the treatment site. There are other cytokines and chemokines that are induced directly or indirectly following imiquimod treatment that may play role in its pharmacologic action such as TNF, interleukins, chemotactic and pro-inflammatory proteins.

#### 4.4.2 Pharmacodynamics

No pharmacodynamics trials were included in this submission.

#### 4.4.3 Pharmacokinetics

In addition to PK study GW01-0706 conducted with 3.75% imiquimod cream in support of this submission, sponsor submitted PK data from 2 previously completed trials with imiquimod 5% cream (1520-IMI and 1402-IMI). The purpose was comparison of systemic absorption levels between lower and higher concentrations of imiquimod formulations. Brief description of the GW01-0706 study is provided in section [7.2.5 Metabolic, Clearance, and Interaction Workup](#). The following table is provided for comparison purposes. Included are selected pharmacokinetic parameters from the three trials with available PK data pertinent to AK development program.

**Table 1 Summary of PK Data of Imiquimod for the Actinic Keratoses Clinical Program**

study-concentration	weekly dose	C-max-mean(SD)	AUC mean (SD)	site	area	N	duration of treatment	comment
GW01-0706 3.75%	131.25 mg	0.323(0.159)	5.974 (3.088)	face or scalp	>25cm <sup>2</sup>	17	3 weeks	Steady state after 2 weeks
1520 IMIQ 5%	150 mg	0.958 (1.18)	24.3(26.9)	head, torso and extremities	>25cm <sup>2</sup> up to >25% BSA	13	16 wks	Steady state after 1 month
1402-IMI 5%	37.5 mg *	0.120(0.06)	2.06 (1.7)	face	25 cm <sup>2</sup>	23	16 wks	
	75 mg **	0.214 (0.09)	4.89(4.41)	scalp	>25 cm <sup>2</sup>	11	16 wks	
	225 mg ***	3.53(6.52)	55.4(76)	hands and arms-3 pks on each side	300-400cm <sup>2</sup>	24	16 wks	

GW01-0706 2pks (18.75) daily-7 days/week-PK study

1520-IMI 1-6 pks (75mg) 2xweekly – from long term safety trial with 551 pts 1, 2, or 3 16 wk cycles

1402-IMI \*1pkt 12.5mg 3x weekly  
 \*\*2 pks (25 mg) 3x week  
 \*\*\* 6 pks (75mg) 3xweek

Within each trial, C<sub>max</sub> and AUC data show marked data variability evident from high standard deviations.

There is no direct, head to head comparison of the absorption of the 3.75% and 5% formulations. Comparison of the systemic exposure between these three trials (more precisely, between 5 dosing regimens) is difficult because of multiple variables that have to be considered such as cumulative weekly dose, surface area, dosing frequency, and the site of the treatment.

Pharmacokinetic parameters tend to increase with the dose, but it does not appear to be linear dose proportionality between C<sub>max</sub> and the applied dose, or between AUC and the applied dose. For example, in 1402-IMIQ trial, increase from 37.5 mg to 225 mg (six fold) resulted in almost 30 fold increase in C<sub>max</sub>.

One reason for the disparity may be the uncertainty of the surface area which is usually the key factor that affects percutaneous penetration of topical products. Second reason may be the site itself that is affecting absorption by the virtue of the different structure of the stratum corneum. From the clinical prospective the most comparable trial to GW01-0706 is 1402-IMIQ trial with 75 mg weekly dose (shaded area in the Table 1) which is showing lower systemic absorption of 5% cream when applied to scalp three times a week. In addition to previously mentioned reasons for variability, in this comparison different dosing intervals have to be considered as well. From a pharmacokinetic standpoint, there is low but detectable systemic absorption of imiquimod from the 3.75% cream. Comparison to levels produced by the 5% cream reveal a high degree of variability, most likely due to a combination of different dosing regimens and patient disease factors.

## 5 Sources of Clinical Data

### 5.1 Tables of Clinical Trials

The data reviewed were from trials conducted by the sponsor. There are total of 5 trials: 2 pivotal (GW01-0702 and GW01-0706), 2 supportive (GW01-0703 and GW01-0705) and one pharmacokinetic (GW01-0706). See Table 2 for a listing and summary of these trials (modified from sponsor's Table 2.7.4).

**Table 2 Summary of Trials of Imiquimod for the Actinic Keratoses Clinical Program**

Study Number/ Status	Number of Subjects	Treatments	Brief Study Description/Comments	IND Submission Date/Serial No.
GW01-0706 / Completed	19	Two packets applied to the entire face or balding scalp 3.75% IMIQ QD for 3 weeks	Pharmacokinetic study conducted under maximal use conditions in AK subjects. Study designed to demonstrate steady-state conditions.	Date: May 13, 2008 Serial No: 0161 AM 1: Sept 23, 2008 Serial No. 0168

GW01-0702 / Completed	242	Up to two packets applied to the entire face or balding scalp 2.5% IMIQ QD for two 2-week treatment cycles 3.75% IMIQ QD for two 2-week treatment cycles Placebo QD for two 2-week treatment cycles	Phase 3 study of the 2-week treatment cycle regimen (2 weeks on treatment, 2 weeks of no treatment, followed by 2 weeks on treatment). Primary endpoint of complete clearance at 8 weeks after treatment (Week 14; EOS)	Date: Jan 4, 2008 Serial No: 0154
GW01-0704 / Completed	237	Same treatments as Study GW01-0702	Duplicate of study GW01-0702 conducted at independent study centers.	Date: Jan 4, 2008 Serial No: 0154
GW01-0703 / Completed	240	Up to two packets applied to the entire face or balding scalp 2.5% IMIQ QD for two 3-week treatment cycles 3.75% IMIQ QD for two 3-week treatment cycles Placebo QD for two 3-week treatment cycles	Phase 3 study of the 3-week treatment cycle regimen (3 weeks on treatment, 3 weeks of no treatment, followed by 3 weeks on treatment). Primary endpoint of complete clearance at 8 weeks after treatment (Week 17; EOS)	Date: Jan 4, 2008 Serial No: 0154
GW01-0705 / Completed	250	Same treatments as Study GW01-0703	Duplicate of Phase 3 study GW01-0703 conducted at independent study centers.	Date: Jan 4, 2008 Serial No: 0154
GW01-0803 / Ongoing	>190	No treatment (long-term follow-up of AK recurrence)	Observational study of subjects who are completely clear at the End of Study visit in the four Phase 3 studies (GW01-0702, GW01-0703, GW01-0704, and GW01-0705).	Date: Apr 7, 2008 Serial No: 0160

## 5.2 Review Strategy

The two identical pivotal Phase 3 trials are reviewed in detail and presented in this section. These are GW01-0702 and GW01-0704. The design of the identical protocols is presented first. The discussion of individual clinical trial efficacy and safety results is presented afterwards.

Two supportive trials, GW01-0703 and GW01-0705, are reviewed in general and briefly presented in this section. The reason for abbreviated presentation is that sponsor is seeking approval based upon results from the trials utilizing shorter, 2-week regimen.

Review of the pharmacokinetic trial, GW01-0706, was deferred to Clinical Pharmacology. Only key review points are presented in section [7.2.5 Metabolic, Clearance, and Interaction Workup](#). However, all of the safety data from this trial are included in integrated safety analysis in section [7 Review of Safety](#).

Efficacy evaluation regarding this NDA is presented in section [6 Review of Efficacy](#) as a comparative review of the pooled data from the pivotal and supportive trials.

Safety evaluation regarding this NDA is presented in section [7 Review of Safety](#). The review includes all of the safety data from pivotal, supportive, and pharmacokinetic trials.

All of the data analysis is based on ITT population.

Current label for Aldara® 5% cream, published literature, internal FDA data and Clinical Review of NDA 20-723 SE 015 were used for reference.

### 5.3 Discussion of Individual Clinical Trials

#### 5.3.1 Design of Pivotal Trials GW01-0702 and GW01-0704

These two identical trials are Phase 3, randomized, double –blinded, placebo controlled, multicenter trials evaluating imiquimod cream for treatment of multiple AK on the face or scalp. The enrollment was planned for 240 adult patients per study with 5-20 visible or palpable AKs in the area that exceeded 25 cm<sup>2</sup> on either face or the balding scalp. Patients were randomized in a 1:1:1 ratio to 2.5% imiquimod cream, 3.75% imiquimod cream, or placebo cream. Trials were conducted between January 15, 2008 and July 3, 2008 in 26 US sites (13 each). There were no protocol amendments for either GW01-702 or GW01 -704 trials.

The design consisted of: screening period up to 4 weeks, first treatment cycle (2 weeks), no treatment period (2 weeks), second treatment cycle (2 weeks), and 8 weeks of no treatment. The overall trial design is represented in Table 3 (electronically copied and reproduced sponsor’s Table 2.5-2)

**Table 3 Design of Pivotal Trials**

Screening	Treatment Cycle 1			Treatment Cycle 2			Follow-up	End of Study
Week -4 to 0	Week 0	Week 1	Week 2	Week 4	Week 5	Week 6	Week 10	Week 14
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9

Note: A no-treatment period of 2 weeks occurred between the 2 treatment cycles.

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#### Trial Objective

The objective was to evaluate the efficacy and safety of 2.5 % imiquimod cream and 3.75% imiquimod cream v. placebo in the treatment of AK of the face or balding scalp.

#### Key Inclusion Criteria

Patients were eligible for trial participation if they were males or females 18 years of age and older, and:

- Had 5 to 20 typical visible or palpable AKs in an area that exceeded 25 cm<sup>2</sup> on either the face or the balding scalp (the treatment areas). The treatment area was either the full face (excluding ears) or the balding scalp, but not both;
- Were in good general health as confirmed by a medical history, physical examination, and laboratory tests at the screening visit;
- Were free of any significant findings (e.g., tattoos) in the treatment area;
- Were willing to eliminate tanning bed use and excessive sun exposure while in the study.

#### Key Exclusion Criteria

Patients were excluded from trial participation if they had any of the following exclusion criteria:

- Had any atypical keratoses (including hyperkeratotic, hypertrophic keratoses with an elevated component above the skin surface of 1 mm or more, or a surface area at the skin surface for an individual lesion of >1 cm<sup>2</sup>) within the treatment area;
- Had any dermatological disease and/or condition in the treatment or immediate surrounding area that might be exacerbated by treatment with imiquimod or cause difficulty with examination (eg, rosacea, psoriasis, atopic dermatitis, or eczema);
- Had melanoma anywhere on the body or a history of melanoma;
- Had a non-melanoma skin cancer in the treatment area within 90 days of treatment initiation;
- Had previously received treatment with imiquimod;
- Had any evidence of clinically significant disease.
- Had any AK treatment within 90 days prior to study initiation

#### Concomitant Medications

The following medications were prohibited during the trial: imiquimod 5% cream, interferon or interferon inducers, cytotoxic drugs, immunomodulators, immunosuppressants, oral or parenteral corticosteroids, topical steroids if greater than 2 g/day and any topical prescription medications in the treatment area.

All other medications were permitted for use during the trial, and were recorded on the case report forms (CRF).

#### Visits and Procedures

There were 9 visits during the trial as seen from the Table 4 (electronically copied and reproduced sponsor's Table 9-2).



the face or scalp. Two lower doses of imiquimod cream (2.5% and 3.75%) were selected for this application in order to allow both, daily dosing and treatment of >25cm<sup>2</sup> treatment area. Sponsor's intention was to avoid "a high incidence of severe application site reactions" that was reported with Aldara® cream when applied more than twice per week on < 25cm<sup>2</sup> area. Patients received study medication on Visit 2, supplied in study medication kit, packaged in single use packets containing 250 mg. Each treatment cycle kit contained two boxes of study cream, each containing a 1 week supply of creme (15 packets). Study staff monitored compliance on each visit by counting and recording any used and unused study packets.

Primary Efficacy Endpoint:

- Complete clearance rate, defined as the proportion of subjects at the Week 14 visit with no clinically visible or palpable AK lesions in the treatment area.

Secondary Endpoints:

- Partial clearance rate, defined as the proportion of subjects at the Week 14 visit with at least 75% reduction in the number of AK lesions counted at baseline in the treatment area.
- Percent change from Baseline to Week 14 in investigator counts of AK lesions.

Tertiary Efficacy variables:

- Complete clearance rate at interim study visits
- Partial clearance rate at interim study visits
- Change from baseline in actinic keratosis lesion counts at interim study visits
- Percent change from baseline in actinic keratosis lesion counts at interim study visits
- Time to complete clearance and to achieve partial clearance

Other efficacy variable:

- Investigator's Global Integrated Photodamage (IGIP) Score: At the end of the study, the investigator gave an overall assessment of the subject's change from baseline in photodamage in the treatment area based on the subject's appearance at the baseline visit. The IGIP score was summarized by frequency counts and mean score.

Safety Parameters were:

- Adverse reactions (AEs) including separate category of application skin reactions,
- Local skin reactions (LSRs),

- Number and duration of rest periods during the treatment period,
- Results of clinical laboratory tests
- Vital signs

Local skin reactions were assessed independently from AEs, and were recorded as AEs only if they extended beyond the immediate surrounding area (defined as 0.5 cm beyond the border of the treatment area), if they required any medical interventions, or if the LSR resulted in subject discontinuation from the study. Local skin reactions were defined and quantified as represented in Table 5 (electronically copied and reproduced sponsor’s Table 9-3).

**Table 5 Local Skin Reactions**

Local Skin Reaction	Severity Definitions			
	0	1 (Mild)	2 (Moderate)	3 (Severe)
Erythema	None	Faint to mild redness	Moderate redness	Intense redness
Edema	None	Mild visible or barely palpable swelling/induration	Easily palpable swelling/induration	Gross swelling/induration
Weeping/exudate	None	Minimal exudate	Moderate exudate	Heavy exudate
Flaking/scaling/dryness	None	Mild dryness/flaking	Moderate dryness/flaking	Severe dryness/flaking
Scabbing/crusting	None	Crusting	Serous scab	Eschar

Local Skin Reactions	Severity Definitions		
	0	1	2
Erosion/ulceration	None	Erosion	Ulceration

### Statistical Considerations

Per sponsor, statistical preparation, management, and analysis were the responsibility of TKL Research, Inc. The primary analysis of efficacy and safety was performed on the intent-to-treat (ITT) population with imputations for missing data points using last observation carried forward (LOCF).

Additional analysis was performed on per-protocol (PP) population that used observed cases only. PP population included compliant subjects from ITT population who completed the study without any significant protocol violations.

### 5.3.2 Demographics and Drug Exposure of Pivotal Trials GW01-0702 and GW01-0704

**Table 6 Number of Subjects in Analysis Populations GW01-0702 and GW01-0704**

	Populations	2.5%	3.75%	Placebo	Overall
GW 01-0702	ITT population	81	81	80	242
	PP population	75	73	70	218
GW 01-0704	ITT population	79	79	79	237
	PP population	67	68	72	207

*Comment: There were 242 patients enrolled in GW01-0702 trial and 237 patients enrolled in GW01-0704 trial. Analysis of raw data set reveals total of 238 entries in GW01-0704 trial and not 237 as per sponsor's report. The disparity was clarified with sponsor and it is the result of erroneous double entry for one subject.*

Patients were between the ages 36 and 90 and predominantly males with Fitzpatrick skin type I-III. Majority of patients underwent treatment of the face with approximately 11 AK lesions present. Data are presented in Tables 7 and 8.

**Table 7 Demographic characteristics of subjects - GW01-0702**

	2.5 % group	3.75% group	placebo	Total
Age (mean )	63.7	63.8	63.6	63.7
Sex (male)	72.8 %	85.2%	87.5%	81.8%
Fitzpatrick skin type I-III	83%	84%	85%	84%
Treatment area location (face)	75.3%	81.5	75%	77.3%
AK number (mean )	11.11	10.89	11.74	11.72

**Table 8 Demographic characteristics of subjects - GW01-0702**

	2.5 % group	3.75% group	placebo	Total
Age (mean )	65	65	65	65
Sex (male)	86.1%	79.7%	75.9%	80.6%
Fitzpatrick skin type I-III	84.8%	93.7%	91.1%	89.8%
Treatment area location (face)	70.9%	69.9%	74.7%	71.7%
AK number (mean )	10.77	11.16	10.82	10.9

*Comment: Demographic characteristics in both trials are comparable and probably reflective of the prevalence of this condition in general population. The distribution of AK lesions on the treatment area is not clear. Furthermore, no justification is provided for inclusion of patients*

*with 5-8 lesions for which other currently available treatments may be more suitable (e.g. cryotherapy). This subpopulation comprises 37.6 % and 37.4 % of each trial respectively. One subject had high number of base line AK (29) that is outside of inclusion criterion but was randomized. In reviewer's opinion this isolated event did not alter the results.*

### Subject Disposition

Total of 364 subjects were screened, and 242 (66.5%) were randomized in GW01-0702 trial. In GW01-0704 trial 328 subjects were screened, and 237 (72.3%) were randomized. Information about screening failures was provided. The most frequent reason for screen failure was that the subject did not have between 5 and 20 visible or palpable AK lesions on either the face or the balding scalp (47.5% and 50.5% respectively).

Total of 227 patients completed GW01-0702 trial. Fifteen patients did not complete the trial for the reasons presented in Table 9. Active arms had one subject each that did not complete the trial because of the safety reason.

**Table 9 Subject Disposition- GW01-0702**

Reason	2.5 % arm	3.75% arm	Placebo arm	Total
Safety	1(tachycardia, CP, HTN)	1 ( increased tremors)	2 (headache) (worsening migraine)	4
Subject's request (not due to AE)	1 (unknown)	3 (time constrain) (cosmetic appearance) (unknown)	2 (unknown) (unknown)	6
Concomitant medication		1		1
Lost to follow up	1	2	1	4
Total	3	7	5	15

Total of 226 patients completed GW01-0704 trial. 11 patients did not complete the study for the reasons listed in Table 10.

