CLINICAL REVIEW

Application Type	NDA 505 (b)(1)
Application Number(s)	201153
Priority or Standard	Standard
Submit Date(s)	February 8, 2010
Received Date(s)	February 24, 2010
PDUFA Goal Date	December 8, 2010
Division / Office	DDDP/OND
Reviewer Name(s)	Milena Lolic, M.D.
Review Completion Date	October 6, 2010
Established Name	Imiquimod
(Proposed) Trade Name	Zyclara cream 3.75%
Therapeutic Class	Not determined
Applicant	Graceway
Formulation(s)	Cream
Dosing Regimen	Daily for up to 8 weeks
Indication(s)	External genital warts and perianal warts
Intended Population(s)	12 years and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that NDA 201153, Zyclara 3.75% cream for the treatment of external genital and perianal warts/condyloma acuminata in patients 12 years or older be approved.

Two phase 3 trials (GW01-801 and GW01-0805) demonstrated the short term efficacy and safety of imiquimod 3.75% cream for patients with external genital warts (EGW).

External genital warts are primarily associated with a sexually acquired infection with human papilloma virus (HPV). During Guidance meeting held July 27, 2007, applicant was advised that the inclusion criteria for age should be 12 years and older, and that applicant "would not need to target enrollment of a particular number of younger pediatric subjects"
The data base for adolescent population in these trials is limited to 3 subjects between 15 and 17 years of age, however reviewer is in agreement with pediatric consultant (7.6.3) that approval down to 12 years does not need additional clinical data. The justification comes from the following:

- the EGW indication for imiquimod 5% cream was expanded in 2002 by the Division of Dermatology and Dental Products to patients 12 years of age and older, based on the available data in the adult population,
- submitted phase 3 trials may support the extrapolation of efficacy down to the age of 12 years,
- safety data from the enrolled subjects as well as previous safety information from imiquimod 5% cream are sufficiently supportive of safety for imiquimod 3.75% cream when used in ages 12-18. The supportive data include safety data from molluscum contagiosum program (trials conducted in children 2-12 years of age) and literature review. In both instances, the safety findings for patients less then 18 years of age approximate those in adult population.

1.2 Risk Benefit Assessment

Applicant did not conduct dose-ranging trials prior to this submission but instead proceeded to phase 3 trials utilizing two different imiquimod cream concentrations (2.5% and 3.75%) against vehicle.
Risk benefit assessment of the two concentrations was based on analysis of individual and pooled data from phase 3 trials. The superiority of 3.75% imiquimod cream over vehicle was confirmed in both phase 3 trials, while 2.5% cream failed to reach statistical

significance in one of them. Furthermore, 3.75% cream had slightly higher observed clearance rates than the 2.5% cream across all categories.
Safety profiles of both concentrations closely resemble the profile of imiquimod 5% cream that has been marketed over 20 years. There were no new safety concerns, thus risk benefit assessment for two imiquimod concentrations used in phase 3 trials favors 3.75% cream for approval.

There are different treatments available for the treatment of EGW (2.2) including imiquimod 5% cream [currently marketed as brand (Aldara®) and generic product]. The applicant's product differs from imiquimod 5% cream in three ways:

- lower concentration (3.75% v. 5%)
- dosing regimen (daily application v. three times weekly)
- duration of treatment (8 weeks v. 16 weeks).

Direct comparison of these two concentrations was not done. While the question on comparative effectives remains unanswered, treatment with imiquimod 3.75% cream concentration offers more intuitive regimen and is shorter then treatment with 5% creme.
In the category of patient applied therapies for EGW, addition of imiquimod 3.75% cream provides for another choice of treatment.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for a specific postmarket risk management plan. The presence of two different concentrations of imiquimod creams on the market may cause the potential risk of inadvertently wrong dosing (for example, using 5% cream daily instead of three times weekly). However, products containing 5% cream have different names and separate package inserts that should alert to the differences. 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.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no postmarketing requirements and commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Imiquimod was developed for the treatment of several skin disorders where activation of immune system was expected to be beneficial. The mechanism of its action is not fully understood but involves activation of Toll like receptor 7 in the skin (Gibson, 2002) and consequent induction of several cytokines including interferon α, TNF α and interleukins 1, 6 and 8 (Imbertson, 1998). These in turn activate various immune cells that carry-out activity. Imiquimod 5% cream (Aldara) has been marketed for over 8 years for the treatment of external genital and perianal warts/condyloma acuminata in patients 12 years or older, with three-times weekly dosing regimen for up to 16 weeks.

(b) (4)

The aim of the current submission is approval of imiquimod 3.75% cream (Zyclara) for the treatment of external genital and perianal warts/condyloma acuminata in patients 12 years or older with daily dosing up to 8 weeks.

Applicant took similar approach in product development for the treatment of actinic keratosis (AK). Imiquimod 5% cream (Aldara ®) was approved in 2004 for the treatment of AK involving ≤ 25 cm² area with twice weekly dosing for 16 weeks. As the result of the new development program, imiquimod 3.75% cream (Zyclara™) was approved for the treatment of AK of the whole face or balding scalp in March 2010 with daily dosing for two 2-week cycles.

2.2 Currently Available Treatments for Proposed Indications

External genital warts (EGW)/condyloma acuminata is sexually transmitted disease caused by human papilloma virus (HPV). Clinical warts present as pink, smooth, dome-shaped papules in genital area. They are usually asymptomatic, but cause significant social distress. If left untreated genital warts may resolve, remain unchanged or grow. Even after appropriate treatment, EGW may recur because treatments do not eradicate HPV from normal-appearing peri-lesional skin. There are multiple treatments currently used to treat EGW (not all FDA approved), usually divided in to two categories:

Physician applied:
1. Cryosurgery with liquid nitrogen

2. Electrodissecation/electrocautery
3. Trichloracetic and bichloroacetic acid
4. Podophylin solution 10% and 20%
5. Laser surgery
6. Interferon injections

Patient applied:
1. Podofilox 0.5% solution
2. Veregen (sinecathehin)
3. Aldara 5% (imiquimod) cream

There is no clear advantage of any therapy over the other and the choice of therapy depends on the patient's and physician's preference and extent of the disease. Patient applied therapies are regarded asless aggressive, and more cost-effective (Mayeaux, Frenkl). Podofilox is applied twice daily for 3 consecutive days for maximum of 4 weeks. Veregen is administered 3 times daily for up to 16 weeks. Aldara 5% cream is applied three times weekly for up to 16 weeks.

Comment: New, more intuitive, and shorter duration of patient applied therapy may provide more appealing treatment and increase patient's compliance. However the presence of two imiquimod creams (3.75% and 5%) on the market for the same indication may be confusing because of different dosing regimens.

2.3 Availability of Proposed Active Ingredient in the United States

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

    a) Treatment of external genital and perianal warts/condyloma acuminata in individuals 18 years old and above (February 27, 1997). On September 3, 2002 indication expanded to include patients 12 years or older.
    b) Topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp within surface area of ≤25cm² in immunocompetent adults (March 2, 2004).
    c) 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. Imiquimod cream 5% (generic drug) was approved on February 25, 2010
3. Imiquimod cream 3.75% (Zyclara™) is approved for:

a) Topical treatment of clinically typical, visible or palpable actinic keratoses (AK) of the full face or balding scalp in immunocompetent adults (March 25, 2010).

2.4 Important Safety Issues with Consideration to Related Drugs

Imiquimod is the first generation imidazoquinoline. Imiquimod upregulates the local production of cytokines (mostly interferon α, tumor necrosis factor α, and interleukin 6) and consequently causes a pro-inflammatory response.
Local adverse reactions comprise of erythema, edema and crusting of the skin that can occasionally be severe.
Systemic exposure as the result of the topically applied imiquimod is documented (Smith 2003). More frequent systemic reactions include flu-like signs and symptoms, lymphadenopathy, headache and fever.