**Table 10 Subject Disposition-GW01-0704**

Reason	2.5 % arm	3.75% arm	Placebo arm	Total
Safety		<b>1 (fatigue, headache)</b>	1(tinnitus, uti)	2
Subject's request (not due to AE)	1 (unknown)	<b>1(local skin reaction)</b>	2 (unknown) (unknown)	4
Concomitant medication			1	1
Lost to follow up	1			1
Noncompliance		1		1
Other (not due to AE)	1(left town)	1(left town)		2
Total	3	4	4	11

*Comment: In reviewer's opinion, total of 7 subjects did not complete the trials for safety reasons and three of them were in placebo arm. Of the remaining four subjects, two had possibly imiquimod related AE (fatigue / headache and local skin reaction-in **bold letters**). Not all discontinuing subjects had investigator comments.*

*More comprehensive table (Table 31) includes additional subjects from pivotal trials that discontinued treatments for various AEs.*

### Concomitant Medications

Over 70% of the subjects in GW01-0702 and over 88% of subjects in GW01-0704 received one or more concomitant medications in this study. The most common were lipid modifying agents, ACE inhibitors, antiplatelet agents, and vitamins, followed by anti-inflammatory and anti infective products.

*Comment: It is likely that reported usage and type of medications is representative of the typical population with AK considering that median age of subjects was 65 years and that co-morbid conditions were the ones commonly seen in that age group. There were no meaningful distribution differences between groups.*

### Compliance with Study Medications

Expected total number of applications was 28. All subjects that received fewer than 21 applications of cream during the study (counting rest period days as application days) were considered noncompliant and excluded from PP population analysis. In GW01-0702 trial there were 13 subjects who met this criterion (1 in 2.5% arm, 5 in 3.75 % arm, and 7 in placebo arm). The total number of missed doses (ITT population) was 59 for 2.5% group, 63 for 3.75% and 40 for placebo group.

In GW01-0704 trial noncompliant subjects were: 1 in the 2.5% imiquimod treatment group, 4 in the 3.75% imiquimod treatment group, and 2 in the placebo treatment group. The total number of missed doses (ITT population) was 47 for 2.5% group, 80 for 3.75% and 55 for placebo group.

*Comment: Any expected dose that was not applied (either by error or not taken during the rest period) was considered missed dose for this calculation. Higher number of missed doses in 3.75% arm is suggestive of tolerability issue.*

### Dosing Information/Exposure

On average, subjects received 27.3 applications of 2.5% imiquimod, 26.2 applications of 3.75% imiquimod, and 26.8 applications of placebo during the study that lasted from 7-31 days (median 28 days for all three arms). Rest days and missed doses are not included in the count of application. See Table 29. Protocol allowed up to 2 packets per application (day). Median was 1.93 and ranges 1-2.14 packets per day for GW01-0702 and 0.93-2.36 packets per day for GW01-0704.

*Comment: There were no notable differences between the groups, although it is noted that subjects in the 3.75% imiquimod arm had an average of about one fewer application (27.3 v. 26.2) than subjects in the 2.5% imiquimod arm mainly because of the lesser use in the second cycle.*

#### Protocol Deviations and Violations

A total of 24 protocol deviations and one violation occurred during GW01-0702 trial. Most of deviations were related to the missed dose and/or missed visit within the visit window. All of these subjects are excluded from PP population analysis (6 from 2.5 % arm, 8 from 3.75 %, and 10 from placebo arm) prior to unblinding. One subject in 3.75% arm (13-225) who received cytotoxic drug within 28 days of enrollment was included in the PP population despite violation because this was discovered after unblinding.

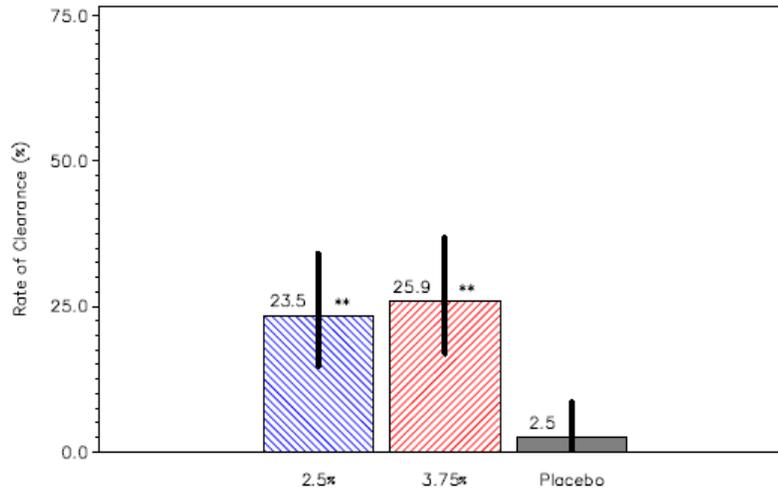
A total of 30 protocol deviations and 6 violations occurred during GW01-0704 trial .Most of deviations were related to the missed visit within the visit window and concomitant use of prohibited drugs. All of these subjects are excluded from PP population analysis (12 from 2.5 % arm, 11 from 3.75 %, and 7 from placebo arm) prior to unblinding. Five subjects were mis-randomized (Site 30) without use of the IVRS and one subject (Site 27) received the 3.75% kit instead of 2.5%. Sponsor included these 6 subjects in PP analysis stating that “blind was not compromised.”

*Comment: Center 30 in addition to randomization issues had the highest complete clearance rate for 3.75% imiquimod (5/5, 100%) among the centers. However, exclusion of this site from the primary efficacy analysis would not significantly alter the results (see statistical review).*

#### 5.3.3 Review of Efficacy for Pivotal trials GW01-0702 and GW01-0704

Primary end point was defined as complete clearance at the week 14 visit. In GW01-0702 trial this was achieved by 23.5 % subjects from 2.5% group, and by 25.9% from 3.75% group. In placebo group complete clearance was reached in 2.5% subjects. Refer to Figure 1 (electronically copied and reproduced sponsor’s Figure 11-1).

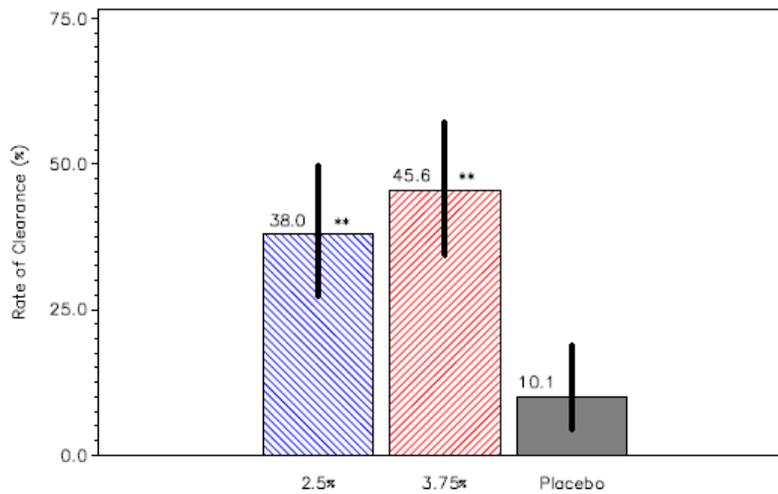
**Figure 1 Rates of Complete Clearance at Week 14 - ITT Population of GW01-0702**



Note: Bars marked with \*\* show statistically significant difference from placebo. Dark vertical lines represent 95% confidence intervals on the rates.

In GW01-0704 trial, results were higher in each arm showing 38%, 45.6%, and 10.1% clearance rate for 2.5%, 3.75%, and placebo groups respectively. See Figure 2 (electronically copied and reproduced sponsor's Figure 11-1).

**Figure 2 Rates of Complete Clearance at Week 14 ITT Population of GW01-0704**



Note: Bars marked with \*\* show statistically significant difference from placebo. Dark vertical lines represent 95% confidence intervals on the rates.

*Comment: In both trials, both active arms showed superiority over placebo ( $p < 0.001$ ). The reason for overall higher clearance rates (in all three arms) in GW01-0704 is not clear. This is further explained in section 6.1.4 Analysis of Primary Endpoint.*

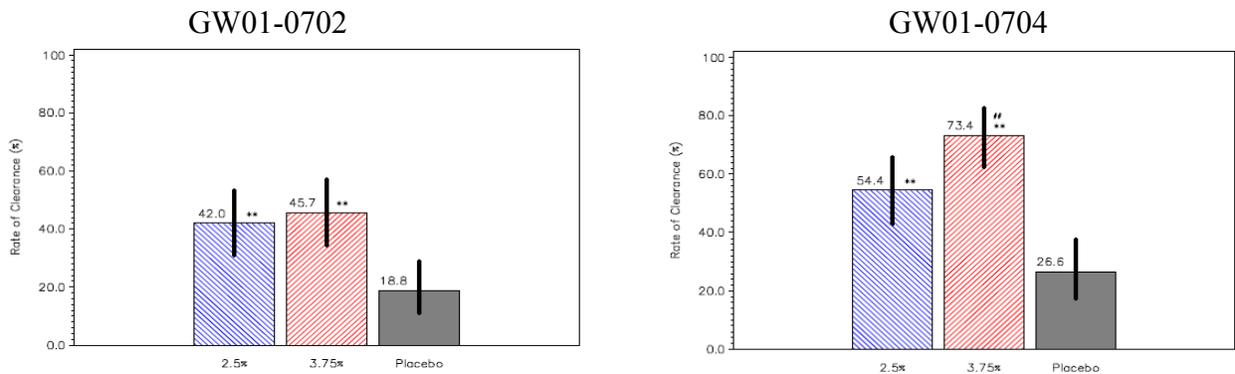
Secondary endpoints analysis includes two outcomes:

1. Partial clearance rate (defined as at least a 75% reduction in the number of AK lesions in the treatment area compared with baseline), and
2. Percent change from baseline to end of study in AK lesion counts.

Results are presented in graphic form below (reproduced from sponsor's Figures 11-2 and 11-3).

For both trials, partial clearance rate was significantly higher in active treatment arms v. placebo. This time the efficacy was also significantly higher in 3.75% arm v. 2.5% arm but only in GW01-0704 trial.

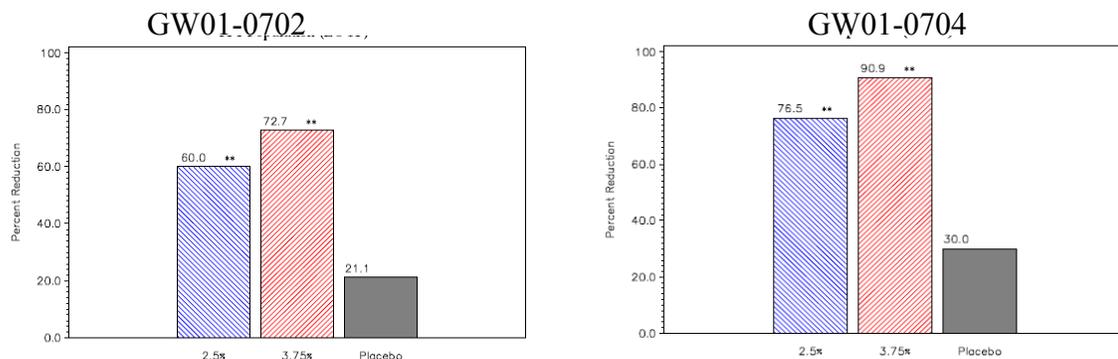
**Figure 3 Rates of Partial Clearance at Week 14- GW01-0702 and GW01-0704 (End of Study - ITT)**



\*\* significantly different ( $p < 0.001$ ) from placebo  
# significantly different ( $p = 0.014$ ) from 2.5% arm

In both trials, both active arms were superior to placebo in reducing the number of AK lesion at week 14. Higher efficacy overall is seen in GW01-0704. There was a trend of higher efficacy for 3.75% imiquimod cream in the same trial, but the difference did not reach statistical significance ( $p = 0.06$ ).

**Figure 4 Percent Change from Baseline to end of Trials in AK Lesion Counts GW01-0702 and GW01-0704**



\*\* significantly different ( $p < 0.001$ ) from placebo

Results of tertiary variable analysis as well as IGIP scores supported primary efficacy findings- both treatments were statistically significantly superior to placebo (data reviewed, but not presented).

Analysis of efficacy across trials is provided in section [6 Review of Efficacy](#).

#### 5.3.4 Review of Safety for Pivotal Trials GW01-0702 and GW01-0702

##### Death and Serious Adverse Events (SAEs)

There were no deaths reported during study GW01-0702. There were 9 **serious** adverse events (SAEs) reported by 7 patients, as follows:  
2 pneumonias, 2 small intestinal obstructions and one of each: acute myocardial infarction, noncardiac chest pain, cerebrovascular accident, atrial fibrillation and prostatitis. Distribution among groups was as follows: 4 events in 2.5%, 3 in 3.75%, and 2 in placebo group.  
One case of pneumonia was community acquired and second developed postoperatively (after knee replacement). One case of myocardial infarction developed during the course of pneumonia in an 81 y old patient with history of hypertension, hyperlipidemia and LBBB. Cerebrovascular accident developed in patient with history of atrial fibrillation and TIA. It is unclear from the case narrative whether atrial fibrillation was reoccurrence or increased rate only. One patient with SBO had previous episode of obstruction secondary to colorectal cancer and colostomy. Second patient developed SBO 32 days after last treatment and while taking high dose opiates for chronic back pain.

*All of these events were considered unrelated to the imiquimod treatment by investigators. The reviewer is in agreement with that assessment. The events did not require discontinuation of the treatment and resolved without sequale.*

*Case review: The reviewer requested additional information from the sponsor regarding one patient from 2.5% arm (01/210), who experienced ventricular tachycardia assessed by investigator as non serious event of mild intensity.*

*Per received report, patient initially received pharmacologic intervention followed by cardiac ablation for ventricular arrhythmia (type of arrhythmia is poorly specified). It is unclear whether defibrillator was implanted but patient is undergoing assessment every three months ("external cardiac monitoring"). In reviewer's opinion this event should be included in SAE. Overall, the received report was not detailed enough, but causal relationship to imiquimod could not be excluded.*

There were no deaths reported during study GW01-0704. There were 5 **serious** adverse events (SAEs) reported by 5 patients, as follows:  
2 chest pains and one of each: anxiety, atrial fibrillation, and diarrhea. Distribution among groups was as follows: 2 events in 2.5%, 3 in 3.75%, and 0 in placebo group. All resolved without sequelae.

One of the reported SAE (diarrhea) was considered to be related to the treatment (3.75% imiquimod) and required discontinuation of the product. One case of chest pain required stent placement. That subject had history of previous coronary stent placement and this event occurred 46 days after completion of the study. Second case of chest pain occurred in 65 years old female with previous coronary angioplasties. Catheterization revealed non obstructive CAD. The event occurred 19 days after completion the study. Subject who experienced atrial fibrillation also had a history of recurrent palpitations, atrial flutter and paroxysmal atrial fibrillation.

Case review of the treatment related AE: One subject in 3.75% arm (36/415) developed nausea and diarrhea that required hydration in ER. Subject was not admitted to the hospital. One week later, same subject was admitted because of nausea, weakness, tiredness and acute renal failure. Initial creatinine was 2.9, but subsequently was found to be a laboratory mistake. Subject improved on hydration.

*Comment: In the absence of definitive etiology for this event, it is reasonable to consider it related to imiquimod cream exposure.*

*All other reported conditions are common at this age group. Narratives of the events were reviewed. The reviewer is in agreement with the investigators' assessments considering the other events unrelated to imiquimod cream.*

#### Severe Adverse Events

In GW01-702 trial ten subjects experienced AE (total of 16) that were categorized **severe** by investigators. Distribution of these events was as follows: 9 in 2.5 % group (oral herpes, sinusitis, pneumonia, application site infection, bacterial pneumonia, application site irritation, pruritic rash, procedural pain, and cartilage injury), 3 in 3.75% group (cerebrovascular accident, gout, and atrial fibrillation), and 4 in placebo group(urinary tract infection, abdominal pain, intestinal obstruction, and back pain).

One subject had 2 severe AE (application site irritation and application site infection). He completed the study with additional medication prescribed.

*Comment: In reviewer's opinion application site AE and pruritic rash were treatment related.*

In GW01-704 trial seven subjects experienced 14 AE that were categorized **severe** by investigators. Distribution of these events was as follows: 9 in 2.5 % group (bronchiectasis, influenza-like illness twice, cheilitis, lymphadenopathy twice, angina pectoris, atrial fibrillation, and arteriosclerosis), 5 in 3.75% group (influenza-like illness, chest pain, diarrhea, vascular graft, and anxiety) and 0 in placebo group.

*Comment: The following subjects had treatment related severe AE per reviewer's opinion:*

*- subject (34/421 in 2.5% arm) is of particular interest because he had total of 5 severe AE (2 influenza like illnesses, 2 lymphadenopathies and cheilitis). It appears that his lymphadenopathy*

*and influenza like illness reoccurred after restarting of temporary interrupted treatment. There was no narrative for this subject.*

*-subject from 3.75% imiquimod group who had influenza like illness.*

*-subject from 3.75% imiquimod group (previously described in SAE section) who had diarrhea.*

*Described presentations are representative of imiquimod- related immune system modulation.*

### Common Adverse Events

More than 30% of all subjects experienced treatment emergent adverse events. In GW01-702 trial the most common were URI, application site pruritus and headache. In GW01-704 trial headache, nasopharyngitis and application site pruritus and irritation were the most common followed by arthralgia, influenza like illness and lymphadenopathy.

**Table 11 Number (%) of Subjects with Most Frequent Treatment-Emergent Adverse Events - GW01-702**

(>2% for any group presented by preferred term from sponsor's table 12-3)

	<b>2.5%(N=81)</b>	<b>3.75%(N=81)</b>	<b>Placebo(N=80)</b>
Subjects with any AE, n (%)	35 (43.2%)	40 (49.4 %)	29 (36.3 %)
Upper respiratory tract infection	3 ( 3.7)	4 ( 4.9)	5 ( 6.3)
Application site pruritus	3 (3.7)	2 (2.5)	1 (1.3)
Headache	2 (2.5)	1 (1.2)	3 (3.8)
Nasopharyngitis	2 (2.5)	2 (2.5)	2 (2.5)
Back pain	0	2 (2.5)	3 (3.8)
Application site pain	2 (2.5)	2 (2.5)	0
Fatigue	2 (2.5)	2 (2.5)	0
Nausea	1 (1.2)	1 (2.50)	2
Oral herpes*	4 (4.9) *	0	0
Sinusitis	2 (2.5)	0	2 (2.5)
Urinary tract infection	0	2 (2.5)	2 (2.5)
Application site irritation	2 (2.5)	1 (1.2)	0
Basal cell carcinoma	0	1 (1.2)	2 (2.5)
Hypertension	2 (2.5)	0	1 (1.3)
Influenza like illness	3 (3.7)	0	0
Pain	0	3 (3.7)	0
Pharyngolaryngeal pain	2 (2.5)	0	1 (1.3)
Pneumonia	2 (2.5)	0	1 (1.3)
Anorexia	0	2 (2.5)	0
Cheilitis	2 (2.5)	0	0
Dermatitis	0	2 (2.5)	0
Herpes simplex	0	2 (2.5)	0
Joint sprain	0	0	2 (2.5)
Rhinitis	2 (2.5)	0	0

\* AE with significantly higher frequency (p<0.05) than placebo

**Table 12 Number (%) of Subjects with Most Frequent Treatment-Emergent Adverse Events - GW01-704**

(>2% in any group presented by preferred term from sponsor's table 12-3)

	2.5%(N=79)	3.75%(N=79)	Placebo(N=79)
Subjects with AE, n (%)	35 (44.3)	37 (46.8)	24 (30.4)
Headache *	1 (1.3)	9 (11.4) *	2 (2.5)
Nasopharyngitis	2 (2.5)	2 (2.5)	6 (7.6)
Application site pruritus*	3 (3.8)	5 (6.3) *	0
Application site irritation *	2 (2.5)	4 (5.1)*	0
Arthralgia*	4 (5.1)*	2 (2.5)	0
Fatigue*	0	5 (6.3) *	0
Lymphadenopathy	3 (3.8)	2 (2.5)	0
Nausea *	0	5 (6.3)*	0
Dizziness *	0	4 (5.1)*	0
Cough	2 (2.5)	0	2 (2.5)
Diarrhea	2 (2.5)	2 (2.5)	0
Influenza like illness	3 (3.8)	1 (1.3)	0
Pyrexia*	0	4 (5.1)*	0
Urinary tract infection	0	2 (2.5)	2 (2.5)
Application site pain	0	3 (3.8)	0
Bronchitis	3 (3.8)	0	0
Chest pain	0	3 (3.8)	0
Herpes simplex	0	2 (2.5)	1 (1.3)
Squamous cell carcinoma	0	2 (2.5)	1 (1.3)
Anorexia	0	2 (2.5)	0
Diabetes mellitus	0	0	2 (2.5)
Food poisoning	0	2 (2.5)	0
Vomiting	0	2 (2.5)	0

\* AE with significantly higher frequency (p<0.05) than placebo

*Comment: Most of the reported AEs are in concurrence with those reported for Aldara®. Overall, frequency of specific AEs was low, but some reached statistical significance:*

▪ *Arthralgia and oral herpes occurred more frequently in 2.5 % imiquimod groups than in placebo.*

▪ *Same comparison for 3.75% imiquimod group reveals the following AEs: headache, application site pruritus, application site irritation, fatigue, nausea, dizziness, and pyrexia. Interestingly, all of these events were reported only in the second pivotal trial. The reason for this disparity between two pivotal trials is unclear. Clinical importance of these separate events is that most of them may be linked to imiquimod action through it's activation of immune response. It appears that development of these AE is dose dependent.*

Distribution of the adverse events by system organ class revealed infections and infestations as being the most common. Distribution between different arms was similar in both trials. Second most common system organ class was general disorders and administration site conditions. In GW01-702 trial active groups had much higher frequency of AE then placebo (in 2.5% group 12/81 or 14.8%, in 3.75 % group 11/81 or 13.6% v. placebo 4/80 or 5%).

Similarly in GW01-704 trial for general disorders and administration site conditions AE were reported by 8/79 subjects or 10.1% in 2.5% group, 19/79 subjects or 24.1% in 3.75% group and 0 in placebo group.

*Comment: Significantly higher number of AE for active groups v. placebo (p<0.05) in general disorders and administration site organ class was reported earlier and thus is not unexpected.*

### Application Site Adverse Events

Adverse events at the application site for pivotal trials are further presented below in Tables 13 and 14. (modified from sponsor's Table 12-6)

**Table 13 Number (%) of Subjects with Application Site Adverse Events - GW01-702**

	2.5% (N=81)	3.75% (81)	Placebo(N=80)
Subjects with any Application Site AE, n (%)	6 ( 7.4)	6 ( 7.4)	2 ( 2.5)
Application site pruritus	3 ( 3.7)	2 ( 2.5)	1 ( 1.3)
Application site pain	2 ( 2.5)	2 ( 2.5)	0
Application site irritation	2 ( 2.5)	1 ( 1.2)	0
Application site paraesthesia	0	1 ( 1.2)	1 ( 1.3)
Application site infection	1 ( 1.2)	0	0
Application site scar	0	1 ( 1.2)	0
Application site swelling	0	1 ( 1.2)	0

*Comment: Analysis of application site adverse events in GW01-702 trial revealed more AE in active treatment groups with pruritus being the most common. Only one subject developed local infection (from 2.5% group). Results are comparable to site reactions associated with other imiquimod formulation.*

**Table 14 Number (%) of Subjects with Application Site Adverse Events - GW01-704**

	2.5% (N=79)	3.75% (79)	Placebo(N=79)
Subjects with any Application Site AE, n (%)	4 ( 5.1)*	11 ( 13.9)*	0

Application site pruritus*	3 ( 3.8)	5 ( 6.3)*	0
Application site pain	0	3 ( 3.8)	0
Application site irritation *	2 ( 2.5)	4 ( 5.1)*	0
Application site infection	0	0	0
Application site scar	0	0	0
Application site dryness	1(1.3)	0	0
Application site swelling	0	1 ( 1.2)	0

\* AE with significantly higher frequency (p<0.05) than placebo

*Comment: In GW01-704 trial more subjects in active arms (four and eleven, respectively) experienced application site adverse events than in placebo arm (no AE were reported). The difference is statistically significant (p<0.05) for each arm v. placebo. Overall, more AE were observed in 3.75 % arm then in 2.5% suggesting dose dependant pattern..*

### Local skin reactions

Local skin reactions were assessed independently of the “application site reaction” to further describe specifics of skin AEs. According to predetermined categories and severity scale, local skin reactions for pivotal trials are presented in Tables 15 and 16 (source: sponsor’s Table 12-6). For comparative purposes, mean scores for each LSR are presented in [Table 35](#).

**Table 15 Frequency Distribution of Most Intense Post-baseline Local Skin Reactions in the Treatment Area - ITT Population for GW01-702**

Type of Reaction	Intensity	2.5% (N=81)	3.75%(N=80)	Placebo(N=80)
Erythema	0=None	3 ( 3.7)	2 ( 2.5)	15 (18.8)
	1=Faint to mild redness	19 (23.5)	4 ( 5.0)	47 (58.8)
	2=Moderate redness	47 (58.0)	50 (62.5)	18 (22.5)
	3=Intense redness	12 (14.8)*	24 (30)*	0
	> 0 (any reaction)	78 (96.3%)*	78 (97.5%)*	65 (81.3%)*
Edema	0=None	21 (25.9)	10 (12.5)	66 (82.5)
	1=Mild visible/barely palpable swelling/ induration	31 (38.3)	33 (41.3)	13 (16.3)
	2=Easily palpable swelling/induration	25 (30.9)*	32 (40.0)*	1 ( 1.3)
	3=Gross swelling/induration*	4 ( 4.9)*	5 ( 6.3)*	0
	> 0 (any reaction)	60 (74.1%)*	70 (87.5%)*	14 (17.5%)*
Weeping/Exudate	0=None	53 (65.4)	37 (46.3)	78 (97.5)
	1=Minimal exudate	20 (24.7)*	27 (33.8)*	2 ( 2.5)
	2=Moderate exudate	7 ( 8.6)*	13 (16.3)*	0
	3=Heavy exudate	1 ( 1.2)	3 ( 3.8)	0
	> 0 (any reaction)	28 (34.6%)*	43 (53.8%)*	2 (2.5%)*
Flaking/Scaling/ Dryness	0=None	9 (11.1)	6 ( 7.5)	15 (18.8)
	1=Mild dryness/flaking	42 (51.9)	30 (37.5)	48 (60.0)
	2=Moderate dryness/flaking	28 (34.6)	37 (46.3)	16 (20.0)
	3=Severe dryness/flaking	2 ( 2.5)	7 ( 8.8)*	1 (1.3)

	> 0 (any reaction)	72 (88.9%)	74 (92.5%)	65 (81.3%)
Scabbing/Crusting	0=None	17 (21.0)	5 ( 6.3)	46 (57.5)
	1=Crusting	24 (29.6)	21 (26.3)	32 (40.0)
	2=Serous scab	34 (42.0)*	44 (55.0)*	2 ( 2.5)
	3=Eschar	6 ( 7.4)*	10 (12.5)*	0
	> 0 (any reaction)	64 (79.0%)	75 (93.8%)	34 (42.5%)
Erosion/Ulceration	0=none	45 (55.6)	33 (41.3)	73 (91.3)
	1=Erosion	31 (38.3)	41 (51.3)	7 (8.8)
	2=Ulceration	5 (6.2)*	6 (7.5)*	0
	>0 (any reaction)	36(44.4%)*	47 (58.8%)*	7 (8.8%)

\*AE with significantly higher frequency (p<0.05) than placebo

**Table 16 Frequency Distribution of Most Intense Post-baseline Local Skin Reactions in the Treatment Area - ITT Population for GW01-704**

Type of Reaction	Intensity	2.5% (N=79)	3.75%(N=79)	Placebo(N=79)
Erythema	0=None	3 ( 3.8)	3 ( 3.8)	20(25.3)
	1=Faint to mild redness	22 (27.8)	18 ( 22.8)	45 (57)
	2=Moderate redness	43 (54.4)	42 (53.2)	14 (17.7)
	3=Intense redness	11 (13.9)*	16(20.3)*	0
	> 0 (any reaction)	76 (96.2%)	76(96.2%)	59 (74.7%)
Edema	0=None	38 (48.1)	29 (39.2)	62 (78.5)
	1=Mild visible/barely palpable swelling/ induration	25 (31.6)	31 (39.2)	16 (20.3)
	2=Easily palpable swelling/induration	14 (17.7)*	15 ( 19)*	1 (1.3)
	3=Gross swelling/induration	2 ( 2.5)	4 (5.1)*	0
	> 0 (any reaction)	41 (51.9%)	50 (63.3)	17 (21.5)
Weeping/Exudate	0=None	44 (55.7)	41 (51.9)	75 (94.9)
	1=Minimal exudate	26 (32.9)*	27 (34.2)*	4 (5.1)
	2=Moderate exudate	8 (10.1)*	5 (6.3)*	0
	3=Heavy exudate	1 (1.3)	6 (7.6)*	0
	> 0 (any reaction)	35 (44.3)*	38 (48.1)*	4 (5.1)
Flaking/Scaling/ Dryness	0=None	10 (12.7)	6 (7.6)	21 (26.6)
	1=Mild dryness/flaking	36 (45.6)	42 (53.2)	41 (51.9)
	2=Moderate dryness/flaking	28 (35.4)	25 (31.6)	16 (20.3)
	3=Severe dryness/flaking	5 (6.3)*	6 (7.6)*	1 (1.3)
	> 0 (any reaction)	69 (87.3)	73 (92.4)	58 (73.4)
Scabbing/Crusting	0=None	8 (10.1)	5 (6.3)	41 (51.9)
	1=Crusting	30 (38)	25 (31.6)	35 (44.3)
	2=Serous scab	32 (40.5)*	37 (46.8)*	3 (3.8)
	3=Eschar	9 (11.4)*	12 (15.2)*	0
	> 0 (any reaction)	71 (89.9)	74 (93.7)	38 (48.1)
Erosion/Ulceration	0=none	31 (39.2)	27 (34.2)	72 (91.1)
	1=Erosion	38 (48.1)*	41 (51.9)*	7 (8.9)
	2=Ulceration	10 (12.7)*	11 (13.9)*	0
	>0 (any reaction)	48 (60.8)*	52 (65.8)*	7 (8.9)

\* AE with significantly higher frequency (p<0.05) than placebo

*Comment: In both trials erythema was the most frequent LSR in all three groups (more than 96% of subjects in each active group). Erythema was also the reaction that was more commonly intense (grade 3) than any other reaction. Most LSR were mild to moderate severity. All other LSR have been reported more frequently in active groups than placebo. The distribution of most intense scores (grade 3) between the imiquimod and placebo treatment groups were significantly different for both of the dosing regimens ( $p < 0.05$ ) in both trials. More frequently severe reactions were seen with 3.75% concentration. This table does not provide the timing of LSR development.*

Rest period is defined as a temporary interruption of dosing due to intolerable local skin reactions (perceived either by patient or investigator). It is distinct from pre-defined “no-treatment” intervals between treatment cycles. Missing dose due to a subject’s non-compliance with the treatment regimen was not considered a rest period.

**Table 17 Summary of Rest Periods for GW01-702**

	2.5% (N=81)	3.75% (N=80)	Placebo (N=80)
Subjects requiring rest period in either cycle n (%)	5 (6.2)*	7 (8.6)*	0 (0)
No. of dosing days missed due to rest periods, mean ± SD	2.6 ± 1.7	5.3 ± 4.7 0	0 (0)

\* significantly different ( $p < 0.05$ ) than placebo

*Comment: There was significantly higher number of subjects on rest periods in active groups v. placebo. There was no significant difference between 2.5 % group (5 subjects) and 3.75% (7 subjects)  $p = 0.549$ . Number of days missed due to rest periods doubled in 3.75% group but did not reach statistical significance ( $p = 0.252$ ).*

**Table 18 Summary of Rest Periods for GW01-704**

	2.5% (N=79)	3.75% (N=79)	Placebo (N=79)
Subjects requiring rest period in either cycle n (%)	6 (7.6)*	10 (12.7)*	0 (0)
No. of dosing days missed due to rest periods, mean ± SD	4.3 ± 2.1	8.2 ± 5.7	0 (0)

\* significantly different ( $p < 0.05$ ) than placebo

*Comment: Similar distribution was observed in the second pivotal study. Both active treatments required rest periods, and placebo group did not. Higher number of subjects required rest periods and missed more days in 3.75% imiquimod group in comparison to 2.5% group.*

Laboratory values and vital signs

Complete laboratory tests and vital signs measurements were done twice during the trial, at the screening and at the last visit.

Vital signs largely remained within reference range. Only pyrexia occurred more frequently in imiquimod arm than in placebo (4 subjects in 3.75% arm v. 0 in placebo). Other outliers were one subject in 2.5% group with elevated blood pressure together with angina pain and atrial fibrillation and one subject in each active arm with tachycardia and bradycardia, respectively. Abnormal laboratory values were more frequent, but scattered: 2 subjects had elevated glucose levels, and there were one subject each with elevated triglycerides, hypercholesterolemia, hypocalcemia and hypokalemia.

Each trial has one case of thrombocytopenia. In GW01-702 subject 05/226 who was treated with 2.5% imiquimod dropped platelet count from 212,000 at screening to 139,000 at the end of the study. In GW01-704 trial subject 30/413 (placebo group) was enrolled with WCC of 2.62 and platelets of 71,000. At the end of the trial WCC was 2.47 and platelets were 46,000. One subject had decreased white cell count.

*Comment: Decrease in red cells, white cells, or platelets have been reported previously with Aldara®. Interested reader is referred to the current label and to the OSE consult.*

Summary of Safety Evaluation of Pivotal Trials GW01-702 and GW01-704

More than 91% of the subjects in each of treatment groups were compliant.

There were no deaths in either trial.

Summary of safety parameters (ITT population) is presented in Table 19 (modified from sponsor's Table 5.3.5.3.2-8).

**Table 19 Summary of Safety Parameters for Pivotal Trials per Treatment Arm**

Safety parameter, n (%)	2.5%	3.75%	Placebo
Total in Population	160	160	159
Requiring Rest Period	11 (6.9) <0.001	17 (10.6) <0.001 0.235	0 (0.0)
Discontinuing the Study Prematurely for Any Reason	6 (3.8) 0.420	11 (6.9) 0.655 0.213	9 (5.7)
Discontinuing the Study Prematurely for Safety Reasons	1 (0.6) 0.311	2 (1.3) 0.647 0.562	3 (1.9)
Any Adverse Event	70 (43.8) 0.056	77 (48.1) 0.007 0.432	53 (33.3)

Any Treatment-Related Event	19 (11.9) 0.001	31 (19.4) <0.001 0.065	4 (2.5)
Any Application Site Reaction	10 (6.3) 0.019	17 (10.6) <0.001 0.159	2 (1.3)
Any Serious Adverse Event	6 (3.8) 0.155	5 (3.1) 0.255 0.759	2 (1.3)
Any Severe Adverse Event	8 (5.0) <0.05	6 (3.8) 0.155 0.428	2 (1.3)
Any Severe LSR	33 (20.6) <0.001	54 (33.8) <0.001 0.008	2 (1.3)

Note: count reflects number of subjects in each treatment group. A subject was counted once only in each row of the table. In blue p value v. placebo; in green p value v. 2.5% arm

Adverse events were reported in dose dependent pattern – 48.1%, 43.8%, and 33.3% of the subjects in 3.75%, 2.5% imiquimod and placebo groups respectively experienced at least one AE.