- Systemically administered interferon α (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).
- Resiquimod is a second generation imidiazoquinoline that is 100 times more potent cytokine inducer than imiquimod (Smith, 2003). (b) (4) [redacted]
- Sotirimod is under development for the treatment of actinic keratosis. (b) (4) [redacted]

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Relevant pre-submission regulatory activity for imiquimod 3.75% for treatment of EGW 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) (b) (4) (b) (4) and genital warts under 21 CFR 312. Agency comments in regard to treatment of EGW included:

- separate PK study in population affected with EGW should be conducted with the to-be-marketed formulation under maximal use condition
- additional Phase 2 dose ranging studies are recommended before proceeding to Phase 3.
- if the new product demonstrates a better benefit/risk profile compared to the 5% then the EGW indication for the 5% cream would be withdrawn
- gender specific dose regimens are not justified with current program
- primary end-point should be proportion of the subjects with complete clearance of all EGW (baseline and new)
- the development program should provide for the assessment of EGW recurrence
- the inclusion criteria for age should be 12 and older, but sponsor "would not need to target enrollment of a particular number of younger pediatric subjects" Sponsor should provide rationale for extrapolating data from older to younger age groups

- On January 20, 2008 a second Guidance Meeting was held to further assist in development program for lower strength and different dosing regimen for the treatment of EGW only:
  - sponsor acknowledged the risk of proceeding with two Phase 3 studies with dose response element instead of conducting Phase 2 trials first
  - phase 3 trials will include an assessment for recurrence at 12 weeks post EOS
  - long term safety should be addressed and previously conducted studies may fulfill that need (as per ICH E1A)
- On May 20, 2008 a teleconference was held and it was concluded that:
  - the agency will accept filing of the NDA with three arms only (2.75%, 3.75% and vehicle) without direct comparison to 5% cream
- On November 18, 200 a Pre-NDA Meeting was held. Discussion included:
  - marketing application may be submitted as an efficacy supplement to NDA 22-483 only if that NDA is approved in the meantime
  - 120 day safety update may include periodic safety report for other imiquimod product if the report is to be generated within 2 month interval
  - in regard to high rate of discontinuation in phase 3 trials, sponsor will conduct additional sensitivity analysis
  - sponsor will need to explain why data from long-term safety studies 1233-IMIQ and 1243-IMIQ done with 5% cream is relevant to 3.75% cream in order for those studies to be accepted

2.6 Other Relevant Background Information

In 2008 the Agency became aware of new safety concerns with Aldara® cream 5%, when used for the treatment of EGW and those were related to difficulty and inability to urinate. To date, 24 such individual cases were reported. In some instances hospitalizations (10 cases) and urinary catheterizations (13) were needed to overcome urinary retention.
It appears that severe local reactions caused the urinary problems. Based upon OSE and Division recommendation, labeling revision was requested and at this time, negotiation with applicant is ongoing.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

3.2 Compliance with Good Clinical Practices

The applicant included a statement that all the trials were carried out in accordance with Good Clinical Practice (GCP) guidelines.
DSI inspection of the clinical sites was not requested.

3.3 Financial Disclosures

None of the investigators reported financial interest.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

From the CMC Review by Shulin Ding, PhD:

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. All facilities involved are in compliance with cGMP, and labels/labeling have adequate information required. Therefore, from a CMC perspective, this NDA is recommended for "Approval**".**

4.2 Preclinical Pharmacology/Toxicology

There is no new non-clinical toxicology data included in this submission. A comprehensive summary of nonclinical information from imiquimod development program was provided as requested by the Agency at the pre-NDA meeting (November 18, 2009). Interested reader is referred to Pharmacology/Toxicology Review for more detailed information on the non-clinical data relevant to this NDA submission. The reviewer recommended approval of this NDA provided that corrected animal multiples of Maximum Recommended Human Dose is incorporated in the labeling.

4.3 Clinical Pharmacology

The reader is referred to the Clinical Pharmacology Review for detailed review.

4.3.1 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-α 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-inflamatory proteins.

4.3.2 Pharmacodynamics

No pharmacodynamics trials were included in this submission.

4.3.3 Pharmacokinetics

Applicant submitted PK data from GW01-0804 study conducted with 3.75% imiquimod cream used for EGW treatment under maximal use conditions. Brief description of GW01-0804 study is provided in section 7.2.5 .
This open-label study was conducted over 3 weeks on 18 subjects with either ≥8 EGW or a total wart area of ≥100 ²mm in the genital/perianal area using one packet of cream daily.

Serum PK results are shown below (electronically copied Table 2.5-2):

Table 1 Pharmacokinetic Data of Imiquimod from 804 Study

	Mean (SD)			
Parameter	**N**	**Day 1 (all subjects)**	**N**	**Day 21**
C_{max} (ng/mL)	18	0.259 (0.223)	15	0.488 (0.368)
T_{max} (hr) (minimum – maximum)	17	12.00 (4.00-16.00)	15	12.00 (1.00-16.00)
AUC_{0-24} (ng•hr/mL)	15	3.748 (2.541)	15	6.795 (3.591)

Note: Day 21 PK results include all PK population subjects except Subject 001-404 (missed applications on Days 8 and 18), Subject 001-407 (missed an application on Day 20), and Subject 001-416 (missed an application on Day 17).
AUC = area under the concentration-time curve.

In addition, data from several other PK studies conducted with different imiquimod products are included and presented for comparison purposes. The summary is in the Table 2 below (electronically copied Table 2.7.2-10):

Table 2 Summary of PK Data from Multiple Studies

Study (formulation)	Dose of imiquimod	Duration	N	Site	Mean (SD) C_{max} [ng/mL]	Mean (SD) AUC [ng·hr/mL]	Ratio of Mean GW01-0804 C_{max} / Study C_{max}	Ratio of Mean GW01-0804 AUC / Study AUC
Study GW01-0804 (3.75% imiquimod cream)	Up to 1 packet (9.375 mg) daily	21 days	15 [a]	Genital area	0.488 (0.368)	6.795 (3.591)	NA	NA
Study GW01-0706 (3.75% imiquimod cream)	2 packets (18.75 mg) daily	21 days	17 [a]	Face or Scalp	0.323 (0.159)	5.974 (3.088)	1.51	1.14
Study 1253-IMIQ (5% imiquimod cream)	As needed to cover the wart areas; 3x/week	16 weeks	12 [b]	Genital area	0.437 (0.517) [b]	5.324 (3.256) [b]	1.12	1.28
Study 1402-IMIQ (5% imiquimod cream)	1 packet (12.5 mg) 3x weekly	16 weeks	23 [a]	Face	0.120 (0.063)	2.06 (1.70)	4.06	3.30
	2 packets (25 mg) 3x weekly		11 [a]	Scalp	0.214 (0.097)	4.98 (4.41)	2.28	1.36
	6 packets (75 mg) 3x weekly		24 [a]	Hands/Arms	1.35 (0.841) [c]	29.1 (17.1) [c]	0.36	0.23
					3.53 (6.52) [d]	55.4 (76.0) [d]	0.14	0.12
Study 1520-IMIQ (5% imiquimod cream)	6 packets (75 mg) 2x weekly	16 weeks	13 [a]	> 25% of Body Surface Area	0.958 (1.18)	24.3 (26.9)	0.51	0.28
Study R-837-009 (imiquimod capsules)	Single dose of	1 dose						
	100 mg		6 (100 mg)	Not Applicable	120 (60)	573 (301)	0.0041	0.0119
	200 mg		6 (200 mg)		281 (138)	1728 (1183)	0.0017	0.0039
	250 mg		6 (250 mg)		359 (230)	2059 (1405)	0.0014	0.0033
	300 mg		12 (300 mg)		528 (128)	5072 (2294)	0.0009	0.0013
Study R-837-019 (imiquimod capsules)	Single dose of	1 dose						
	100 mg		6 (100 mg)	Not Applicable	126 (90)	585 (520)	0.0039	0.0116
	200 mg		6 (200 mg)		272 (51)	1723 (825)	0.0018	0.0039
	300 mg		6 (300 mg)		424 (146)	4486 (3206)	0.0012	0.0015

Note: All other studies were compared with Study GW01-0804 (bolded).
a: Number of subjects in PK population at steady state.
b: Data from Week 4 – Note that overall mean imiquimod Cmax and AUC for all patients over the 3 doses monitored in Study 1253-IMIQ were 0.405 ng/mL and 5.504 ng/hr/mL, respectively.
c: Data from Harrison et al, 2004 [9] (rejecting outliers that were > 5X the SD of their respective means).
d: Data from the 1402-IMIQ report that includes outliers.

With exception of two oral studies, systemic absorption of imiquimod is low. Daily regimen with one packet of 3.75% cream produces similar systemic levels as approved regimen with 5% cream when used 3 times a week (Cmax 0.488 ng/mL v. 0.437 ng/mL).

Comparison to studies conducted with either 3.75% or 5% cream for AK indication 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. Furthermore, it does not appear to be linear dose proportionality between Cmax and applied dose or AUC and the applied dose.
From a pharmacokinetic standpoint, there is low but detectable systemic absorption from imiquimod 3.75% cream when applied to EGW daily for 3 weeks. Systemic levels are comparable to those reported with currently approved 5% cream regimen for EGW.

5 Sources of Clinical Data

5.1 Tables of Clinical Trials

The data reviewed to support requested indication are from trials conducted by the applicant. There are three trials: 2 phase 3 trials (GW01-801 and GW01-0805) and one pharmacokinetic (GW01-0804).
See Table 3 for listing and summary of these trials (modified from applicant's Table 5.3.5.3.2-2).