Vast majority were unrelated to the treatment and mild-moderate in intensity. The most common adverse events were headache, respiratory events (nasopharyngitis, upper respiratory tract infection, influenza-like illness), application site reactions, and arthralgia, fatigue, nausea, and dizziness.

In regard to system organ class, AE occurred more frequently in “infections and infestations” and “general disorders and administration site conditions” system organ class.

The difference between active treatment groups and placebo group was statistically significant (p<0.05) for “general disorders and administration site conditions” system organ class.

Treatment-related AEs exhibited dose response as well: vehicle had the lowest rates (2.5%), followed by 2.5% imiquimod (11.9%) and 3.75% imiquimod (19.4%). The difference between each active treatment and placebo group was statistically significant. Higher number of subjects in active arms reported application site AEs, fatigue, headache, lymphadenopathy and influenza like illness than placebo.

Serious adverse events (SAEs) were rare. One of the reported SAE (diarrhea) was considered to be related to the treatment (3.75% imiquimod) and required discontinuation of the product. One subject experienced poorly described ventricular tachycardia event. Causality to 2.5% imiquimod cream could not be excluded.

Severe AE occurred in 8 subjects from 2.5% arm, 6 subjects from 3.75% arm, and 2 subjects from placebo arm. Some subjects experienced multiple severe AE. Total number of severe AE was 30. Treatment related severe AE were: influenza-like illness (4 occurrences), lymphadenopathy (2 occurrences), and application site reactions (2 occurrences). One subject in 2.5% arm had total of 5 severe AE due to reoccurrence of influenza like illness and lymphadenopathy. All of the subjects completed the trial.

Application site reactions were significantly higher in each active group than in placebo group. Pruritus was the most common treatment related AE in both pivotal trials ([Table 34](#)).

Severe local skin reactions and number subjects requiring rest periods showed dose dependent relationship with 3.75% treatment group leading.

There was no evidence of clinically meaningful trends in vital signs or clinical laboratory measurements. Elevated temperature occurred more frequently in 3.75% arm than in placebo.

Review of the adverse event datasets revealed that in general, safety profile reported in these pivotal trials is acceptable and similar to Aldara® cream. Higher number of subjects in active arms reported application site AEs, fatigue, headache, lymphadenopathy and influenza like illness than placebo. Some of these reactions were severe in intensity and in one instance reoccurred after restarting the treatment.

Trend was observed towards more AEs in 3.75% imiquimod group. Only in Severe LSR category the difference between two active groups was statistically significant.

### 5.3.5 Summary and Conclusions for Pivotal Trials GW01-0702 and GW01-0704

The analysis of primary and secondary end points in both trials demonstrated that treatment of AK with imiquimod cream was superior to placebo ( $p < 0.001$ ). The 3.75% cream had slightly higher observed clearance rates than the 2.5% cream. It should be noted that sponsor chose to proceed with Phase 3 without carrying out dose ranging studies as strongly recommended by FDA. The safety profile was acceptable, however it appears that higher concentration of imiquimod leads to higher rate of AEs especially local skin reactions some of which were worrisome enough to warrant more rest periods and missed days. Thus overall, the results of the trials demonstrate that patients with 5-20 AK lesions on the either face or balding scalp (on  $> 25\text{cm}^2$ ) significantly improved with imiquimod treatment during 2- 2 week cycles with better tolerability of 2.5% cream. These results support the approval of 2.5% imiquimod cream.

### 5.4.1 Design of Supportive Trials GW01-0703 and GW01-0705

The two supportive trials were identical in design to the pivotal trials except for the length of the treatment cycles and the intervening no-treatment period (3 weeks instead of 2 weeks). The trials consisted of screening period up to 4 weeks, first treatment cycle (3 weeks), no treatment period (3 weeks), second treatment cycle (3 weeks), and 8 weeks of no treatment. Both concentrations of imiquimod cream, 2.5 % and 3.75%, were used in both cycles of supportive trials.

Reader is referred to the appropriate parts of the section [5.3.1 Design of Pivotal Trials GW01-0702 and GW01-0704](#) for an overview of the protocol.

#### 5.4.2 Review of Efficacy for Supportive Trials GW01-0703 and GW01-0705

Number and characteristics of the enrolled subjects were comparable to pivotal trials (see [Table 28](#)). Exposure to the drug was higher in supportive trials secondary to longer treatment cycles.

The ITT population consisted of 164 subjects in 2.5% arm, 162 subjects in 3.75 % arm, and 164 subjects in placebo arm (combined trials).

Imiquimod cream was superior to placebo in treating AK. In GW01-0703 trial primary end point -complete clearance of AK was achieved in 23.2% of subjects treated with 2.5% cream and in 32.5% of subjects treated with 3.75% cream in comparison to placebo group where success rate was 5.1% (p< 0.001 for both concentrations). For GW01-0705 trial complete clearance rate was slightly higher in all three arms -26.8%, 35.4% and 5.8%, respectively. Secondary end points analysis showed similar superiority of active treatments versus placebo.

**Table 20 Efficacy for Supportive Trials GW01-0703 and GW01-0705**

<b>End point</b>	<b>2.5%</b>	<b>3.75%</b>	<b>Placebo</b>
<b>complete clearance</b>			
GW01-0703	19/82 (23.2%)	26/80 (32.5%)	4/78 (5.1%)
GW01-0705	22/82 (26.8%)	29/82(35.4%)	5/86 (5.8%)
<b>partial clearance</b>			
GW01-0703	38/82 (46.3%)	45/80 (56.3%)	9/78(11.5%)
GW01-0705	32/82 (39%)	42/82 (51.2%)	12/86 (14%)
<b>median % change from baseline</b>			
GW01-0703	-66.7	-82.3	-23.6
GW01-0704	-66.7	-78.9	-22.5

#### 5.4.3 Review of Safety for Supportive Trials GW01-0703 and GW01-0705

All the data pertinent to safety evaluation of these two trials is presented in section [7 Review of Safety](#) where pooled data across regimens is analyzed. Briefly, active arms in supportive trials had higher number of AE in comparison to the respected arms in pivotal trials. For common AE ([Table 38](#)) the difference is approximately 7% and for the treatment related AE ([Table 37](#)) 15 % for each active treatment arm. Application site reactions and severe local skin reactions had even larger difference ([Table 39](#)). These results led to sponsor’s decision to select 2 week-cycle treatment for approval.

#### 5.4.4 Summary and Conclusions for Supportive Trials GW01-0703 and GW01-0705

Treatment with both concentrations of imiquimod resulted in significant improvement of AK lesions ( $p < 0.001$  v. placebo) when primary and secondary end points were analyzed. The safety profile was acceptable, however there was higher number of treatment related adverse events in supportive trials than in pivotal trials leading to conclusion that 2 week treatment cycle should be considered for approval.

## 6 Review of Efficacy

### Efficacy Summary

Analysis of pivotal trials showed that both imiquimod cream concentrations, 3.75% and 2.5% were effective as the topical treatments for actinic keratosis of the face or balding scalp. Primary endpoint defined as complete clearance rate at Week 14 visit was achieved in 35.6% of subjects treated with 3.75% cream ( $p < 0.001$  v. placebo) and in 30.6% of subjects treated with 2.5% cream ( $p < 0.001$  v. placebo).

There was no statistical significant difference in direct comparison of two concentrations when primary end point was analyzed ( $p = 0.379$ ).

Response rates were higher across all three arms in GW01-0704 pivotal trial without reasonable explanation.

Subpopulation analysis revealed that efficacy was not significantly impacted by gender, age or treatment area. However, slightly higher response rates were observed in women, and in the treatment of the face.

There were two secondary end-points selected. First one was Partial clearance rate, defined as the proportion of subjects at the Week 14 visit with at least 75% reduction in the number of AK lesions counted at baseline in the treatment area. Second was Percent change from Baseline to Week 14 in counts of AK lesions. Both concentrations were superior to placebo ( $p < 0.001$ ) but this time 3.75% cream had minimal statistical advantage over 2.5% ( $p < 0.048$ ). See [Table 24](#).

Three week cycles utilized in supportive trials did not provide higher efficacy in comparison to 2 week cycles.

In summary, efficacy of imiquimod cream over placebo was proven for both concentrations in all endpoints. There was a trend observed of somewhat higher efficacy rate for 3.75% arm, but clinical importance of that trend is not clear.

## 6.1 Indication

The sponsor is proposing that imiquimod 3.75% receive the following indication: for the topical treatment of clinically typical visible or palpable actinic keratoses of the face or balding scalp in immunocompetent adults.

### 6.1.1 Methods

The separate reviews of the two phase 3 pivotal trials (GW01-0702 and GW01-0704) submitted to this application are presented in section [5.3.3 Review of Efficacy for Pivotal trials GW01-0702 and GW01-0704](#). The combined efficacy results across pivotal trials will be discussed in this section.

Efficacy analysis from supportive trials (GW01-0703 and GW01-0705) will be presented for comparison only.

### 6.1.2 Demographics

The ITT population for GW01-0702 trial was 242 and for GW01-0704 237 subjects. There were no notable differences in demographic characteristics between either arms or trials. For details, please refer to [Table 7](#) and [Table 8](#).

### 6.1.3 Subject Disposition

Approximately 5 % of subjects dropped out of trials GW01-0702 and GW01-0704. There was no single dominant reason and distribution across arms was comparable (see [Table 9](#) and [Table 10](#)).

### 6.1.4 Analysis of Primary Endpoint

The primary endpoint was complete clearance rate, defined as the proportion of subjects at the Week 14 visit with no clinically visible or palpable AK lesions in the treatment area.

Efficacy versus vehicle was demonstrated for both concentrations ( $p < 0.001$ ) in both trials.

Combined trials success rate was 30.6% for 2.5% group and 35.6% for 3.75% rate.

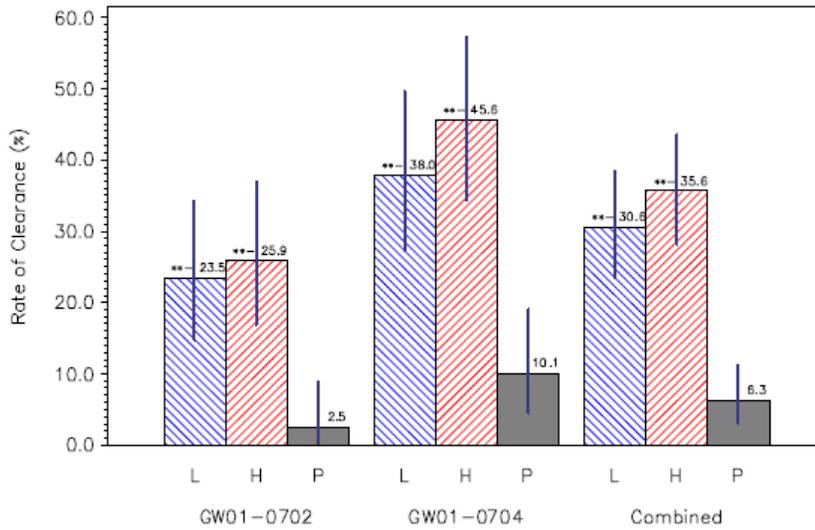
Data are presented in tabular (Table 21) and a graphic form (Figure 5- reproduced sponsor's Figure 5.3.5.3.1.1).

**Table 21 Complete Clearance Rates at Week 14- Combined Pivotal Trials**

<b>trial</b>	<b>2.5%</b>	<b>3.75%</b>	<b>Placebo</b>
GW01-0702	19/81 (23.5%)*	21/81 (25.9%)*	2/80 (2.5%)
GW01-0704	30/79 (38%)*	36/79 (45.6%)*	8/79 (10.1%)

\* significantly different ( $p < 0.001$ ) than placebo

**Figure 5 Complete Clearance Rates at Week 14-Combined Pivotal Trials**

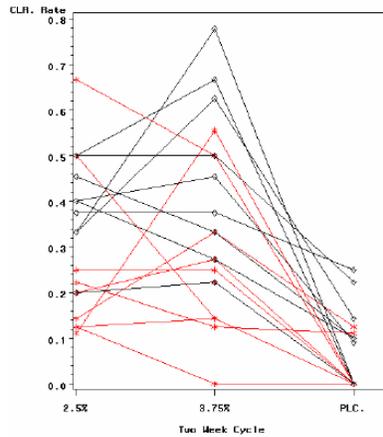


L= 2.5% group H=3.75% group P= placebo  
\* significantly different (p<0.001) than placebo

*Comment: Response rates in all treatment groups in trial GW01-0704 were higher in comparison with GW01-0702. The reason for higher response rates in trial GW01-0704 is not clear. Analysis by investigational site reveals that trial GW01-0704 seems to have a higher number of “responder sites” (ie, sites with greater rates of complete clearance) - See Figure 6 (modified Figure 1 from Appendix to Section 5.3.5.3.1 – ISE).*

*Multiple reanalysis by statistical reviewer did not reveal a credible and significant reason for this difference. However, the results of the two pivotal trials will need to be listed separately in the label.*

**Figure 6 Complete Clearance Rate by Site**



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Note: Red star labeled lines represent trial sites in GW01-0702 while the black diamond labeled lines represent sites in GW01-0704 trial.

### 6.1.5 Analysis of Secondary Endpoints

Partial clearance was defined as at least a 75% reduction in the number of AK lesions in the treatment area at week 14 compared with Baseline. Efficacy versus vehicle was demonstrated for both concentrations ( $p < 0.001$ ) in both trials.

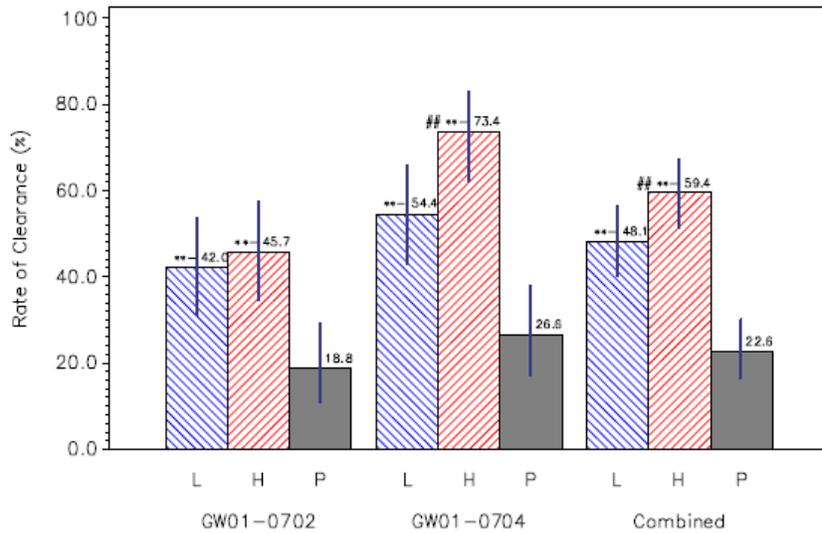
Combined trials success rate was 48.1% for 2.5% group and 59.4% for 3.75% group. The difference between two active arms was statistically significant ( $p < 0.05$ ).

Data are presented in tabular (Table 22) and a graphic form (Figure 7- reproduced sponsor's Figure 5.3.5.3.1.2).

**Table 22 Partial Clearance at Week 14-Combined Pivotal Trials**

trial	2.5%	3.75%	Placebo
GW01-0702	34/81 (42.0%)	37/81 (45.7%)	15/80 (18.8%)
GW01-0704	43/79 (54.4%)	58/79 (73.4%)	21/79 (26.6%)

**Figure 7 Partial Clearance at Week 14-Combined Pivotal Trials**



L= 2.5% group H=3.75% group P= placebo  
 \* significantly different (p<0.001) than placebo  
 ## significantly different from 2.5% arm (p=0.014) for GW01-0704  
 ## significantly different from 2.5% arm (p<0.05) combined

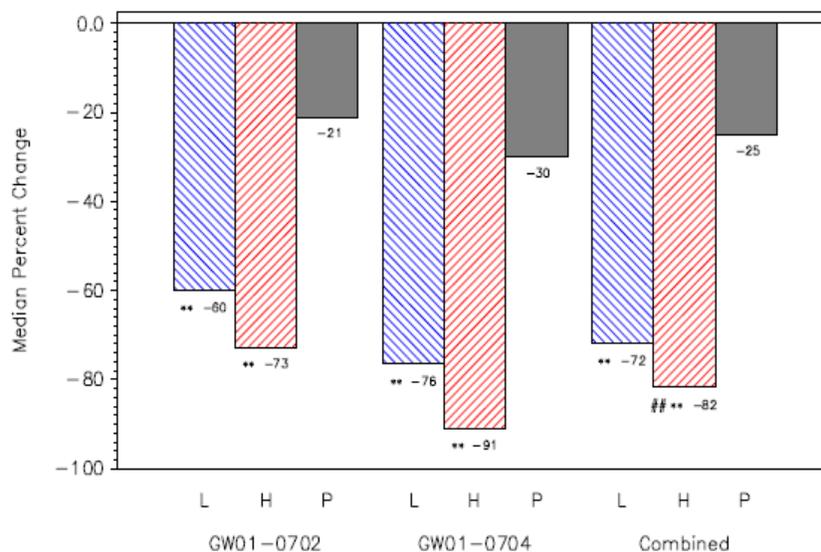
**Percent Change in Number of AK Lesions**

This secondary end point was calculated at the end of week 14 and expressed as median percent change in number of AK lesions in comparison to baseline. Efficacy versus placebo was demonstrated for both concentrations (p<0.001). Data are presented in tabular (Table 23) and graphic form (Figure 8- reproduced sponsor’s Figure 5.3.5.3.1.3).

**Table 23 Median Percent Change in Number of AK Lesions - Combined Pivotal Trials**

trial	2.5%	3.75%	Placebo
GW01-0702	- 60%	-72.7%	-21.1%
GW01-0704	-76.5	-90.9	-30%

**Figure 8 Median Percent Change in Number of AK Lesions -Combined Pivotal Trials**



L= 2.5% group H=3.75% group P= placebo

\* significantly different (p<0.001) than placebo  
 # significantly different from 2.5% arm (p<0.05) combined studies

**Primary and Secondary Efficacy Endpoints, Combined Pivotal Trials and Analyzed Within Regimens**

Complete clearance rate was achieved in 30.6% subject treated with 2.5 % imiquimod cream and in 35.6% subjects treated with 3.75% cream. Placebo group had complete clearance at 6.3% rate. Both concentration showed consistently higher efficacy over placebo at p<0.001 in both primary and secondary end points analysis as seen in Table 24 (modified from sponsor’s Table 5.3.5.3.1-9)

**Table 24 Primary and Secondary Efficacy Endpoints, Analysis Within Regimens - Combined Pivotal Trials**

End Points	2-Week Treatment Cycle Regimen		
	2.5% (N=160)	3.75% N=160	Placebo (N=159)
Complete Clearance n (%)	49 (30.6)*	57 (35.6)*	10 (6.3)
Partial Clearance	77 (48.1)*	95 (59.4)*#	36 (22.6)
Percent Reduction in Number of AK Lesions from Baseline (median)	71.8*	81.8*	25

\* significantly different (p<0.001) from placebo  
 # significantly different (p=0.048) from 2.5% arm

*Comment: Response rates for all endpoints were slightly higher for 3.75% imiquimod cream than for 2.5%. The difference in secondary efficacy points between two active arms reached statistical significance. It is noted that trials were not powered to detect this difference.*

### 6.1.6 Other Endpoints

Imiquimod appeared to improve the mean Investigator’s Global Integrated Photodamage (IGIP) score to a greater extent than placebo. Mean score in 2.5 % group was 1.54, in 3.75% 1.94 and in placebo group 0.73 (combined pivotal studies).

### 6.1.7 Subpopulations

The review will consider only the complete clearance rate, as this is regarded the most clinically meaningful treatment outcome. Subgroup analysis data are presented in Tables 25 and 26 for respected individual trials (reproduced from sponsor’s Tables 14.2.1.1).

**Table 25 Rate of Complete Clearance (subgroup analysis) for GW01-0702**

	Imiquimod Cream		Placebo (N= 80)	Combined (N=242)
	2.5% (N= 81)	3.75% (N= 81)		
<b>Sex</b>				
Male	8/59 (13.6)	18/69 (26.1)	2/70 (2.9)	28/198 (14.1)
Female	11/22 (50.0)	3/12 (25.0)	0/10 (0.0)	14/44 (31.8)
<b>Age</b>				
< 65	10/45 (22.2)	11/44 (25.0)	2/49 (4.1)	23/138 (16.7)
≥65	9/36 (25.0)	10/37 (27.0)	0/31 (0.0)	19/104 (18.3)
<b>Skin Type</b>				
Type I or II	9/44 (20.5)	17/48 (35.4)	1/31 (3.2)	27/123 (22.0)
Type III, IV, or V	10/37 (27.0)	4/33 (12.1)	1/49 (2.0)	15/119 (12.6)
<b>Baseline Lesion Count</b>				
≤10	13/44 (29.5)	13/45 (28.9)	2/42 (4.8)	28/131 (21.4)
>10	6/37 (16.2)	8/36 (22.2)	0/38 (0.0)	14/111 (12.6)
<b>Treatment Area</b>				
Face	16/61 (26.2)	19/66 (28.8)	1/60 (1.7)	36/187 (19.3)
Scalp	3/20 (15.0)	2/15 (13.3)	1/20 (5.0)	6/55 (10.9)

**Table 26 Rate of Complete Clearance (subgroup analysis) for GW01-0704**

	Imiquimod Cream		Placebo (N= 79)	Combined (N=237)
	2.5% (N= 79)	3.75% (N= 79)		
<b>Sex</b>				
Male	21/68 (30.9)	28/63 (44.4)	4/60 (6.7)	53/191 (27.7)
Female	9/11 (81.8)	8/16 (50.0)	4/19 (21.1)	21/46 (45.7)
<b>Age</b>				
< 65	10/43 (23.3)	17/38 (44.7)	4/41 (9.8)	31/122 (25.4)
≥65	20/36 (55.6)	19/41 (46.3)	4/38 (10.5)	43/115 (37.4)
<b>Skin Type</b>				
Type I or II	15/47 (31.9)	22/48 (45.8)	7/46 (15.2)	44/141 (31.2)
Type III, IV, or V	15/32 (46.9)	14/31 (45.2)	1/33 (3.0)	30/96 (31.3)
<b>Baseline Lesion Count</b>				
≤10	23/42 (54.8)	20/37 (54.1)	6/43 (14.0)	49/122 (40.2)
>10	7/37 (18.9)	16/42 (38.1)	2/36 (5.6)	25/115 (21.7)
<b>Treatment Area</b>				
Face	25/56 (44.6)	26/55 (47.3)	7/59 (11.9)	58/170 (34.1)
Scalp	5/23 (21.7)	10/24 (41.7)	1/20 (5.0)	16/67 (23.9)

*Comment: Efficacy was greater in females than in males when treated with 2.5% imiquimod cream in both trials, even more so in 2.5% imiquimod arm. In total, fewer females were enrolled in the trials which can make a smaller difference in success rate appear bigger. Also, most women received treatment to the face where efficacy was also somewhat higher.*

*Efficacy was not significantly affected by age in any active group. Trend was observed towards higher efficacy in GW01-0704 trial only for 2.5% arm in subjects < 65 years of age. Clinical importance of this trend is not clear.*

*Efficacy was slightly higher when the baseline lesion count was less than 10 suggesting that milder disease may have better treatment outcome. Same trend was observed in placebo groups perhaps in part due to known spontaneous regression of AK.*

*Efficacy was greater for the face than the scalp for the both dosing regimens in both trials. This may be in part due to better visualization than bolding scalp and perhaps larger overall surface. Both reasons may contribute to higher absorption rates (~25%) in facial application as shown in clinical pharmacology review.*

*Meaningful efficacy analysis based on race or skin type was not possible due to enrollment of predominantly white subjects with skin type I-III known to be affected with AK more than any other group.*

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Sponsor submitted two dosing regimens for consideration: two 2-week treatment cycles and two 3 week cycles. In both treatment cycles, analysis of primary and secondary end points showed statistically significant improvement ( $p < 0.001$ ) of either concentration over placebo (please refer to Table 27).

**Table 27 Combined Efficacy End Points for Pivotal and Supportive Trials**

End Points	2-Week Treatment Cycle			3-Week Treatment Cycle		
	2.5% (N=160)	3.75% N=160	Placebo (N=159)	2.5% (N=164)	3.75% (N=162)	Placebo (N=164)
<b>Complete Clearance n (%)</b>	49 (30.6)*	57 (35.6)*	10 (6.3)	41 (25)*	55 (34)*	9 (5.5)
<b>Partial Clearance</b>	77 (48.1)*	95 (59.4)*#	36 (22.6)	70 (42.7)*	87 (53.7)*	21 (12.8)
<b>Percent Reduction in Number of AK Lesions from Baseline (mean)</b>	-59.2 (41.4)*	-68.7 (43.4)*	-27.6 (52.1)	-57 (45.4)*	-64.3 (43)*	-24.5 (47)

\* significantly different ( $p < 0.001$ ) from placebo

# significantly different ( $p = 0.048$ ) from 2.5% arm

*Regimen review: The pooled data analysis showed that the 3 week cycle treatment cycle did not provide higher efficacy than 2 week cycle. The clearance rates for the 3-week cycle studies fell between those observed in the two 2-week cycles studies.*

*Thus, in reviewer's opinion the two week treatment regimen should be selected. In addition, it is likely that shorter duration of treatment will enhance compliance.*

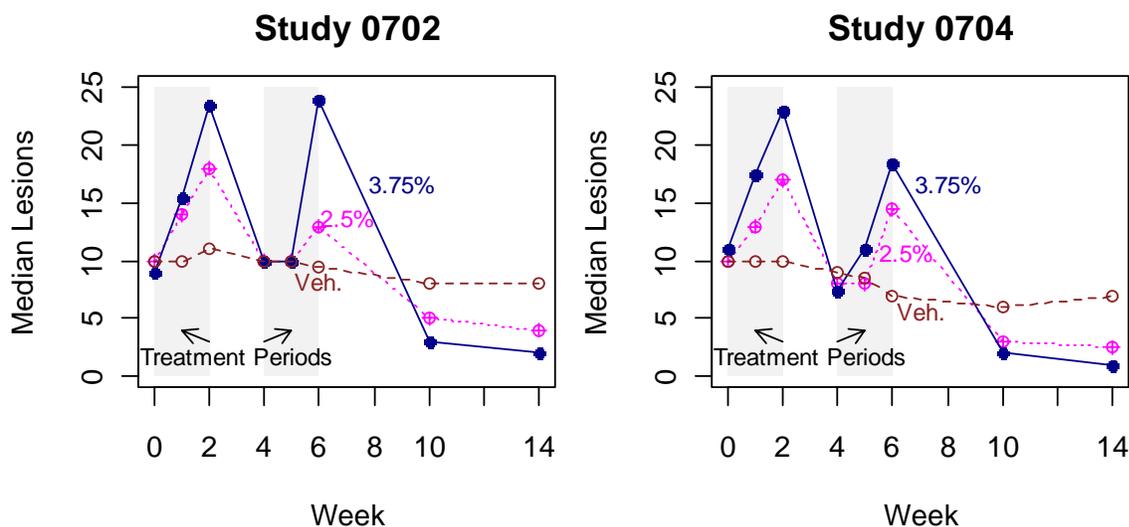
*Dosing concentration review: The efficacy analysis of daily dosing 2.5% v. 3.75% imiquimod cream for two 2-week treatment cycles shows that both concentrations were superior to placebo ( $p < 0.001$ ) at primary and secondary end-points. The efficacy trended upwards for 3.75%, but that does not provide convincing evidence that 3.75% imiquimod is more clinically effective than 2.5% in the treatment of AK. In reviewer's opinion, lower concentration should be selected since it is likely to cause less adverse effects.*

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Approximately 85% of subjects in the active treatment groups experienced an increase in AK lesion count post Baseline. The median percent change in lesion count increased from Baseline during Treatment Cycle 1 and again during Treatment Cycle 2 in both the 2.5% and 3.75% imiquimod treatment groups and then decreased during the follow-up period.

These effects were most pronounced in the 3.75% imiquimod treatment group (see Figure 9- curtesy of biostatistics reviewer, Kathleen Fritsch, Ph.D.). A post baseline increase in AKs may represent the unmasking of subclinical AK lesions which become evident on treatment. This phenomenon has been reported with other agents (e.g. 5-FU). It is also well documented that AK may spontaneously appear and/or regress over time.

**Figure 9 Median Change from Baseline Actinic Keratosis Lesion Count vs Study Week**



Persistence of treatment efficacy is subject of ongoing long-term follow-up study GW01-0803. About 200 subjects from pivotal trials who achieved complete clearance will be followed for up to 12 months.

There is no sufficient data to examine the development of tolerance in this submission.

### 6.1.10 Additional Efficacy Issues/Analyses

Although not to be directly compared, it is worth mentioning that complete clearance rate for Aldara® cream was almost 50% when it was approved for AK on <25cm<sup>2</sup>. The success rate in the submitted pivotal trials, defined as complete clearance rate, was achieved in approximately one third of subjects, regardless of concentration. The sponsor selected higher concentration for approval based upon upward trend in efficacy primarily seen in secondary endpoints and only in trial GW01-0704. While supportive, this numerical advantage does not necessarily lead to clinically meaningful higher success rate of imiquimod 3.75% cream over 2.5%. More precise measurement than trend would be needed for convincing efficacy superiority considering that, in the natural course of AK, lesion count is changeable.

There are no comparative studies of the current product versus other therapies in the field treatment of actinic keratosis and potential advantage is not known. As for lesion directed therapy (considering that 37% of all treated subjects in pivotal trials had 5-8 lesions), other currently available treatments may be more suitable (e.g. cryotherapy).

## 7 Review of Safety

### Safety Summary

Data base for safety evaluation contained 665 subjects exposed to imiquimod in comparison to 323 subjects exposed to placebo.

More than 93% of enrolled subjects completed the trials.

The exposure to the drug was adequate to uncover safety issues. It should be noted that duration of the exposure is not the same across the trials due to different dosing regimens. In order to capture potential safety signal, all the data were reviewed but for analysis purposes are grouped according to the treatment paradigm with emphasis on 2 weeks cycles.

All safety measures were analyzed using the ITT data sets. The safety evaluation consisted of investigator- and subject-reported adverse events, skin assessments, local skin reactions, vital signs, and routine laboratory tests. There were no EKG data in this submission. Rest periods as the indicators of local intolerance were reported separately.

The combined safety data base for 2-2week cycles application of topical imiquimod cream comprises 479 subjects (160 randomized to 2.5% cream, 160 to 3.75% cream and 159 to placebo).

There were no deaths reported.

Treatment related AE were reported in 11.9% of subjects treated with 2.5% cream in comparison to 19.4 % treated with 3.75% and 2.5% in placebo group. Three most common were application site reactions (pruritus, irritation and pain) followed by lymphadenopathy and influenza like-illness.

Application site reactions were reported by 6.3% subjects in 2.5% arm, 10.6% in 3.75% arm and in 1.3% subjects using placebo. Pruritus was the most common.

The most common local skin reaction was erythema evenly distributed among different groups. However, other local skin reactions (edema, weeping, flaking/scaling, scabbing and erosions) were more common in active groups. More severe reactions were seen more frequently in 3.75% group than in 2.5% group (33.8% v. 20.6 %).

Summary of rest periods showed that overall, slightly more subjects in the 3.75% arm required rest periods than in the 2.5% arm, and the rest periods were slightly longer, particularly in the second treatment cycle.

Supportive trials utilized 3 week cycle regimen and in general showed higher and more severe reactions than in 2-week cycle.

The adverse event profile was largely consistent with what is known about topical imiquimod from previous clinical trials and from the post-approval use of the product (Aldara® cream). Potential new safety concern is pancytopenia that occurred in one subject treated with 3.75% imiquimod. Isolated decrease in blood cell counts were reported earlier with Aldara®, but not pancytopenia. Causality regarding imiquimod exposure was not obvious because of subject's comorbidities. Some systemic adverse reactions such as flu-like symptoms and lymphadenopathy appear to be dose dependent, more frequent and more severe than previously reported, perhaps as a result of more intense treatment (daily) and larger surface. There was one case of unexplained ventricular tachycardia that raises concern about imiquimod effect on cardiac arrhythmias.

Safety evaluation supports 2 week cycle regimen with 2.5% imiquimod cream because of lower rate of AEs. Rest periods may be necessary for potential systemic and skin reactions. Patients and physicians should be advised to stop the treatment if lymphadenopathy and flu-like symptoms occur.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data were reviewed from 5 clinical trials and those are: two pivotal trials: GW01-0702 and GW01-0704; two supportive trials: GW01-0703 and GW01-0705; and one pharmacokinetic trial GW01-0706. The 2 pivotal trials utilized two 2-week treatment cycles separated with a 2-week no-treatment period, and the 2 supportive trials utilized two 3-week treatment cycles separated with 3-week no-treatment period. All of these four trials were randomized, double-blind, multicenter, placebo-controlled. Pivotal trials have been described in detail in section 5.3. Pharmacokinetic trial was an open label trial in duration of 3 weeks utilizing 3.75% imiquimod creme.

### 7.1.2 Categorization of Adverse Events

In the opinion of this reviewer, the sponsor adequately categorized the adverse events using MedDRA classification Version 11.0, terminology.

### 7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Pooling of safety data for this review was done by sponsor and included paired data from 4 Phase 3 clinical trials. Data from pharmacokinetic GW01-0706 trial are included in analysis by reviewer and those are application site AEs, and only one systemic AE (moderate in intensity) and that AE led to subject's discontinuation.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 665 adult subjects in five trials received imiquimod. Target population demographics were similar between all trials and reflective of typical population affected with AK.

**Table 28 Demographic Characteristics across Regimens**

	2-Week Treatment Cycle Regimen			3 Week Treatment Cycle Regimen		
	2.5 %	3.75%	Placebo	2.5%	3.75%	Placebo
Total (n)	160	160	159	164	162	164
Age (mean)	64.3	64.5	64.3	66	64.3	63.7
Male (%)	79.4	82.5	81.8	78	75.9	82.3
White (%)	100%	100%	99.4	100%	98.8%	99.4

### 7.2.2 Explorations for Dose Response

It should be noted that sponsor did not conduct any Phase 2 dose ranging studies, but instead proceeded directly to Phase 3.