Table 3 Summary of Submitted Trials for EGW

Type of Study	Study Number	Objectives	Study Design and Type of Control	Test Products	Number of Subjects in ITT Population (3.75%/2.5%/ Placebo)	Number of Subjects in Safety Population (3.75%/2.5%/ Placebo)	Duration of Treatment
EGW Clinical Studies – Conducted with 3.75% Imiquimod Cream							
PK study	GW01-0804	Multiple-dose PK in EGW patients to determine serum imiquimod and metabolite concentrations under maximal use conditions	Phase 1, open-label, nonrandomized	3.75% imiquimod cream, topical, applied once daily	18 (all subjects received 3.75% imiquimod)	18 (all subjects received 3.75% imiquimod)	21 days
Safety and Efficacy study	GW01-0801	Pivotal efficacy and safety	Phase 3, randomized, double-blind, placebo-controlled	3.75% and 2.5% imiquimod creams, topical, applied once daily	470 (195/178/97)	470 (195/178/97)	Up to 8 weeks of treatment.
Safety and Efficacy study	GW01-0805	Pivotal efficacy and safety	Phase 3, randomized, double-blind, placebo-controlled	3.75% and 2.5% imiquimod creams, topical, applied once daily	511 (204/202/105)	511 (205[a]/201[a]/105)	Up to 8 weeks of treatment.

a: Subject 0805-04/025 (female) was originally randomized to the 2.5% imiquimod treatment group; however, at Week 2, the subject incorrectly received a 3.75% imiquimod treatment group kit assigned to another subject. For the safety analysis the highest dose received (3.75%) is used and for the efficacy analysis, the original randomized treatment of 2.5% is used.
b: Number of subjects included in the AE tables

Additional trials included in this submission (identified by applicant as supportive) are:

1. From imiquimod 5% cream (Aldara®) program:
   - 1233-IMIQ and 1243-IMIQ long term safety and efficacy trials for EGW indication
   - 1253-IMIQ pharmacokinetic trial for EGW
   - 1520-IMIQ long term safety AK (overexposure)
   - 1402 –pharmacokinetic trial for AK

2. From imiquimod 3.75% cream (Zyclara ™) program:
   - GW01-0706- pharmacokinetic trial in AK
   - GW01-0702, GW01-0703, GW01-0704, GW01-0705-phase 3 trials for AK

3. From early imiquimod program (oral dosing)
   - R-837-009 safety and pharmacokinetics in healthy subjects

It should be noted that completed GW01-0803 long term recurrence trial for AK with imiquimod 3.75% is not included in this submission.

5.2 Review Strategy

Protocols of two identical phase 3 trials are reviewed and presented in this section. These are GW01-801 and GW01-0805. The discussion of phase 3 clinical trials efficacy and safety results is presented in Sections 6 and 7.

The pharmacokinetic trial, GW01-0804 is reviewed in general and briefly presented in Section 7.2.5. However, all the safety data from this trial are included in Section 7
In regard to supportive trials, only brief reviews will be presented in Section 5 to the extent of their relevance to the current submission.

5.3 Discussion of Individual Clinical Trials

5.3.1. Phase 3 Trials GW01-801 and GW01-0805

These two identical trials are randomized, double-blind, placebo controlled, multicenter trials that were conducted between June 2008 and June 2009 at 30 US sites. There were no amendments to the protocol.

The design consisted of: screening period (up to 4 weeks), treatment period (8 weeks), and no-treatment period (8 weeks). Subjects who achieved clearance of all warts at any time until Week 16 [end-of-study (EOS)] were eligible to immediately enter the follow-up period for determination of recurrence. During that time they were monitored every 4 weeks for up to 12 weeks. The overall trial design is represented in Table 4 (electronically copied and reproduced Table 2.5.-4 and Table 2.5.-5).

Table 4 Design of Pivotal Trials

Screening	Treatment Period					No-treatment Period			
Week -4 to 0	Week 0	Week 2	Week 4	Week 6	Week 8 / EOT	Week 10	Week 12	Week 14	Week 16 / EOS
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10

Follow-up Period (Only in subjects with complete clearance of all warts in all anatomic areas)		
Week 4 Post-EOS	Week 8 Post-EOS	Week 12 Post-EOS
Follow-up Visit 1	Follow-up Visit 2	Follow-up Visit 3

Trial Objective

The objective was to evaluate efficacy and safety of 2.5% imiquimod cream and 3.75% imiquimod cream v. vehicle applied in the treatment of EGW.

Key Inclusion Criteria

Subjects were eligible for trial participation if they were males or females at least 12 years of age and:

- had a diagnosis of external genital / perianal warts with at least 2 warts and no more than 30 warts located in one or more of the following anatomic locations:
  - In both sexes: inguinal, perineal, and perianal areas;
  - In men: over the glans penis, penis shaft, scrotum, and foreskin;
  - In women: on the vulva;
- had total wart areas of at least 10 mm^2

Key exclusion criteria:

- received any topical and/or destructive treatments for external genital warts within 4 weeks (within 12 months for imiquimod and within 12 weeks for sinecatechins) prior to enrollment (ie, the randomization visit)
- any of the following conditions:
  - known human immunodeficiency virus (HIV) infection;
  - current or past history of high risk HPV infection (eg, HPV 16, 18, etc);
  - an outbreak of herpes genitalis in the wart areas within 4 weeks prior to enrollment;
  - internal (rectal, urethral, vaginal/cervical) warts that required or were undergoing treatment;

• a dermatological disease (eg, psoriasis) or skin condition in the wart areas which may have caused difficulty with examination;

Prohibited medications were:

1. Imiquimod 5% cream (Aldara®);
2. Any marketed or investigational HPV vaccines;
3. Sinecatechins (Veregen);
4. Interferon or interferon inducers;
5. Cytotoxic drugs;
6. Immunomodulators or immunosuppressive therapies;
7. Oral or parenteral corticosteroids (inhaled/intranasal steroids are permitted);
8. Oral antiviral drugs (with the exception of oral acyclovir and acyclovir related drugs for suppressive or acute therapy herpes; or oseltamivir for prophylaxis or acute therapy of influenza);
9. Topical antiviral drugs (including topical acyclovir and acyclovir related drugs) in the treatment areas;
10. Podophyllotoxin/Podofilox in the treatment areas;
11. Any topical prescription medications in the treatment areas;
12. Dermatologic/cosmetic procedures or surgeries in the treatment areas.

Randomization and Controls

Subjects were randomly assigned to trial treatment in a 2:2:1 ratio (2.5% imiquimod cream, 3.75% imiquimod cream, and vehicle cream respectively).

Visits and Procedures

Subjects were instructed to wash the treatment area with mild soap and water and allow the area to dry. Study cream was applied in thin layer to each wart once daily (preferably evening), left on for 8 hours and then washed with soap and water. Up to one packet of trial cream was allowed per application.
Temporary interruption of dosing due to intolerable reaction (perceived either by subject or investigator) was permitted. During that time subject was on rest period.
There were 9 visits during the evaluation period and 3 during follow-up. Laboratory tests were preformed twice, urinary pregnancy test three times and Pap smear once during the trial.
Details are presented in the Table 5 below (electronically copied and reproduced table 9-3)

Table 5 Trial Visits and Procedures

	Screening	Evaluation Period[a] (Continued until complete clearance)					Follow-up Period (only subjects with clearance of all warts)
STUDY VISIT / PROCEDURES	−4 weeks	Randomization / Day 1	Weeks 2, 4, and 6	Week 8 (EOT)	Weeks 10, 12, and 14	Week 16/ EOS[b]	Weeks 4, 8, and 12 (times relative to date of EOS)
Review/sign subject Informed Consent	X						
Review Inclusion and Exclusion Criteria	X	X					
Review genital wart history	X						
Obtain history of therapy for warts	X	X					
Obtain medical history and perform physical exam[c]	X						
Pelvic exam/Pap smear[d]	X						
Perform clinical laboratory tests (serum pregnancy test as applicable)[e]	X					X	
Assess warts and affected area for eligibility	X	X					
Confirm eligibility and obtain Subject/Randomization Number		X					
Urine pregnancy test (as applicable)[f]	X	X	UPT done every 4 weeks			X	
Wart evaluations		X	X	X	X	X	X
Take photographs (at selected centers)		X	X	X	X	X	
Daily treatment with study cream		◄———	———	———	**No Tx**	**No Tx**	
Dispense study medication and review proper application schedule		X	X				
Collect used/unused study medication, review application compliance, update Drug Accountability Log			X	X			
Review and record local skin reactions		X	X	X	X	X	
Review and record adverse events		X	X	X	X	X	X
Review and record concomitant medications		X	X	X	X	X	X

Study Medication Dose Selection, Dispensing and Compliance

Aldara 5% cream is currently marketed for the treatment of EGW (3 times per week for up to 16 weeks). Daily dosing with 5% cream was found to be too irritating. Two lower doses (2.5% and 3.75%) were selected for this application in order to allow daily dosing regimen which in turn will allow shorter duration of treatment (up to 8 weeks). Treatment supplies for each subject included treatment kits for 8 weeks of treatment. Each treatment kit contained 4 supply boxes of study cream and one emergency box, each box containing a 2-week supply of study cream. Study personnel monitored compliance on each visit by counting and recording any used and unused study packets.

Primary Endpoint:

- Proportion of subjects achieving complete clearance of all warts (baseline and new) on or before Week 16 (EOS)

Secondary Endpoints

- Time to complete clearance of all warts (baseline and new)

- Proportion of subjects with at least 75% reduction in the number of baseline warts on or before Week 16
- Proportion of subjects who are clear at EOS and remain clear at the end of the Follow-up Period
- Percent change from baseline to end of the trial in total number of warts

Safety Parameters

- Adverse reactions (AE)
- Local skin reactions (LSR) and application site reactions
- Number and duration of rest periods during the treatment period

Local skin reactions were quantified as represented in Table 6 (electronically copied and reproduced Table 9-4). They were actively assessed by investigator during the trial period and recorded as AEs if:

-they extended beyond the anatomic treatment area,
-they required any medical interventions, or
-the LSR resulted in subject discontinuation from the study.