Two different concentrations of creme (2.5 % and 3.75%) and two different durations of treatment (two week and three week cycles) were tested in order to select one optimal treatment.

**Table 29 Overall Exposure at Appropriate Doses across Regimens**

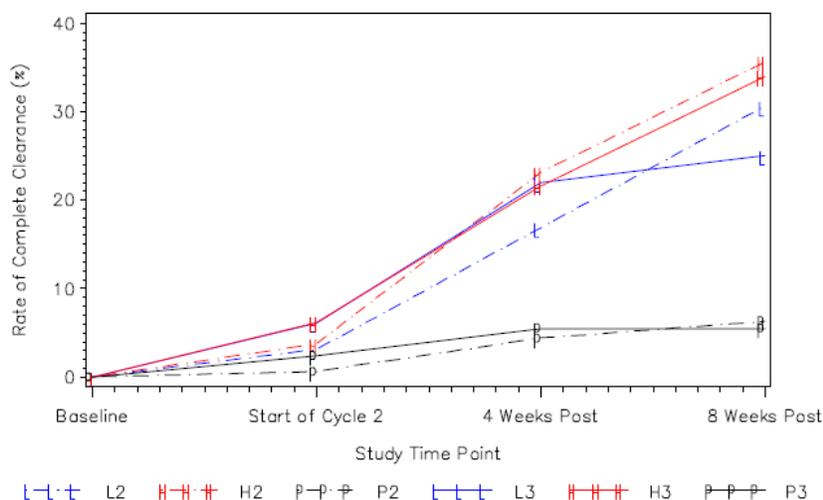
	2-Week Treatment Cycle Regimen			3 Week Treatment Cycle Regimen		
	2.5 %	3.75%	Placebo	2.5%	3.75%	Placebo
Total (n)	160	160	159	164	162	164
Drug (mg)*	290.9	400.5	0	410.5	571.1	0
Applications (n)	27.3	26.2	26.8	39	37.3	40.8
Packets used (n)	52	47	53	74	63	78
Duration (days)	28	28	28	42	42	42

\*Total amount of drug used is the number of packets times 250 mg per packet times the drug concentration.

The duration of treatment and number of doses differs according to different protocols for pivotal and supportive trials. However, the difference between the expected number of packets used (for 2 week cycle up to 56) and actual use is highest for 3.75% arm (nine packets). The difference is even higher in three week cycle. While this may be related to the arbitrary size of the treatment area, it is possible that tolerance decreases with higher concentration and even more with longer duration of treatment. Overall, the exposure was adequate to analyze safety. Data are summarized in the Table 29 (modified from sponsor's table 5.3.5.3.2-7).

Dose response was assessed through primary endpoint at the end of the trials (either week 14 for pivotal or week 17 for supportive trials). Several tertiary end-points were assessed at interim trial visits. See graph below (source: Figure 5.3.5.3.1.4 from sponsor's ISE).

**Figure 10 Dose Response-Rate of Complete Clearance, Combined Studies, ITT Population**



L2=2.5% 2-Week Treatment Cycle regimen, L3=2.5% 3-Week Treatment Cycle regimen, H2=3.75% 2-Week Treatment Cycle regimen, H3=3.75% 3-Week Treatment Cycle regimen, P2=Placebo 2-Week Treatment Cycle regimen, P3=Placebo 3-Week Treatment Cycle regimen.

The highest rate of complete AK clearance was observed with 3.75% imiquimod cream (used in 3 week treatment cycle followed by 2 week treatment cycle).

### 7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was needed given the sponsor's right to cross reference the nonclinical studies completed during Aldara® cream (imiquimod 5%) development.

### 7.2.4 Routine Clinical Testing

The schedule of clinical assessment for each of the studies consisted of vital signs, general physical examination, skin quality assessments, routine laboratory testing, and monitoring for

AE. The methods and tests used as well as the frequency of testing were adequate. Routine EKG evaluation was not included in safety testing. Consult was requested from cardiac and QT Interdisciplinary Review Team regarding the lack of the EKG evaluation. In the memorandum dated May 28, 2009 the QT-IRT responded: “No, ECGs were not performed in the clinical development program for the imiquimod 3.75% cream, including studies 1520-IMI and 1402-IMI where subjects had supra-therapeutic exposures... The proposed dosing regimen for 3.75% cream will provide greater exposure compared to the approved dosing regimen of Aldara® 5% cream for actinic keratosis... Cardiac AEs in the studies were confounded because of co-morbidities and concomitant medications but no ECG effects are reported in the narratives. 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... However, if the Division is concerned about the potential of affect cardiac repolarization, then the sponsor should conduct a TQT study...”

In reviewer’s opinion, the TQT studies should be conducted with submission of interval and waveform data to address potential effect of imiquimod on supraventricular and ventricular cardiac rhythm. The rationale includes: a) cases of supraventricular arrhythmias from AERS data base potentially related to Aldara® cream by virtue of rechallenge\* b) unexplained case of ventricular tachycardia from this submission, c) unexplained sudden death of healthy 71 years old treated with 5% Aldara\* (b) (4)

\_\_\_\_\_ ) and g) lack of human EKG data from imiquimod development program.

#### 7.2.5 Metabolic, Clearance, and Interaction Workup

For the complete analysis of the pharmacokinetic trial GW01-0706, a reader is referred to the Clinical Pharmacology review. An overview of that trial is presented below.

This was an open-label, single center, pharmacokinetic trial designed to quantify the PK profile of imiquimod and its metabolites following 3 weeks of once daily applications of 3.75% imiquimod cream. Population consisted of 19 subjects with at least 10 AK on the face or balding scalp and area of treatment was defined as not less than 200cm<sup>2</sup>.

PK parameters for imiquimod and its two metabolites were calculated from the serum samples collected on Days 1, 7, 14, 21, and 22.

The sponsor found that serum concentrations of imiquimod were relatively low. Peak and total serum concentrations increased 3-4-fold between Day1 and Day 21. (C<sub>max</sub> 0.323+/-0.159). Steady state was achieved by Day 14. C<sub>max</sub> on Day 21 was lower in male subjects who applied imiquimod 3.75% cream to balding scalp rather than the face. The reason may be potentially smaller area of treatment.

Serum concentrations of two metabolites (S-26704 and S-27700 combined) were measured, but not assessed because the data were too sparse. Clearance and interaction workup was not conducted base upon the fact that systemic exposure was low.

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\* 2.6 Other Relevant Background Information

## 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Imiquimod is first drug in class known as imidalazoquins. Imiquimod 5% cream has been used for over 20 years and its safety profile is known from Phase 3 and 4 trials as well as post-approval data base. The most common adverse events are related to local skin reaction, upper respiratory infections, and flu-like symptoms.

(b) (4) is second generation imidalazoquin under development in topical and oral form. Oral (b) (4) is about 100 times more potent cytokine inducer than imiquimod. Its adverse reactions are said to be similar to interferon and include fever, headache, shivering, and lymphopenia (Pokros, 2007).

*Comment: The applicant's effort to detect these specific AEs was adequate.*

## 7.3 Major Safety Results

### 7.3.1 Deaths

There were no deaths reported in current submission. However, one subject (17/302 from supportive trial GW01-0703) passed away 3 weeks after completing study. The cause of death is unknown.

Case review: Narrative for this subject was provided as well as additional requested information. Subject was 82 years old randomized to 3.75% imiquimod treatment group with PMH significant for hypercholesterolemia, hypothyroidism, hypertension, congestive heart failure, pulmonary fibrosis, ischemic cardiomyopathy, coronary artery disease, chronic renal insufficiency, type 2 diabetes mellitus, and bladder leakage treated with band placement. On Study Day 25 he underwent replacement of a urinary bladder band that had failed. Postoperatively he developed CHF but improved and was discharged home. Dosing of imiquimod was never interrupted and he completed the study. Three weeks later he passed away at his home.

*Comment: It is likely that subject's cause of death was related to significant cardio-pulmonary morbidities.*

### 7.3.2 Nonfatal Serious Adverse Events

There were total of 26 subjects that experienced 33 SAE in reported Phase 3 trials. 12 subjects used 3.75% imiquimod, 10 subjects used 2.5% and 4 subjects used placebo. PK study did not have any SAE.

**Table 30 All Serious Adverse Events across Regimens**

Adverse event	2 week treatment			3 week treatment			Total
	2.5 %	3.75%	placebo	2.5 %	3.75%	placebo	
Cerebrovascular accident		1					1
Atrial fibrillation	1	1					2
Small intestine obstruction		1	1				2
Chest pain	1	1		1		1	4
Anxiety		1					1
Diarrhea		<b>1</b>					1
Pneumonia	2			1	1		4
AMI	1						1
Non cardiac chest pain	1						1
Prostatitis			1				1
Ventricular tachycardia	<b>1</b>						1
Breast cancer					1		1
Surgery					1		1
Dyspnea					1		1
Hip fracture					1		1
Arthralgia					1		1
Wound infection					1		1
CAD					1		1
Non Hodgkin lymphoma					1		1
Pancytopenia					<b>1</b>		1
Aortic valve stenosis				1			1
Syncope				1			1
Bronchitis				1			1
Mental status change						1	1
Orthostatic hypotension						1	1

Cardiovascular events of various presentations account for 13 AE. Chest pain was the most common. Considering demographic characteristics of enrolled population, this was not unexpected. One case of ventricular tachycardia is insufficiently characterized to make decision about relationship to imiquimod. Case is presented in [section 5.3.4 Review of Safety for Pivotal Trials GW01-0702 and GW01-0702](#).

The review of 4 pneumonia events did not reveal a safety signal, and there are all considered non-related to the treatment.

Two subjects developed serious adverse events (in shaded cells) that were considered treatment related; both subjects used 3.75% imiquimod and those are further described below:

1. Subject 36/415 from 2-week treatment cycle experienced diarrhea that was severe and required hospitalization. Event lasted 11 days and resolved without sequelae (case presentation is in [section 5.3.4 Review of Safety for Pivotal Trials GW01-0702 and GW01-0702](#)).
2. Subject 51/539 from 3-week treatment cycle developed pancytopenia. He was subsequently diagnosed with Non-Hodgkin's lymphoma.

Case presentation: Complete medical history for subject 51/539 was requested and reviewed. Subject is 70 years old man with PMH significant for DM, HTN, CHF, BPH, gout, hypothyroidism, MI, CABG, easy bruising, and sleep apnea.

- May 2004-the earliest abnormal hematologic data is from May 2004 showing WCC 3.6, HTC 41.6, and PLT 92,000. From the available repeat counts in the next three years, the only abnormal finding was mild thrombocytopenia (100,000-132,000).
- February 20, 2008-screening day hematological values were WCC 8.6, HTC 37, and PLT 130,000.
- February 28 to March 17, 2008- subject was treated with imiquimod creme. During that time he was also taking Coreg, Metformin, Colchicine, Actos, Amaryl, Nitroglycerin, Furosemide, Lexapro, Levothyroxine, Celebrex, Allopurinol, and ASA.
- April 8, 2008- subject reported fatigue and lightheadedness that were gradually developing over period of 4 weeks.
- April 9, 2008- blood tests revealed WCC 3.3, HTC 22 and PLT 71,000.
- (b)(4) repeated test showed WCC 3.6, ( neutrophils 27%, lymphocytes 66%), HTC 22 and PLT 73,000. Subject was transfused.
- On (b)(6) he underwent bone marrow biopsy. Bone marrow biopsy showed only 10% cellularity with predominant lymphocytes (flow cytometry confirmed presence of CD5, CD19, and CD20 positive cells). His peripheral blood showed WCC 7.2, HTC 20 and PLT 68,000. There were no significant findings on CT of the chest and abdomen.
- On April 28, 2008 subject was diagnosed with small cell non-Hodgkin lymphoma and started on Rituxan. Treatment is ongoing.

*Reviewer's comment: Subject's history of abnormal peripheral blood counts precedes the adverse event for approximately 4 years. Small cell B lymphoma (or CLL) has usually very gradual and subtle onset with indolent and slow course. It can go undetected for years, until patient develops symptoms, in this case, symptoms of anemia. For that reason it is not likely that short exposure to imiquimod played a role in lymphoma development.*

*Pancytopenia may be present in this type of lymphoma and it is postulated that it is autoimmune phenomenon. Another possible explanation for development of pancytopenia is idiosyncratic reaction to colchicine exposure from January 2008 to April 2008. In reviewer's opinion, either lymphoma itself or colchicine use provide better explanation for pancytopenia occurrence than imiquimod exposure.*

*However, isolated decrease in red cells, white cells or platelet count (but not pancytopenia) has been identified in post-approval use of Aldara® cream. In this particular case, timeline of pancytopenia development coincides with imiquimod exposure and causal relationship can not be excluded.*

### 7.3.3 Dropouts and/or Discontinuations

Discontinued subjects from pivotal trials are presented in [Table 9](#) and [Table 10](#). In this section an overview of all adverse that led to subject discontinuation or drug discontinuation will be presented ( from sponsor's Listings 5.3.5.3.2.11). There were total of 29 subjects (3%) across all five trials that fell under this description: 17 subjects were enrolled in supportive trials, 11 in pivotal trials, and one in PK trial.

The distribution and nature of events is summarized below:

**Table 31 All AE Leading to Subject Discontinuation from the Study or Study Drug**

regimen	subject	AE (preferred term)	Cycle
3.75%	<b>37/405</b>	headache, fatigue, pain, application site pain *	2 week
	<b>36/415</b>	nausea, diarrhea, fatigue	2 week
	36/416	dizziness	2 week
	37/405	headache	2 week
	05/206	tremor	2 week
	01/202	Parkinson's disease	2 week
	<b>19/307</b>	application site irritation*	2 week
	<b>51/539</b>	pancytopenia, non-Hodgkin's lymphoma*	3 week
	<b>14/332</b>	influenza like illness	3 week
	<b>14/324</b>	application site dermatitis	3 week
	<b>14/336</b>	nausea, chills	3 week
	<b>14/335</b>	pruritus	3 week
	<b>42/523</b>	influenza like illness	3 week
	<b>47/507</b>	fatigue	3 week
	<b>42/508</b>	influenza like illness	3 week
	51/524	CAD	3 week
	45/513	basal cell carcinoma	3 week
	16/315	breast cancer	3 week
<b>01/619</b>	fatigue, body ache	3 week-PK	
2.5%	05/219	tachycardia, angina pectoris, blood pressure increased	2 week
	<b>14/315</b>	application site swelling, application site pain	3 week
	<b>23/311</b>	application site pain	3 week
	<b>47/509</b>	influenza like illness, fatigue, anxiety	3 week
	<b>50/516</b>	application site pain, application site bleeding, rash*	3 week
	44/504	dysgeusia	3 week
	17/311	respiratory tract congestion, sinus congestion, blurred vision, dysgeusia	3 week
placebo	08/216	headache *	2 week
	09/223	migrane	2 week
	31/404	tinnitus	2 week

**bold letters**= treatment related

\* severe AE

*Comment: 16 subjects (55%) had AE considered imiquimod related (in bold numbers). This assumption was made based on rates in treatment and placebo groups and presumable imiquimod's mechanism of action. The distribution was: 12 subjects in 3.75 % group, 4 in 2.5 %, and 0 in placebo group. Analyzing regimen and cycle categories, it appears that longer duration of therapy and higher concentration of imiquimod leads to higher rate of AE related discontinuations.*

*Majority of subjects had AE that were mild to moderate in intensity. Five subjects (labeled with\*) had severe AE that led to discontinuation. Three of those were application site reactions – (2 in 3.75% group and one in 2.5% group), one was pancytopenia in 3.75% group and one was headache in placebo group.*

From the clinical prospective, the type of some treatment related AE allows them to be grouped together. These events were also the most common and are presented in Table 32.

**Table 32 Most Common AE related to Discontinuations**

Imiquimod cream %	Flu-like adverse events		Application site adverse events	
	subject	AE	subject	AE
3.75%	37/405	headache, fatigue,	19/307	application site irritation
	36/415	nausea, diarrhea, fatigue	14/324	application site dermatitis
	14/332	influenza like illness	37/405	application site pain
	14/336	nausea, chills		
	42/523	influenza like illness		
	47/507	fatigue		
	42/508	influenza like illness		
	01/619	fatigue, body ache		
2.5%	47/509	influenza like illness, fatigue, anxiety	14/315	application site swelling, application site pain
			23/311	application site pain
			50/516	application site pain, application site bleeding,

*Comment: Nine subjects from the treatment groups developed flu like AE and none from placebo groups. While these events, presumably related to immune system stimulation, were noted in previous imiquimod trials, they were not worrisome enough to cause discontinuations. Perhaps the defining factor is larger treatment area and more frequent dosing then before.*

#### 7.3.4 Significant Adverse Events

Severe adverse events were rare. Detailed presentation of those from pivotal trials is in section [5.3.4 Review of Safety for Pivotal Trials GW01-0702 and GW01-0702](#) . An overview of all serious AE in all 5 trials from this submission is presented in Table 33(source: Table 5.3.5.3.2.8)

**Table 33 Summary of Severe AE, Combined Trials**

	2-Week Treatment Cycle Regimen			3-Week Treatment Cycle Regimen		
	3.75% (N=160)	2.5% (N=160)	Placebo (N=159)	3.75% (N=162)	2.5% (N=164)	Placebo (N=164)
Any Severe AE	6 (3.8%)	8 (5.0%)	2 (1.3%)	9 (5.6%)	6 (3.7%)	0 (0.0%)
Anxiety	1 (0.6)	0	0	0	0	0
Atrial fibrillation	1 (0.6)	1 (0.6)	0	0	0	0
Cerebrovascular accident	1 (0.6)	0	0	0	0	0
Chest pain	1 (0.6)	0	0	0	1 (0.6)	0
Diarrhoea	1 (0.6)	0	0	0	0	0
Gout	1 (0.6)	0	0	0	0	0
Influenza like illness	1 (0.6)	1 (0.6)	0	1 (0.6)	0	0
Vascular graft	1 (0.6)	0	0	0	0	0
Abdominal pain	0	0	1 (0.6)	0	1 (0.6)	0
Angina pectoris	0	1 (0.6)	0	0	0	0
Application site infection	0	1 (0.6)	0	0	0	0
Application site irritation	0	1 (0.6)	0	0	0	0
Arteriosclerosis	0	1 (0.6)	0	0	0	0
Back pain	0	0	1 (0.6)	0	0	0
Bronchiectasis	0	1 (0.6)	0	0	0	0
Cartilage injury	0	1 (0.6)	0	0	0	0
Cheilitis	0	1 (0.6)	0	0	1 (0.6)	0
Intestinal obstruction	0	0	1 (0.6)	0	0	0
Lymphadenopathy	0	1 (0.6)	0	1 (0.6)	0	0
Oral herpes	0	1 (0.6)	0	0	0	0
Pneumonia	0	1 (0.6)	0	0	1 (0.6)	0
Pneumonia bacterial	0	1 (0.6)	0	0	0	0
Procedural pain	0	1 (0.6)	0	0	0	0
Rash pruritic	0	1 (0.6)	0	0	0	0
Sinusitis	0	1 (0.6)	0	0	0	0
Urinary tract infection	0	0	1 (0.6)	0	1 (0.6)	0
Anaemia	0	0	0	1 (0.6)	0	0
Animal bite	0	0	0	0	1 (0.6)	0
Application site pain	0	0	0	0	1 (0.6)	0
Arthralgia	0	0	0	1 (0.6)	0	0
Biopsy breast	0	0	0	1 (0.6)	0	0
Breast cancer	0	0	0	1 (0.6)	0	0
Bronchitis	0	0	0	0	1 (0.6)	0
Cardiac failure congestive	0	0	0	1 (0.6)	0	0

Note: Counts reflect number of subjects in each treatment group reporting one or more adverse events. The subject may be counted once only in each row of the table.