Application site reactions other than those described as LSRs (eg, pain, burning, itching, bleeding, pruritus etc.) were recorded as AEs.

Table 6 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 (b) (4) The statistical plan for efficacy analysis was to use Cochran-Mantel-Haenszel test stratified by center and gender with imputations for missing data using last observation carried forward (LOCF).
Applicant performed additional sensitivity analyses of the primary efficacy variable in which all missing observations were considered as failures.

5.3.2. Supportive Trials

Protocol: 1233-IMIQ
Title: An open label, multicenter safety, and efficacy study of topical imiquimod 5% cream in the treatment of visible external genital warts in male and female patients
Phase 3b
Sponsor: 3M pharmaceuticals
Study Initiation Date: September 1996
Study Completion Date: December 1998
Number of Subjects: 784 (469 males and 315 females)
Age of Subjects: 15-77 (mean 31.5)
Inclusion criteria (main): presence of visible EGW (total number of warts and treatment area approximated)
Study Design: open label, multicenter (101 US sites)
Study Objectives: efficacy and long term safety of 5% imiquimod for EGW
Study Plan: Subjects were treated with 5% imiquimod cream (one packet per treatment) 3 times per week for up to 16 weeks. Subjects who were completely clear of EGW at any time during the treatment were entered in 6 month follow up. Subjects who did not clear (but with significant reduction of EGW) were allowed second 16 week treatment and if cleared during that treatment were followed up for 6 months. Thus subjects could potentially be treated for up to 32 weeks and be followed for 6 months (one time).
Safety evaluation: adverse events and local skin reactions were recorded at each clinic visit
Efficacy evaluation: complete and partial clearance of treated warts (present on the baseline visit) and recurrence rates

SPONSOR'S RESULTS:

Disposition:

Of 784 subjects, 300 discontinued prematurely (133 [17%] lost to follow-up and 75 [9.6%] because of inadequate response) during first treatment period. There were three subjects who discontinued because of pregnancy. Additional 198 subjects discontinued during either second treatment period or follow up (leading causes were lost to follow up-101 subjects and inadequate response-38 subjects).

Total of 37 subjects discontinued treatment because of adverse events (25 during the first treatment, 10 during the second treatment and 2 during the follow-up) for the following reasons:

- 31 subjects had intolerable local skin reactions (burning, tenderness, itching, pain)
- 2 subjects had flu-like symptoms
- 1 subject had fatigue
- 1 subject had bacterial infection at the wart site
- 1 subject had urethral irritation
- 1 subjects had intraepithelial vulvar neoplasia

Safety results:

There were 3 deaths during the trial:

- subject 05/10- 16 years old female from suicide (during second treatment)
- subject 15/08-39 years old male from HIV complications (did not apply cream at all)
- subject 68/04- 51 years old male from acute pancreatitis secondary to ethanol use

There were 13 SAE as follows:

Site # / Sub #	Age (yrs)	Gender	Event
05 / 008	29	Male	Acute appendicitis
13 / 009	29	Male	Skull fracture
14 / 003	33	Female	Increased depression/suicide attempt
16 / 007	24	Male	Suicide attempt; drug overdose
17 / 004	50	Male	Inferior myocardial infarction
21 / 001	42	Female	Pyelonephritis
36 / 005	41	Male	Pacemaker generator exchange
55 / 008	43	Male	Pancreatitis
58 / 006	38	Female	Cervical cancer
60 / 007	40	Male	Exacerbation of depression
63 / 008	21	Female	Incomplete abortion
70 / 003	25	Female	Possible infection of GI tract
81 / 004	33	Female	Heroin addiction

Source: Applicant's Table 5.3.5.5.-8

Comment: Narratives were not provided. CFR's were reviewed. One case will be described below:
Subject 63/08 was screened in April 1997. Some pages of CFR are missing but it appears that subject was pregnant since March 1997.It should be noted that protocol allowed for a waiver from the sponsor in regard to meeting inclusion/exclusion criteria. One of inclusion criteria was for female patients to have negative urine pregnancy test and to use an approved and effective method of contraception.
In (b) (4) (b) (4) *she experienced vaginal bleeding secondary to incomplete abortion and underwent D&C. It is not clear whether she applied any cream treatment.*
The exposure to the drug (if any) would be about 3 weeks thus imiquimod role can not be excluded.
There were three cases of depression. Depression is listed as AE in the current label.

Most common adverse events: AE reported by >2% of subjects:

AE	Frequency
Application site reactions	26.7%
Infection	3.8%
Upper respiratory infection	3.3%
Headache	2.5%
Fatigue	2.1%
Nausea	2.1%
Herpes simplex	2.1%
Myalgia	2.0%

Total of 187 subjects reported at least one application site reaction. The most common was erythema, followed by excoriations and erosions. From severity stand-point, 95 subjects had reaction described as mild (12.7%), 75 as moderate (10%) and 17 (2.3%) as severe.

Comment: There are no new safety concerns. In regard to LSR, reactions were more frequently reported during first (25.8 %) then second treatment (15.9%). The explanation is not clear, but similar pattern was seen in subjects who underwent multiple treatments for AK.

Efficacy results

Datasets were not included in this submission, thus it is not possible to independently confirm applicant's calculations.

	Status of warts	% based on n=784
Treatment period 1 (n=784)	cleared	271 (34.6%)
	remained clear in 6 months follow up	138 (17.6%)
	recurrence during 6 month follow up	59 (7.9%)
Treatment period 2 (n=213)	cleared	50 (6.4%)
	remained clear in 6 month follow-up	20 (2.6%)
	recurrence during 6 month follow up	19 (2.4%)

Source: Modified Table 14.2.1.1

Summary of recurrence rates:

Subjects	Recurrence rate at 3 months	Recurrence rate at 6 months
All (286) At 6 months(236)	53 (18.5%)	78 (33.1 %)
Male (124) At 6 months (93)	29 (23.4%)	41 (44.1%)
Female (162) At 6 months(143)	24 (14.8%)	37 (25.9%)

Source: Modified Table 11.4.1.4.3.2

Total of 213 subjects entered treatment 2 and were exposed to two treatments (up to 32 weeks). 50 subjects were followed for one year. First treatment led to effectiveness of 34.6 % which is less than previously reported in Phase 3 trials (50%) but this was different design (open label) with higher number of discontinued subjects. Second treatment resulted in only 6.4% more subjects with complete clearance. Sustained clearance rate was achieved in 20.2 % of all subjects after 6 months of follow-up. As expected, recurrence rates increased over the time. At 6 month months of follow-up 33.1% of all subjects had recurrence (more so in males).

Protocol: 1243-IMIQ
Title: same as 1233
Phase same as 1233
Sponsor: same as 1233
Study Initiation Date: January 1997
Study Completion Date: December 1999
Number of Subjects: 943 (533 males and 410 females)
Age of Subjects: 16-78 (mean 31.2)
Inclusion criteria (main): same as 1233
Study Design: open label, multicenter (114 sites in 20 countries)
Study Objectives: same as 1233
Safety evaluation: same as 1233
Efficacy evaluation: same as 1233

SPONSOR'S RESULTS:

Disposition:

Of 943 subjects, 309 (32.8%) discontinued prematurely during treatment period 1 (97 [10.3%] lost to follow-up and 101 [10.7%] because of inadequate response). Additional 203 subjects discontinued either in treatment period two or during the follow-up (88 lost to follow-up and 63 due to inadequate response).

Total of 105 subjects discontinued treatment because of adverse events (92 during the first treatment, 12 during the second treatment and 1 during the follow-up) for the following reasons:

- 89 subjects had LSR (burning, tenderness, itching, pain)
- 8 subjects had flu-like symptoms
- 3 headache, chills and fever
- 1 subject had worsening of psoriasis
- 1 subjects had generalized itching
- 1 subject had diarrhea
- 1 subject had vaginal candidiasis
- 1 subject had fatigue

No deaths were reported in this trial.

Fourteen subjects reported SAE as follows:

Site # / Sub #	Age (yrs)	Gender	Event
251 / 008	25	Female	Alteration in speech and sensation of spaciness
300 / 001	26	Male	Fracture of left clavicle
302 / 005	25	Male	Exacerbation of eczema at non-wart site
317 / 007	28	Male	Rectal pain due to internal warts-remote site
317 / 008	24	Female	Nephrotic syndrome
357 / 001	34	Female	Carcinoma of vulva
603 / 007	43	Female	Vulval pain (with anorexia and fatigue)
603 / 007	43	Female	Depression
603 / 007	43	Female	Lymphangitis due to dog bite
752 / 006	56	Male	Axillary abscess
752 / 008	23	Male	Laryngeal cancer
855 / 006	31	Female	Vomiting and abdominal pain
858 / 005	28	Male	Cholecystectomy
858 / 005	28	Male	Flu[a]
900 / 002	38	Female	Tonsil abscess
904 / 003	41	Female	Metrorrhagia
952 / 010	26	Female	Acute fetal distress

Source; Table 5.3.5.3.2-10

Comment: Narratives were reviewed and some were found to be limited due to inconsistencies with documentation practices. Two selected case are presented:

- *357/001- 34 years old woman diagnosed with minimally invasive carcinoma of the vulvae after 2 months in the trial with comment that cancer was probably present before the study. She was hospitalized one month later for depression. It is unclear whether she was using the cream at that time.*
- *952/10-26 years old woman was 5 months pregnant when she began taking imiquimod cream. Pregnancy was exclusion criterion for this protocol and furthermore exclusion criteria specified that any subject who became pregnant had to discontinue treatment, and inform their physicians of pregnancy.*

She was admitted because of pregnancy complications and underwent Cesarean section. She delivered a healthy child. At one month follow-up child was normally developed.