*Comment: Vast majority of severe AE were not related to imiquimod cream. Probably treatment related were: influenza like illness 3, application site infection 1, application site irritation 1, lymphadenopathy 1 and pruritic rash 1. There was no meaningful difference between active arms or treatment regimens. Flu-like illness and lymphadenopathy were previously reported in clinical trials, but not as sever AE.*

Application site reactions and local skin reactions are further analyzed by type and severity in the Tables 34 and 35 (modified from sponsor’s Tables 5.3.5.3.2-14 and 5.3.5.3.2-12).

**Table 34 Summary of Treatment-Emergent Application Site Reactions in Descending Order of Incidence**

	2-Week Treatment Cycle Regimen			3-Week Treatment Cycle Regimen		
	2.5% (N=160)	3.75% (N=160)	Placebo (N=159)	2.5% (N=164)	3.75% (N=162)	Placebo (N=164)
Any Application Site Reaction	10 (6.3%)	17(10.6%)	2 (1.3%)	28 (17.1%)	39 (24.1%)	5(3.0%)
Application site pruritus	6 ( 3.8)	7 ( 4.4)	1 ( 0.6)	12 ( 7.3)	15 ( 9.3)	1 ( 0.6)
Application site irritation	4 ( 2.5)	5 ( 3.1)	0	6 ( 3.7)	9 ( 5.6)	1 ( 0.6)
Application site pain	2 ( 1.3)	5 ( 3.1)	0	11 ( 6.7)	15 ( 9.3)	0
Application site swelling	0	2 ( 1.3)	0	3 ( 1.8)	1 ( 0.6)	0
Application site paraesthesia	0	1 ( 0.6)	1 ( 0.6)	0	0	0
Application site scar	0	1 ( 0.6)	0	0	0	0
Application site dryness	1 ( 0.6)	0	0	0	0	0
Application site infection	1 ( 0.6)	0	0	1 ( 0.6)	0	0
Application site abscess	0	0	0	0	1 ( 0.6)	0
Application site bleeding	0	0	0	2 ( 1.21)	5 ( 3.1)	1 (0.6)

*Comment: Number of application site reactions increased with longer duration of treatment and higher concentration of the cream. Pruritus was the most common. More severe reaction such as infection, abscess, and scar were rare.*

*In PK study application site pruritus, and application site pain occurred in 2 subjects each (10.5%). Skin irritation was reported in one subject (5.5%).*

Local skin reactions (LSR) in the treatment and/or immediate surrounding area were clinically identified by the following categories: erythema, edema, weeping/exudate, flaking/scaling/dryness, scabbing/crusting, and erosion/ulceration. The intensity of each category was graded 0-3 (none to severe). Frequency distribution and mean score for each category is presented in Table 34 (modified from sponsor’s Table 5.3.5.3.2-12).

**Table 35 Frequency Distribution of Post-Baseline LSRs in the Treatment Area**

Any reaction n, (%) Mean Score (SD)	2-Week Treatment Cycle Regimen			3-Week Treatment Cycle Regimen		
	2.5% (N=160)	3.75% (N=160)	Placebo (N=160)	2.5% (N=160)	3.75% (N=160)	Placebo (N=160)
Any erythema Mean Erythema, Score (SD)	154 (96.3) 1.81(0.72)	154 (96.3) 2.05(0.72)	124 (78) 0.98 (0.65)	160 (97.6) 2.09 (0.71)	158 (97.5) 2.29 (0.75)	149 (99) 1.19(0.56)
Any edema Mean Edema Score (SD)	101 (63.1) 0.95(0.87)	120 (75) 1.16(0.86)	31 (19.5) 0.95 (0.87)	120 (73.2) 1.18 (0.91)	124 (76.5) 1.34 (0.98)	36 (22) 0.24(0.47)
Any exudate Mean Exudate Score (SD)	63 (39.4) 0.51(0.72)	81 (50.6) 0.74(0.87)	6 (3.8) 0.04 (0.19)	91 (55.5) 0.92 (0.97)	110 (67.9) 1.09 (0.96)	14 (8.5) 0.09(0.28)

Any flaking/scaling/dryness Mean Score (SD)	141 (88.1) 1.32(0.74)	147 (91.9) 1.48 (0.75)	123 (77.4) 1.00 (0.69)	157 (96.9) 1.61 (0.75)	155 (94.5) 1.71 (0.72)	144 (87.8) 1.12(0.57)
Any scabbing/crusting Mean Score (SD)	135 (84.4) 1.44(0.87)	149 (93.1) 1.72(0.78)	72 (45.3) 0.48 (0.56)	153 (94.4) 1.78 (0.88)	151 (92.1) 2.03 (0.88)	66 (40.2) 0.46(0.59)
Any erosion/ulceration Mean Score (SD)	84 (52.5) 0.62(0.65)	99 (61.9) 0.73(0.64)	14 (8.8) 0.09 (0.28)	128 (79) 0.97 (0.72)	119 (72.6) 1.10 (0.71)	13 (7.9) 0.08(0.27)

Subject 05/208 (2-week 3.75% group), Subject 17/311(3-week 2.5% group), Subject 26/314 (3-week 3.75% group), and Subjects 42/527 and 44/505 (3-week placebo group) did not have post-baseline visits and were excluded from the analysis.

*Comment: All of these events increased during active treatment with imiquimod, and returned to baseline levels after treatment.*

*Erythema was the LSR reported with the greatest frequency and the greatest mean intensity. In the pivotal trials, erythema was reported in 96.3% of subjects overall in the 3.75% imiquimod group, in 96.3% of subjects in the 2.5% imiquimod group, and in 78.0% of subjects in the placebo treatment group. The mean intensity score was highest in the active treatment groups (2.05 and 1.81 in the 3.75 and 2.5% imiquimod groups, respectively) compared with 0.98 in the placebo group. The incidence of severe erythema (intense redness) was 25.2%, 14.4% and 0% in the 3.75% imiquimod, 2.5% imiquimod, and placebo groups, respectively.*

*Similarly, 3.75% imiquimod cream had higher mean intensity scores in each LSR.*

*In supportive trials LSR increased in frequency and severity in both active treatment groups.*

*In PK study erythema was reported in all 19 subjects. Severe reactions were only observed for erythema and occurred in 5 of the 19 subjects (25%).*

Rest periods are presented in Table 36 (modified from sponsor’s Table 5.3.5.3.2-15).

**Table 36 Summary of Rest Periods across Regimens**

	2-Week Treatment Cycle Regimen			3-Week Treatment Cycle Regimen		
	2.5% (N=160)	3.75% (N=160)	Placebo (N=159)	2.5% (N=164)	3.75% (N=162)	Placebo (N=164)
Subjects Required Rest Period, n (%)	11 ( 6.9)	17 ( 10.6)	0 ( 0.0)	28 ( 17.1)	44 ( 27.2)	0 ( 0.0)
Number of Dosing Days Missed Due to Rest Period	11	17	0	28	44	0

*Comment: There were no missed days due to the rest periods in either of placebo groups. Both, number of subjects and missed days show dose and treatment duration dependency. The range for subjects spreads from 11 subjects in 2.5% group from pivotal trials to 44 subjects in 3.75% group from supportive trials. The same 4-fold increase is observed in number of missed days.*

*Within 2-week treatment, 3.75% group leads in both categories suggesting that higher imiquimod concentration is less tolerable.*

*There was no provision in PK study for taking rest periods, and thus data are not available.*

### 7.3.5 Submission Specific Primary Safety Concerns

Significant adverse events presented in Table 37 represent events that were considered by investigator as treatment related. Subjected was counted only once for specific category. Data are reproduced from sponsor's Table 5.3.5.3.2-7.

**Table 37 Number (%) of Subjects with Treatment Related Adverse Events in Descending Order of Incidence**

	2-Week Treatment Cycle Regimen			3-Week Treatment Cycle Regimen		
	2.5% (N=160)	3.75% N=160	Placebo (N=159)	2.5% (N=164)	3.75% (N=162)	Placebo (N=164)
Subjects with any Treatment-Related AE, n (%)	19(11.9%)	31(19.4%)	4 (2.5%)	44(26.8%)	60 (37.0%)	4 (2.4%)
Application site pruritus	6 ( 3.8)	7 ( 4.4)	1 ( 0.6)	12 ( 7.3)	14 ( 8.6)	1 ( 0.6)
Application site irritation	4 ( 2.5)	5 ( 3.1)	0	6 ( 3.7)	9 ( 5.6)	1 ( 0.6)
Application site pain	2 ( 1.3)	5 ( 3.1)	0	11 ( 6.7)	15 ( 9.3)	0
Fatigue	0	4 ( 2.5)	0	5 ( 3.0)	7 ( 4.3)	0
Headache	1 ( 0.6)	4 ( 2.5)	2 ( 1.3)	4 ( 2.4)	4 ( 2.5)	0
Dizziness	0	3 ( 1.9)	0	0	0	0
Lymphadenopathy	3 ( 1.9)	3 ( 1.9)	0	4 ( 2.4)	5 ( 3.1)	0
Nausea	1 ( 0.6)	3 ( 1.9)	0	1 ( 0.6)	2 ( 1.2)	0
Application site swelling	0	2 ( 1.3)	0	3 ( 1.8)	1 ( 0.6)	0
Arthralgia	0	2 ( 1.3)	0	1 ( 0.6)	0	0
Pain	0	2 ( 1.3)	0	0	0	0
Pyrexia	0	2 ( 1.3)	0	0	5 ( 3.1)	0
Anorexia	0	1 ( 0.6)	0	0	0	0
Application site paraesthesia	0	1 ( 0.6)	1 ( 0.6)	0	0	0
Application site scar	0	1 ( 0.6)	0	0	0	0
Chills	0	1 ( 0.6)	0	1 ( 0.6)	2 ( 1.2)	0
Decreased appetite	0	1 ( 0.6)	0	0	0	0
Dermatitis	0	1 ( 0.6)	0	0	0	0
Diarrhoea	0	1 ( 0.6)	0	0	0	0
Herpes simplex	0	1 ( 0.6)	0	2 ( 1.2)	2 ( 1.2)	0
Inflammation	0	1 ( 0.6)	0	0	0	0
Influenza like illness	4 ( 2.5)	1 ( 0.6)	0	6 ( 3.7)	12 ( 7.4)	0
Lethargy	1 ( 0.6)	1 ( 0.6)	0	0	2 ( 1.2)	0
Musculoskeletal stiffness	1 ( 0.6)	1 ( 0.6)	0	0	0	0
Pruritus	0	1 ( 0.6)	0	0	1 ( 0.6)	0
Rash papular	0	1 ( 0.6)	0	0	0	0
Sunburn	0	1 ( 0.6)	0	0	0	0
Upper respiratory tract infection	0	1 ( 0.6)	1 ( 0.6)	0	0	0

*Comment: In 2 week cycle overall incidence of treatment related AE was 10-20% in comparison with 3 week cycle where it almost doubled (26-37%) for respected active groups. Application site reactions were the most common and that is not unexpected. Adverse events considered potentially representative of the systemic effects of imiquimod or interferon-alpha induction (eg, headache, fatigue, nausea, pyrexia, anorexia, pain, diarrhea, chills, influenza-like illness, lethargy, and myalgia) followed. Most common systemic treatment related AE were influenza-like illness in 23 subjects, fatigue in 16 subjects, headache in 15 subjects and lymphadenopathy in 15 subjects.*

*Lymphadenopathy (predominantly cervical) was seen in both active groups and might be due to hyperplasia from immunologic stimuli. All of the swelling resolved spontaneously. There was no recognizable pattern of onset or duration of lymphadenopathy. Most of the cases lasted about 10 days. Again noted is higher number of events in 3 week cycle and in 3.75% groups.*

*Similar distribution was observed in PK study where 8/19 subjects (42.1%) experienced treatment related AE. The most frequent events were experienced by 2 subjects each (10.5%) and included application site pain, application site pruritus and fatigue.*

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Almost 50% of subjects in active arms of pivotal trials reported AEs in comparison to 33 % in placebo group. Supportive trials show comparable results. Most frequent AE that occurred in >1% of subjects are presented in Table 38 (reproduced sponsor's Table 5.3.5.3.2-9).

**Table 38 Number (%) of Subjects in the Phase 3 Studies with Treatment-Emergent Adverse Events with Incidence >1% the 3.75% Imiquimod 2-Week Treatment Cycle Group**

	2-Week Treatment Cycle Regimen			3-Week Treatment Cycle Regimen		
	2.5% (N=160)	3.75% N=160	Placebo (N=159)	2.5% (N=164)	3.75% (N=162)	Placebo (N=164)
Subjects with any AE, n (%)	70 (43.8)	77 (48.1)	53 (33.3)	82 (50)	97 (59.9)	53(32.3)
Headache	3 (1.9)	10(6.3)	5 (3.1)	6 (3.7)	8 (4.9)	1 (0.6)
Application site pruritus	6 ( 3.8)	7 ( 4.4)	1 ( 0.6)	12 ( 7.3)	15 ( 9.3)	1 ( 0.6)
Fatigue	2 ( 1.3)	7 ( 4.4)	0	5 ( 3.0)	8 (4.9)	1 ( 0.6)
Nausea	1 ( 0.6)	6 ( 3.8)	2 ( 1.3)	2 ( 1.2)	2 ( 1.2)	0
Application site irritation	4 ( 2.5)	5 ( 3.1)	0	6 ( 3.7)	9 ( 5.6)	1 ( 0.6)
Application site pain	2 ( 1.3)	5 ( 3.1)	0	11 ( 6.7)	15 ( 9.3)	0
Pyrexia	0	5 ( 3.1)	0	1 ( 0.6)	6 ( 3.7)	0
Anorexia	0	4 ( 2.5)	0	0	0	0
Dizziness	1 ( 0.6)	4 ( 2.5)	0	0	1 ( 0.6)	1 ( 0.6)
Herpes simplex	0	4 ( 2.5)	1 ( 0.6)	2 ( 1.2)	2 ( 1.2)	0
Nasopharyngitis	4 ( 2.5)	4 ( 2.5)	8 ( 5.0)	3 ( 1.8)	2 ( 1.2)	1 ( 0.6)

Pain	1 (0.6)	4 (2.5)	0	0	0	0
Upper respiratory tract infection	4 (2.5)	4 (2.5)	6 (3.8)	4 (2.4)	4 (2.5)	1 (0.6)
Urinary tract infection	0	4 (2.5)	4 (2.5)	4 (2.4)	2 (1.2)	1 (0.6)
Back pain	1 (0.6)	3 (1.9)	3 (1.9)	2 (1.2)	1 (0.6)	3 (1.8)
Chest pain	0	3 (1.9)	0	1 (0.6)	1 (0.6)	1 (0.6)
Diarrhoea	2 (1.3)	3 (1.9)	0	1 (0.6)	3 (1.9)	2 (1.2)
Lymphadenopathy	4 (2.5)	3 (1.9)	0	4 (2.4)	7 (4.3)	0
Application site swelling	0	2 (1.3)	0	3 (1.8)	1 (0.6)	0
Arthralgia	4 (2.5)	2 (1.3)	0	3 (1.8)	2 (1.2)	2 (1.2)
Blood glucose increased	0	2 (1.3)	0	3 (1.8)	2 (1.2)	0
Dermatitis	0	2 (1.3)	0	0	2 (1.2)	0
Food poisoning	0	2 (1.3)	0	0	0	0
Insomnia	0	2 (1.3)	0	0	1 (0.6)	0
Seborrhoeic keratosis	0	2 (1.3)	0	0	0	0
Squamous cell carcinoma	0	2 (1.3)	1 (0.6)	2 (1.2)	0	2 (1.2)
Vomiting	0	2 (1.3)	1 (0.6)	0	0	0

*Comment: Local site reactions, headache, fatigue and lymphadenopathy have much higher incidence in treatment groups than in placebo groups. These are the same types of adverse events that were considered treatment related by investigators reiterating again irritancy potential of imiquimod as well as immunomodulating properties. Analysis by system organ class confirms that general disorders and administration site conditions were the most frequently reported adverse events in the active treatment groups.*

*PK study had similar AE frequency and distribution as 3 week treatment cycle using 3.75% cream. 12/19 subjects (63.2%) experienced AE. The following AE were each experienced by 2 subjects (10.5%): epigastric discomfort, application site pain, application site pruritus, fatigue, pain, and dizziness.*

#### 7.4.2 Laboratory Findings

Overall, there were no clinically meaningful trends observed for any of the laboratory parameters. Most frequently reported shift from normal values at screening to high at the end of the trials was blood glucose. This is not unexpected, as subjects were not requested to fast before providing a blood sample. The significance of similar observation for urine protein is not clear. However, the rates among active and placebo groups were similar.

#### 7.4.3 Vital Signs

Except for elevated temperature, there were no clinically meaningful changes in vital signs throughout any of the 5 studies.

Elevated temperature was detected in 12 subjects treated with imiquimod (11 with 3.75% cream), and not in any placebo treated subject, suggesting treatment related causality.

In 2 week trials one subject in 2.5% group had elevated blood pressure together with angina pain and atrial fibrillation. In three weeks trials 2 subjects in 3.75 % group had tachycardia, 3 subjects in 2.5% group and 3 subjects in placebo had increased blood pressure. Two subjects in placebo group also had orthostatic hypotension and weight loss, respectively.

#### 7.4.4 Electrocardiograms (ECGs)

There were no ECG studies done in this submission. For details see [7.2.4 Routine Clinical Testing](#).

#### 7.4.5 Special Safety Studies/Clinical Trials

An observational, Phase 3b trial (GW01-0803) is ongoing in about 200 subjects who completed Phase 3 pivotal studies. The aim of the trial is to assess safety of the imiquimod 2.5% and 3.75% and to address AK recurrence rate.

#### 7.4.6 Immunogenicity

Imiquimod stimulates the immune system. Although not fully understood, this mechanism involves both innate and to less degree acquired aspects of immune response. There was no specific data from this submission that further analyzed different aspects of this quality. Common yet significant local skin reactions as well as flu-like symptoms in subjects are considered to be consequences of immune system activation causing both, treatment and side effects. Excessive activation of immune system was not observed in this submission.

### 7.5 Other Safety Explorations

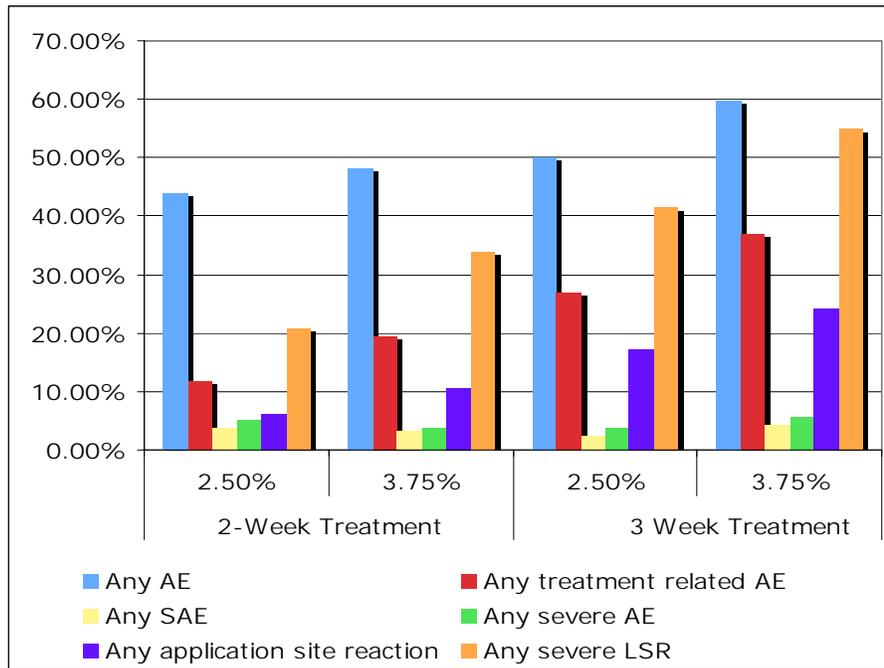
#### 7.5.1 Dose Dependency for Adverse Events

There is trend towards more adverse events with 3.75 % v. 2.5% treatment groups and 3 week v. 2 week treatment. Please see table below (modified from sponsor's Table 5.3.5.3.2.4) and Figure 11.

**Table 39 Dose Dependency for Adverse Events**

	2-Week Treatment		3 Week Treatment	
	2.5 %	3.75%	2.5%	3.75%
Any AE	43.8%	48.1%	50.0%	59.9%
Any treatment related AE	11.9%	19.4%	26.8%	37.0%
Any SAE	3.8%	3.1%	2.4%	4.3%
Any severe AE	5.0 %	3.8%	3.7%	5.6 %
Any application site reaction	6.3 %	10.6%	17.1	24.1%
Any severe LSR	20.6 %	33.8%	41.5%	54.9%

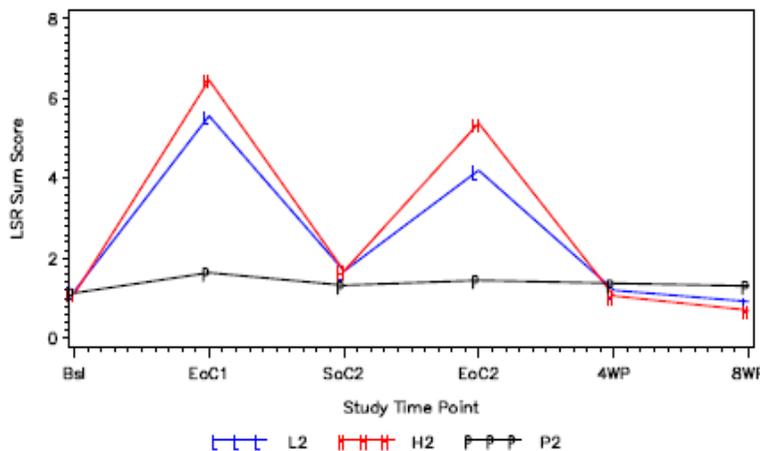
**Figure 11 Dose Dependency for Adverse Events**



7.5.2 Time Dependency for Adverse Events

There was no specific time line for development of systemic adverse events. No important trends were noted in the duration of AEs by dose or regimen across the 4 Phase 3 studies. It was noted that systemic adverse events could developed independently from local skin reactions. Local skin reactions were observed primarily on or after Day 14 of each cycle as seen on Figure 12 (reproduced from sponsor’s Figure 5.3.5.3.2.1). In the post-treatment period most of the reactions resolved.

**Figure 12 Time Dependency for LSR**



Note: Bsl=Baseline, EoC1=End of Cycle 1, SoC2=Start of Cycle 2, EoC2=End of Cycle 2, 4WP=4 Weeks Post-treatment, 8WP=8 Weeks Post-treatment. L2=2.5% 2-week cycle treatment regimen, H2=3.75% 2-week cycle treatment regimen, P2=Placebo 2-week cycle treatment

*Comment: There is a recognizable time dependency for skin related AE. The highest score of LSR is present at the end of the each treatment period (2 weeks). The peak LSR intensity during treatment cycle 2 was less pronounced than the peak during treatment cycle 1. Similar pattern was observed in 3 week cycle.*

### 7.5.3 Drug-Demographic Interactions

There is little difference in incidence of adverse events rate when analyzed by age, sex, or Fitzpatrick skin type. AE seems to be more likely in females and subjects with < 65 years when treated with 2.5% imiquimod cream. There is no suggestive pattern of AE in 3.75% arm. Race could not be analyzed since all but 3 subjects were white. Reader is referred to Table 40 (modified from sponsor's Table 5.3.5.3.2-22).

**Table 40 Number (%) of Subjects with Adverse Events by Subpopulation, Combined Studies – ITT Population**

	2-Week Treatment Cycle Regimen			3-Week Treatment Cycle Regimen		
	3.75%	2.5%	Placebo	3.75%	2.5%	Placebo
Age <65	39 / 82 (47.6)	44 / 88 (50.0)	33 / 90 (36.7)	56 / 94 (59.6)	39 / 75 (52.0)	23 / 86 (26.7)
Age ≥65	38 / 78 (48.7)	26 / 72 (36.1)	20 / 69 (29.0)	41 / 68 (60.3)	43 / 89 (48.3)	30 / 78 (38.5)
Male	64 / 132 (48.5)	53 / 127 (41.7)	38 / 130 (29.2)	74 / 123 (60.2)	60 / 128 (46.9)	43 / 135 (31.9)
Female	13 / 28 (46.4)	17 / 33 (51.5)	15 / 29 (51.7)	23 / 39 (59.0)	22 / 36 (61.1)	10 / 29 (34.5)
Fitzpatrick Skin Type I or II	47 / 96 (49.0)	42 / 91 (46.2)	25 / 77 (32.5)	67 / 100 (67.0)	46 / 83 (55.4)	31 / 90 (34.4)
Fitzpatrick Skin Type III - VI	30 / 64 (46.9)	28 / 69 (40.6)	28 / 82 (34.1)	30 / 62 (48.4)	36 / 81 (44.4)	22 / 74 (29.7)

### 7.5.4 Drug-Disease Interactions

These studies do not provide sufficient data to examine disease interactions with 3.75% or 2.5% imiquimod cream.

### 7.5.5 Drug-Drug Interactions

These studies do not provide sufficient data to examine drug interactions with 3.75% or 2.5% imiquimod cream.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

Phase 4, long term safety study (1520-IMIQ) with 551 subjects treated with approved 5% imiquimod cream did not reveal carcinogenic signal.

### 7.6.2 Human Reproduction and Pregnancy Data

No trials with imiquimod were conducted in pregnant women and there were no pregnancies reported in any of the trials. Imiquimod is category C pregnancy risk based upon pre-clinical data included in initial NDA-22723.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

Actinic keratosis is disease of adults, thus pediatric population was not included in these trials. The PeRC granted a full waiver of pediatric studies for this NDA on June 24, 2009. This decision was based on the criteria that studies would be impossible or highly impracticable because there are too few children with disease/condition to study.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of overdose occurred in any of the submitted studies. It is anticipated that potential overdose may result in more severe local reactions and increase the risk for systemic reaction. The abuse potential for imiquimod is low. Ongoing observational study (GW01-0803) will examine the recurrence of AK lesions.

## 7.7 Additional Submissions

There were no additional submissions for this NDA.

## 8 Postmarketing Experience

Neither 2.5% nor 3.75% imiquimod cream is a marketed product so there is no postmarketing data available. However, long-term follow up safety and efficacy study GW01-0803 is ongoing. Data are provided for Aldara cream (imiquimod 5%) from its Phase 4 study 1520-IMIQ. In addition, Office of Drug Safety provided an overview of AERS data base for imiquimod 5% in 2004.

Information derived from these reports did not change the labeling of Aldara®.

Application site reactions have been the most common adverse event observed since imiquimod 5% cream was approved.

## 9 Appendices

### 9.1 Literature Review/References

1. Gibson S et al Cell Immun 218:74-86, 2002
2. Imbertson L et al, J Invest Dermatol 110:734-739, 1998
3. Testerman T et al, J Leuk Biol 58:356, 1995
4. Dinehart SM, J Am Acad Dermatol Jan 2000:S25-S28
5. Stockfleth E et al, Arch Dermat 138:1498-1502, 2002
6. Feldman SR et al. J Am Acad Dermatol 40:43-47, 1999
7. Tyring S et al., Int J of Dermatol 42: 810-816, 2002))
8. Package Insert, Aldara®, 5% (imiquimod) (Graceway Pharmaceuticals, LLC, Bristol, TN)
9. Package Insert Roferon®-A, (interferon  $\alpha$ ) (Hoffman-Roche Inc, Nutley, NJ)
10. PJ Pockros, D Guyader, H Patton, and others Oral (b) (4) in chronic HCV infection: Safety and efficacy in 2 placebo-controlled, double-blind phase IIa studies. *Journal of Hepatology* 47(2): 174-182. August 2007.

### 9.2 Labeling Recommendations

Sponsor has proposed unique proprietary name Zyclara and separate labeling for imiquimod 3.75% cream. The presence of two marketed products ( Aldara and Zyclara) with same active ingredient could lead to medical errors, for example: a) concomitant prescribing and use of two imiquimod products in the same patient leading to higher product exposure, b) erroneous use of one formulation in a manner consistent with the recommended administration of the other formulation may lead to unwanted exposure and adverse reactions. At this time, Agency is

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Milena Lolic, M.D., M.S.  
NDA 22-483  
Zyclara (imiquimod 3.75%)

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considering incorporating labeling changes to reflect this concern. Comments on the sponsor's draft labeling will be added as an addendum to this review.

### 9.3 Advisory Committee Meeting

No Advisory Committee was convened for this application.

APPEARS THIS WAY IN ORIGINAL



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/

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MILENA M LOLIC  
09/23/2009

JILL A LINDSTROM  
09/23/2009

## ADDENDUM TO CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-483
Priority or Standard	Priority-Class 1 resubmission
Submit Date(s)	January 29, 2010
Received Date(s)	February 2, 2010
PDUFA Goal Date	March 29, 2010
Reviewer Name(s)	Milena M. Lolic, M.D.,M.S.
Review Completion Date	March 1, 2009
Review Revision Date	March 22, 2009
Established Name	Imiquimod 3.75% cream
(Proposed) Trade Name	Zyclara
Therapeutic Class	Immune response modifier
Applicant	Graceway
Formulation(s)	Topical cream
Dosing Regimen	Once daily for two 2- week cycles
Indication(s)	Actinic keratosis
Intended Population(s)	Adults older then 18 years

Clinical review of this resubmission was completed on March 1, 2010 while negotiations with applicant were ongoing regarding post marketing requirement (PMR) and labeling. This amendment with summarize the outcome of those negotiations.

Post marketing commitment

The Agency initiated a teleconference on March 2, 2010 to inform the applicant that their proposed draft protocol synopsis for post marketing clinical trial was not adequate because of population selection, number of subjects and type of ECG monitoring. Applicant submitted second draft protocol proposal on March 15, 2010 that was accepted by the Division.

The PMR reads:

“Conduct a randomized crossover clinical trial (Zyclara Cream, 3.75% vs. vehicle) in patients with actinic keratosis to detect treatment-related change in atrial ectopy “.

The timetable is as follows:

Final Protocol Submission:	September 2010
Trial Completion Date:	September 2011
Final Report Submission:	March 2012

Labeling negotiations:

1. CMC reviewer objected current presentation of the dosage form (Cream) and the strength (3.75%) on the carton and requested that it should appear as follows:

Zyclara  
(imiquimod) Cream  
3.75%

In his memorandum from March 18, 2010, the CMC reviewer concluded:

“In an amendment dated 16-MAR-2010, the sponsor has committed to modify and implement the requested label presentation style once the current supply of printed material is exhausted.

The commitment is deemed acceptable and, therefore, from the CMC perspective, this NDA is now recommended for approval.”

2. DMEPA objected:

- Use of (b) (4) in both, labeling (Section 2 and Section 16) and carton and requested that it be replaced with “Box” and,
- Use of (b) (4) on the carton label and requested that it be removed.

*Reviewer comment: In an amendment dated March 22, 2010 applicant incorporated requested changes. Reviewer recommends approval of the NDA.*

Milena Lolic, M.D., M.S.  
Medical Officer, DDDP

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/

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MILENA M LOLIC  
03/23/2010

JILL A LINDSTROM  
03/23/2010



Weeks of Treatment with Imiquimod Creams for Actinic Keratoses Indication: Actinic Keratoses Pivotal Study #0704 identical to # 0702 Indication: Actinic Keratoses				
15. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16. Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17. Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	There are no foreign data.
<b>SAFETY</b>				
18. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19. Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?		x		2.7.2-3 2.7.2.-4
20. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?	x			
<b>OTHER STUDIES</b>				
21. Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?			x	
22. For an Rx-to-OTC switch application, are the necessary special OTC studies included (e.g., labeling comprehension)?			x	
<b>PEDIATRIC USE</b>				
23. Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			As requested at pre-NDA meeting
<b>ABUSE LIABILITY</b>				
24. If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
<b>FOREIGN STUDIES</b>				
25. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	Phase 3 clinical study sites all in US
<b>DATASETS</b>				
26. Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
27. Has the applicant submitted datasets in the the format agreed to previously by the Division?	x			
28. Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
29. Are all datasets to support the critical safety analyses available and complete?	x			

30. For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints?	x			
<b>CASE REPORT FORMS</b>				
31. Has the applicant submitted all required Case Report forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
32. Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
<b>FINANCIAL DISCLOSURE</b>				
33. Has the applicant submitted the required Financial Disclosure information for study investigators?	x			1.3.4. Form 3455 for one investigator
<b>GOOD CLINICAL PRACTICE</b>				
34. Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			
<b>CONCLUSION</b>				
35. From a clinical perspective, is this application fileable? If "no", please state why it is not?	x			

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. The effect of the product on cardiac repolarization has not been adequately addressed. Provide evidence that the product does not have an impact on cardiac repolarization.

Milena Lolic, M.D., M.S.  


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 Reviewing Medical Officer

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 Clinical Team Leader

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/s/

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Milena Lolic  
2/17/2009 01:15:11 PM  
MEDICAL OFFICER

Jill Lindstrom  
2/27/2009 03:21:58 PM  
MEDICAL OFFICER