Most common adverse events: AE reported in >2% subjects

AE	Frequency
Application site reactions	27.7%
Infection	4.5%
Headache	2.9%
Respiratory infection	2.1%
Myalgia	2%

Overall, 234 (26.1%) subjects had at least one application site reaction. Erythema, erosions, and edema were the most common. In regard to severity, 87 subjects (9.7%) had mild, 105 (11.7%) had moderate and 42 (4.7 %) severe reactions.

Comment: Reported AE are within expected range. The severity of local skin reactions is higher then in 1233 IMIQ trial. Again is seen that more adverse events occur with first treatment.

Efficacy results

Datasets were not included in this submission, thus it is not possible to independently confirm applicant's calculations.

	Status of warts	% based on n=943
Treatment period 1 (n=943)	cleared	443 (47%)
	remained clear in 6 months follow up	281(29.8%)
	recurrence during 6 month follow up	82(8.7%)
Treatment period 2 (n=191)	cleared	52 (5.5%)
	remained clear in 6 month follow-up	30 (3.2%)
	recurrence during 6 month follow up	12 (1.3%)

Summary of recurrence rates:

Subjects	Recurrence rate at 3 months	Recurrence rate at 6 months
All (431) At 6 months(404)	38 (8.8%)	93 (23%)
Male (190) At 6 months (182)	25 (13.1%)	59 (32.4%)
Female (241) At 6 months(222)	13 (5.4%)	34 (15.3%)

Source table 11.4.1.4.3. A and B page

Total of 191 subjects entered treatment 2 and were exposed to two treatments (up to 32 weeks). 52 subjects were followed for one year. First treatment led to effectiveness of 47% % which is comparable to reported in Phase 3 trials (50%) but different then in 1233-IMIQ trial. Second treatment resulted in only 5.5% more subjects with complete clearance. Sustained clearance rate was achieved in 33 % of all subjects after 6 months of follow-up. As expected, recurrence rates increased over the time. At 6 month months of follow-up 23 % of all subjects had recurrence (more so in males).

6 Review of Efficacy

Efficacy Summary

Applicant submitted 2 phase 3 trials (GW01-801 and GW01-0805) utilizing two different imiquimod cream concentrations (2.5% and 3.75%) against vehicle.
Analysis of two phase 3 trials showed that imiquimod 3.75% cream was effective as topical treatment for EGW.
Primary endpoint defined as complete clearance of all warts (baseline and new) in all anatomic areas prior to or at week 16 (EOS) was achieved by 27% of subjects treated with 3.75% concentration in trial GW01-801 and by 29% in trial GW01-0805. Complete clearance rate for vehicle subjects was 10% and 9% for respected trials ($p<0.001$).
In one of the trials, 2.5% cream did not reach statistical significance v. vehicle ($p=0.065$).

Subpopulation analysis revealed that women had higher efficacy rates then men (37% v. 19% respectively). The effect of anatomic location and number of locations on treatment effect appeared to be primarily influenced by gender. Race and age did not significantly influence the effect of the treatment.
Overall about 67% of subjects who cleared with imiquimod 3.75% cream remained clear at the end of 12 weeks follow-up in comparison to 68% of subjects treated with vehicle.
In summary, response rates were consistently higher in 3.75% arm in comparison to 2.5% arm and vehicle across all analyzed variables. Efficacy analysis supports

imiquimod 3.75% cream as effective treatment for EGW when applied daily up to 8 weeks.

6.1 Indication

The applicant is proposing that imiquimod 3.75% receive the following indication: for the treatment of external genital and perianal warts/condyloma acuminata in patients 12 years or older.

6.1.1 Methods

The combined efficacy results across phase 3 trials (GW01-801 and GW01-0805) will be discussed in this section. When appropriate, separate reviews of individual trials will be presented.
Both trials were randomized, double-blind, vehicle- controlled and included subjects of both sexes, 12 years and older who had a diagnosis of external genital / perianal warts with 2 to 30 warts located on at least 10mm² area in one or more anatomic locations.
The analysis of the data was done on ITT (intention-to-treat) population.

6.1.2 Demographics

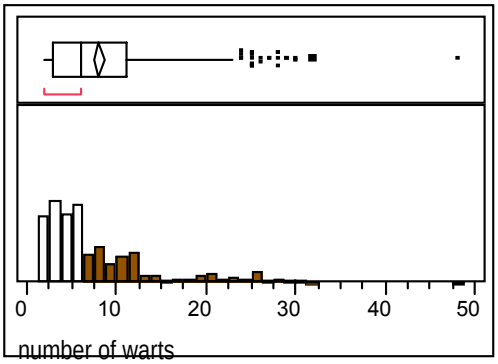
The ITT population (defined as all randomized subjects) was 470 and 511 subjects for 801 and 805 trials, respectively. There were no notable differences in demographic characteristics between either arms or trials. For details, please refer to Table 19 and Table 20.
The per protocol (PP) population excluded subjects who were non-compliant, missed scheduled visits, took restricted medications or failed inclusion/exclusion criteria.

Table 7 Number of Subjects in Pivotal Trials

	Populations	3.75%	2.5%	Vehicle	Overall
GW 01-0801	ITT population	195	178	97	470
	PP population	137	134	76	347
GW 01-0805	ITT population	204	202	105	511
	PP population	144	144	81	369

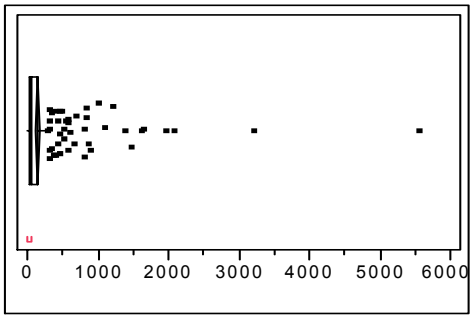
There was high variability in the number of warts (overall from 2-30) and in the wart area (6-5579 mm²), however mean values between arms and trials are comparable. There were few outliers in trial 805 with >30 warts at the baseline (Figure 1), and few in both trials with extreme wart areas (Figures 2 and 3), but in reviewer's opinion that does not significantly impact the outcome.

Figure 1 Wart Count Distribution from Trial 805



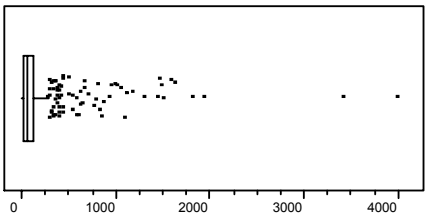
100.0%	maximum	48.000
99.5%		48.000
97.5%		48.000
90.0%		29.800
75.0%	quartile	25.000
50.0%	median	17.000
25.0%	quartile	9.000
10.0%		4.200
2.5%		2.000
0.5%		2.000
0.0%	minimum	2.000

Figure 2 Total Wart Area at Baseline from Trial 801



100.0%	maximum	5579.0
99.5%		2822.8
97.5%		925.0
90.0%		291.0
75.0%	quartile	133.0
50.0%	median	61.0
25.0%	quartile	24.0
10.0%		14.0
2.5%		11.0
0.5%		10.0
0.0%	minimum	6.0

Figure 3 Total Wart Area at Baseline from Trial 805



100.0%	maximum	4000.0
99.5%		2596.4
97.5%		1144.8
90.0%		399.6
75.0%	quartile	128.0
50.0%	median	57.0
25.0%	quartile	24.0
10.0%		15.0
2.5%		11.0
0.5%		10.0
0.0%	minimum	9.0

Distribution of lesions per gender and per location is presented below:

Table 8 Baseline EGW Distribution- 801

	Imiquimod Cream			
	3.75% (N=195)	2.5% (N=178)	Placebo (N=97)	Overall (N=470)
Anatomic location, Males[a], n	95	83	47	225
Inguinal	29 (30.5)	20 (24.1)	13 (27.7)	62 (27.6)
Perineal	7 (7.4)	6 (7.2)	4 (8.5)	17 (7.6)
Perianal	6 (6.3)	8 (9.6)	2 (4.3)	16 (7.1)
Glans penis	9 (9.5)	6 (7.2)	5 (10.6)	20 (8.9)
Penis shaft	77 (81.1)	71 (85.5)	42 (89.4)	190 (84.4)
Scrotum	27 (28.4)	29 (34.9)	8 (17.0)	64 (28.4)
Foreskin	3 (3.2)	4 (4.8)	1 (2.1)	8 (3.6)
Anatomic location, Females[b], n	100	95	50	245
Inguinal	17 (17.0)	11 (11.6)	6 (12.0)	34 (13.9)
Perineal	48 (48.0)	43 (45.3)	22 (44.0)	113 (46.1)
Perianal	44 (44.0)	52 (54.7)	22 (44.0)	118 (48.2)
Vulva	59 (59.0)	60 (63.2)	32 (64.0)	151 (61.6)
Number of treatment anatomic areas, n (%)– Males[a]				
Total Males	95 (100)	83 (100)	47 (100)	225 (100)
1	47 (49.5)	38 (45.8)	25 (53.2)	110 (48.9)
2	34 (35.8)	31 (37.3)	16 (34.0)	81 (36.0)
3	13 (13.7)	12 (14.5)	6 (12.8)	31 (13.8)
4	1 (1.1)	2 (2.4)	0	3 (1.3)
Number of treatment anatomic areas, n (%) –Females[b]				
Total Females	100 (100)	95 (100)	50 (100)	245 (100)
1	49 (49.0)	40 (42.1)	26 (52.0)	115 (46.9)
2	36 (36.0)	40 (42.1)	17 (34.0)	93 (38.0)
3	13 (13.0)	14 (14.7)	6 (12.0)	33 (13.5)
4	2 (2.0)	1 (1.1)	1 (2.0)	4 (1.6)

SD = standard deviation.
a: Denominator based on the number of males in treatment group
b: Denominator based on the number of females in treatment group.

Source: Table 11-3

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Table 9 Baseline EGW Distribution-805

	Imiquimod Cream 3.75% (N=204)	Imiquimod Cream 2.5% (N=202)	Placebo (N=105)	Overall (N=511)
Anatomic location, Males[a], n	88	85	49	222
Inguinal	24 (27.3)	17 (20.0)	19 (38.8)	60 (27.0)
Perineal	6 (6.8)	8 (9.4)	3 (6.1)	17 (7.7)
Perianal	8 (9.1)	6 (7.1)	5 (10.2)	19 (8.6)
Glans Penis	9 (10.2)	11 (12.9)	5 (10.2)	25 (11.3)
Penis Shaft	71 (80.7)	76 (89.4)	39 (79.6)	186 (83.8)
Scrotum	19 (21.6)	16 (18.8)	14 (28.6)	49 (22.1)
Foreskin	0	2 (2.4)	2 (4.1)	4 (1.8)
Anatomic location, Females[b], n	116	117	56	289
Inguinal	11 (9.5)	19 (16.2)	4 (7.1)	34 (11.8)
Perineal	61 (52.6)	53 (45.3)	29 (51.8)	143 (49.5)
Perianal	53 (45.7)	51 (43.6)	26 (46.4)	130 (45.0)
Vulva	86 (74.1)	78 (66.7)	31 (55.4)	195 (67.5)
Number of treatment anatomic areas, n (%)—Males[a]				
Total Males	88 (100)	85 (100)	49 (100)	222 (100)
1	49 (55.7)	48 (56.5)	25 (51.0)	122 (55.0)
2	30 (34.1)	25 (29.4)	12 (24.5)	67 (30.2)
3	8 (9.1)	10 (11.8)	10 (20.4)	28 (12.6)
4	1 (1.1)	2 (2.4)	2 (4.1)	5 (2.3)
Number of treatment anatomic areas, n (%)—Females[b]				
Total Females	116 (100)	117 (100)	56 (100)	289 (100)
1	47 (40.5)	53 (45.3)	28 (50.0)	128 (44.3)
2	46 (39.7)	48 (41.0)	23 (41.1)	117 (40.5)
3	20 (17.2)	12 (10.3)	4 (7.1)	36 (12.5)
4	3 (2.6)	4 (3.4)	1 (1.8)	8 (2.8)

SD = standard deviation.
a Denominator based on the number of males in treatment group.
b Denominator based on the number of females in treatment group.

Source: Table 11-3

Comment: Penis shaft was the most frequent location of EGW for men (approximately 84% of men had warts in this location)) and vulva for women (62-68%). For both, men and women, lesions were most commonly located in either one or two anatomical areas.

6.1.3. Subject Disposition

Subject's disposition from trials 801 and 805 for the 16 week evaluation period is presented below (electronically copied applicant's figure 10-1). Drop out time line is graphically presented in Figures 5 and 6.

Figure 4 Subject Disposition- Trial 801

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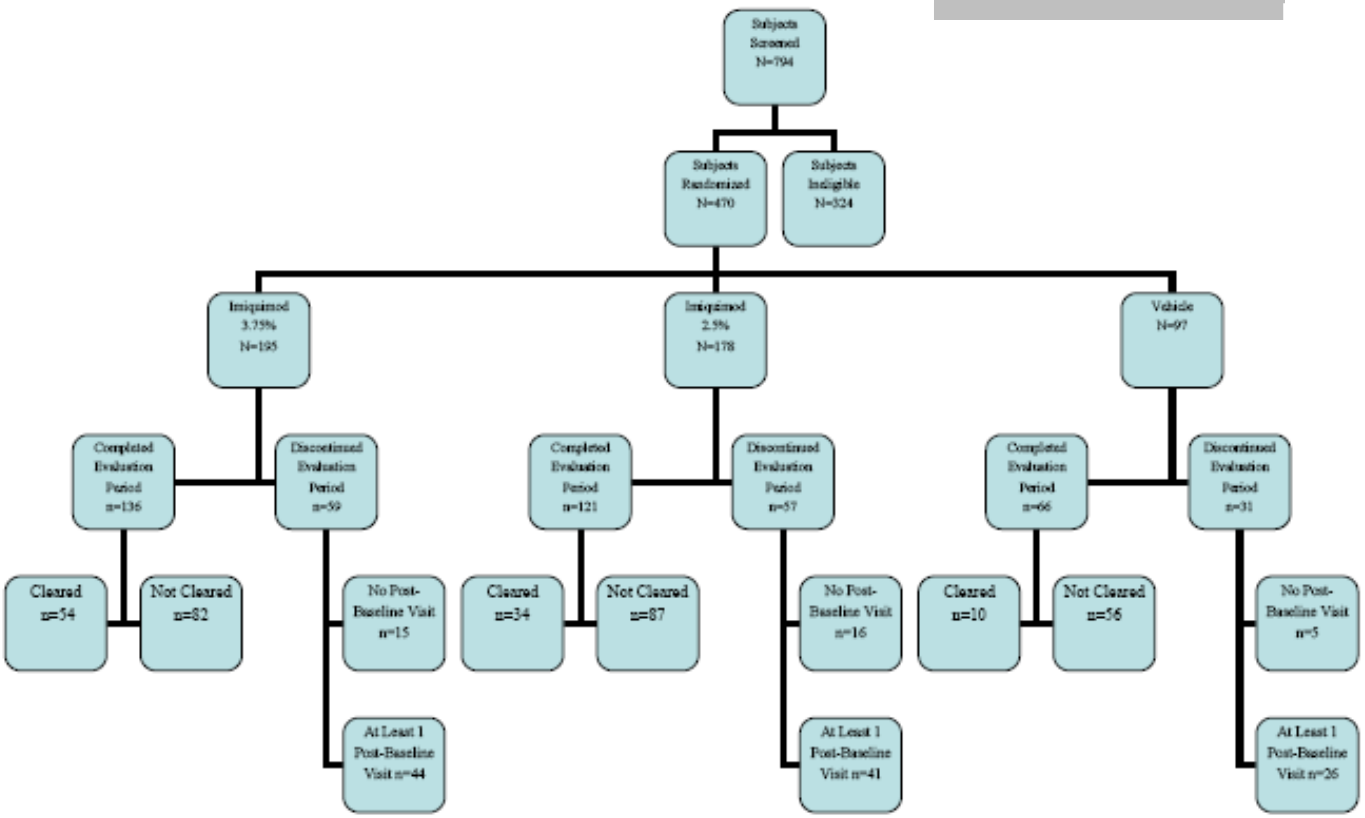
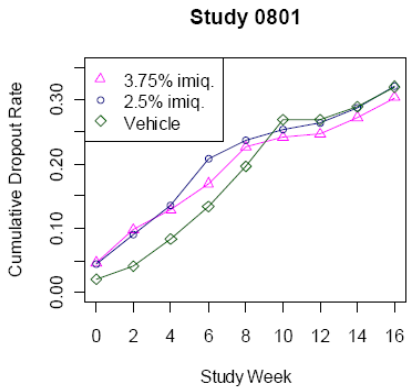


Figure 5 Dropout Rate by Week



Source: Statistical Review by Dr. Fritsch, pg.8

Figure 6 Subject Disposition-Trial 805

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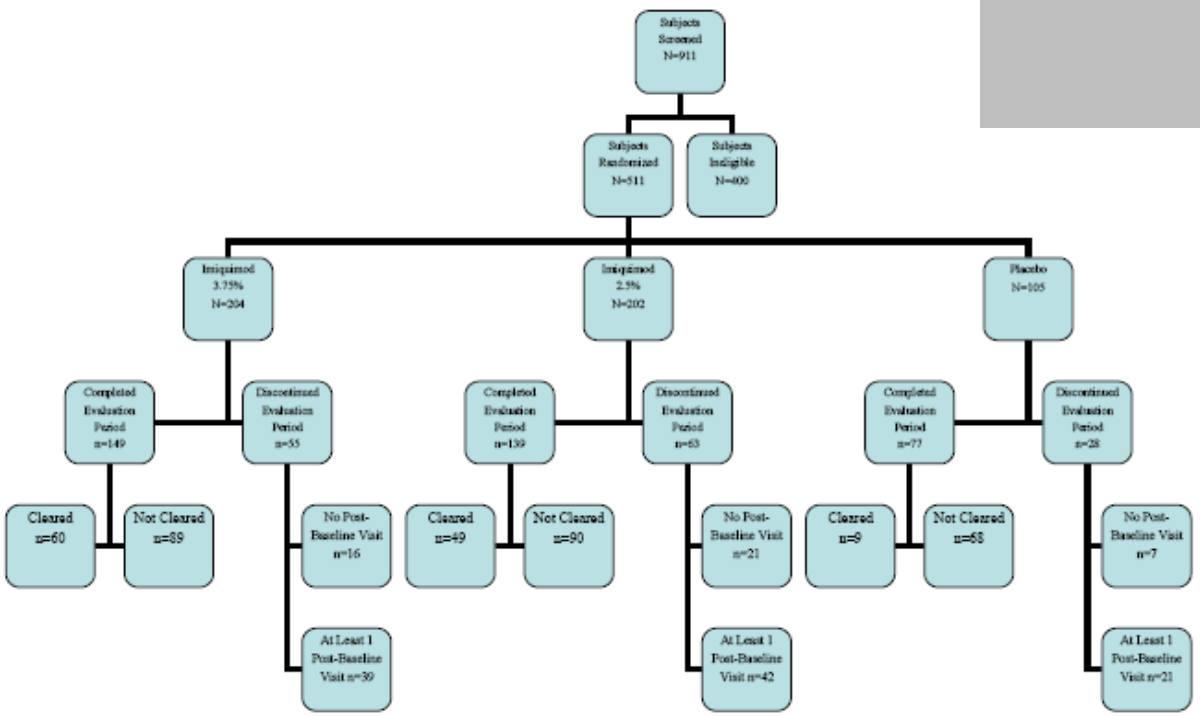
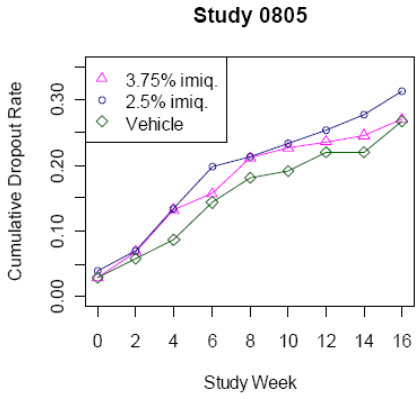


Figure 7 Dropout Rate by Week



Source: Statistical Review by Dr. Fritsch, pg.8

Comment: Approximately 30% of randomized subjects discontinued from the trials (293/981). The most frequent reason for discontinuation was "subject lost to follow-up" (189 subjects), followed by subject's request (50 subjects) and other reasons (22 subjects). More then half of all subjects who dropped out did that during the first half of the trial. Distribution across arms was comparable. Further analysis of discontinued subjects is presented in Table 23 *and* Table 24*.*
High discontinuation rate in clinical trials for EGW is not unusual. In Aldara® trials discontinuation rate was 22% (46/209).

Concomitant medications:

Over 50% of subjects in both trials received one or more concomitant medications during the trial. The most common were analgesics, systemic antibiotics, and anti-inflammatory medications.

Comment: There were no meaningful distribution differences between groups.

Compliance with trial medications:

Non compliance with treatment was defined by applicant as compliance less than 75% or greater than 125% and was based on either packet use compliance or treatment days compliance whichever was closer to 100%.

Comment: It is difficult to evaluate overall compliance because of relatively high number of subjects who dropped out. For majority of those subjects complete data are not available because they were lost to follow up. Drop-out rate across the treatment arms was similar. It appears that compliance as defined was adequate in the population for which data are available (using PP population as the baseline).

Protocol deviations and violations

In 801 trial a total of 123 subjects were excluded from PP population prior to unblinding the treatment codes: one subject because of smaller then required treatment area and 122 because of noncompliance (95 were subjects lost to follow up). In addition one subject received incorrect gender kit, however she was included in analysis according to her actual gender.

In 805 trial a total of 142 subjects were excluded from PP population (94 were subjects lost to follow up). Three subject were excluded because of taking the medication from the exclusion list and one because the subject received two treatment kits. Four

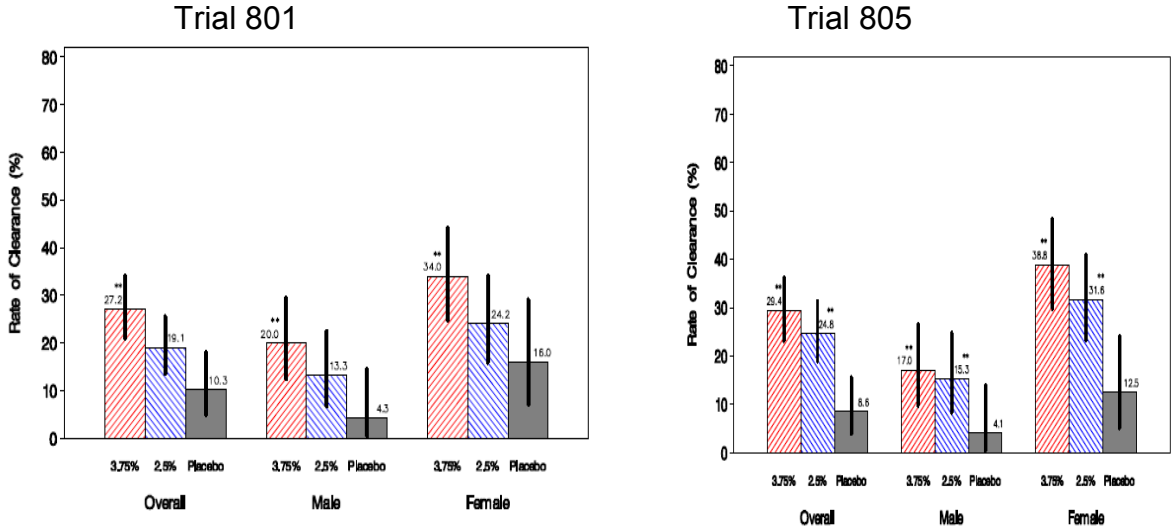
subjects received incorrect gender kit; however, they were analyzed according to their actual gender.
Subject 04/025 (female) was originally randomized to the 2.5% imiquimod treatment group; however, at Week 2, the subject incorrectly received a 3.75% imiquimod treatment group kit assigned to another subject. For the safety analysis the highest dose received (3.75%) was used (3.75 % group ITT=205 with 88 male and 117 females), and for the efficacy analysis, the original randomized treatment of 2.5% was used (3.75% group ITT= 204 with 88 males and 116 females).

Comment: Recorded protocol deviations and violations do not raise any concerns. Vast majority of excluded subjects were lost to follow up.

6.1.4 Analysis of Primary Endpoint

Primary end-point was defined as number of subjects who achieved complete clearance of all warts (baseline and new) in all anatomic areas prior to or at week 16 (EOS).

Figure 8 Complete Clearance Rate- per Trial

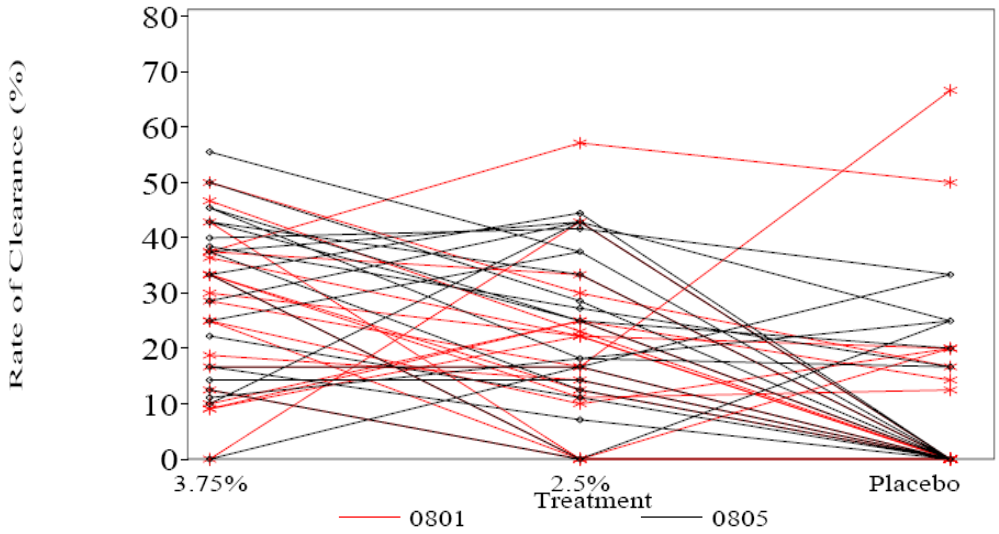


Source; Figure 11-1

*Comment: In both trials, 3.75% imiquimod cream was superior to vehicle (p<0.001). However, 2.5% cream did not reach statistical significance (p=0.065) in comparison to vehicle in trial 801. Further analysis including comparison per trial site (*Figure 9)

showed that overall variability was similar across the trials with exception of 2 sites in 801 trial that had higher clearance rates especially in the placebo group. However, this finding could not account for statistical outcome in trial 801. Reviewer is in agreement that 3.75% concentration should be considered for approval.

Figure 9 Complete Clearance Rate by Trial and Center



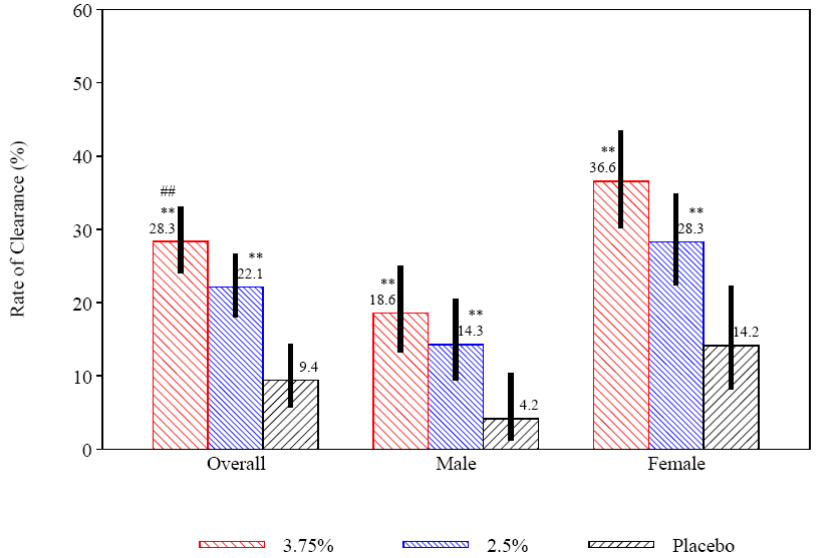
Source: Figure II-1 from ISS-5.3.5.3.1

The combined efficacy results across Phase 3 trials are presented in Table 10 and Figure 10:

Table 10 Proportion of Subjects with Complete Clearance of Warts -EOS

	Imiquimod 3.75%	Imiquimod 2.5%	Vehicle
Complete Clearance Rate			
Overall	28% (113/399)	22% (84/380)	9% (19/202)
Females	37% (79/216)	28% (60/212)	14% (15/106)
Males	19% (34/183)	14% (24/168)	4% (4/96)

Figure 10 Rate of Complete Clearance at EOS-Combined Pivotal Trials



Comment: Imiquimod 3.75% showed consistently higher efficacy over 2.5%. Although not to be directly compared, imiquimod 5% had overall success rate of 50% in pivotal trials. Possible explanation may include more conservative end point (clearance of both baseline and new warts) used for 3.75% cream.

6.1.5 Analysis of Secondary Endpoints

Secondary end-points were:

- number of subjects who achieved partial clearance of baseline warts defined as at least a 75% reduction in the number of baseline warts at EOS visit
- percent change from baseline to EOS in total number of warts
- timeline from baseline to complete clearance
- number of subjects with complete clearance of all warts at EOS that was sustained through the end of the follow-up for recurrence period

Table 11 Proportion of Subjects with Partial Clearance of Warts (≥75%) -EOS

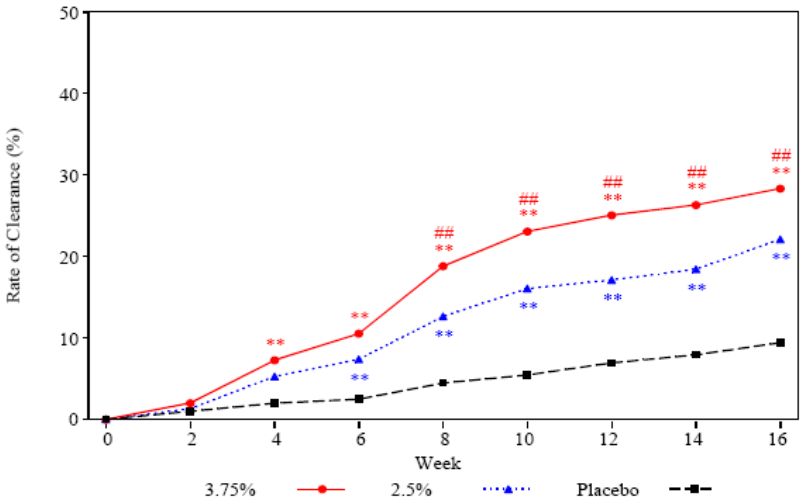
	Imiquimod 3.75%	Imiquimod 2.5%	Vehicle
Partial (≥75%) Clearance			
Overall	38% (153/399)	29% (111/380)	12% (24/202)
Females	47% (103/216)	36% (77/212)	17% (18/106)
Males	27% (50/183)	20% (34/168)	6% (6/96)

Table 12 Summary of Change from Baseline Wart Count -EOS

	Imiquimod 3.75%	Imiquimod 2.5%	Vehicle
Change in EGW count			
Baseline count	8.6 (±7)	8.4 (±6)	9.6 (±8)
EOS count	4.7 (±6)	5.7 (±7)	8.8 (±8)
% Change	43% (-3.9 ±6)	32% (-3.7 ±5)	8% (-1 ± 5)

Comment: Trend observed with primary end point analysis is evident in analysis of selected secondary end points: higher concentration of imiquimod cream and females continue to show higher efficacy rates. Clinical importance of secondary end-points is very limited-partial clearance and mean reduction in the number of warts (4 for imiquimod 3.75% arm and 1 for vehicle) do not reflect meaningful clinical outcome.

Figure 11 Time-line from Baseline to Complete Clearance



Points marked with ** show statistically significant difference from placebo. Points marked with ## show statistically significant difference from 2.5%. Source: ISS Figure 5.3.5.3.1

Comment: About 10% of subjects treated with 3.75% imiquimod cream completely cleared between week 4 and 6 of and 20% at the end of week 8 (end of treatment). The statistical difference between two active treatments started at week 8 and continued until the end of study visit (week 16).

6.1.6 Other Endpoints

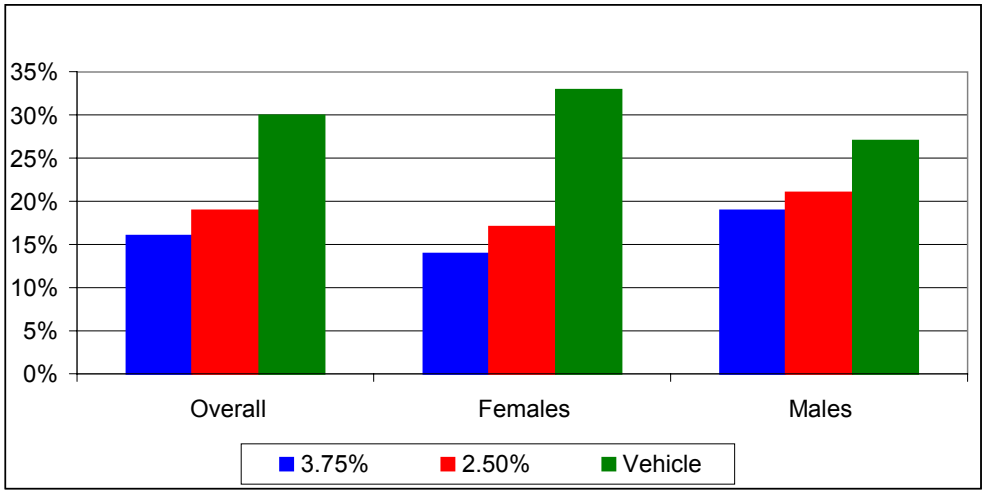
Table 13 Partial Clearance Rates (≥50%) -EOS

	Imiquimod 3.75%	Imiquimod 2.5%	Vehicle
Partial (≥50%) Clearance			
Overall	50% (200/399)	39% (148/380)	20% (40/202)
Females	62% (135/216)	46% (97/212)	26% (28/106)
Males	35% (65/183)	30% (51/168)	12% (12/96)

Table 14 Incidence of Wart Count Increase in Percentages (n/N)

	Imiquimod 3.75%	Imiquimod 2.5%	Vehicle
Wart count increase			
Overall	16% (66/399)	19% (73/380)	30% (61/202)
Females	14% (31/216)	17% (37/212)	33% (35/106)
Males	19% (35/183)	21% (36/168)	27% (26/96)

Figure 12 Incidence of Wart Count Increase in Percentages (n/N)



Comment: The clinical utility of other end points is very limited. Increase in wart counts during the treatment is not unexpected given that imiquimod is not an anti-viral agent and that HPV may persist in the surrounding tissue during and after the treatment.

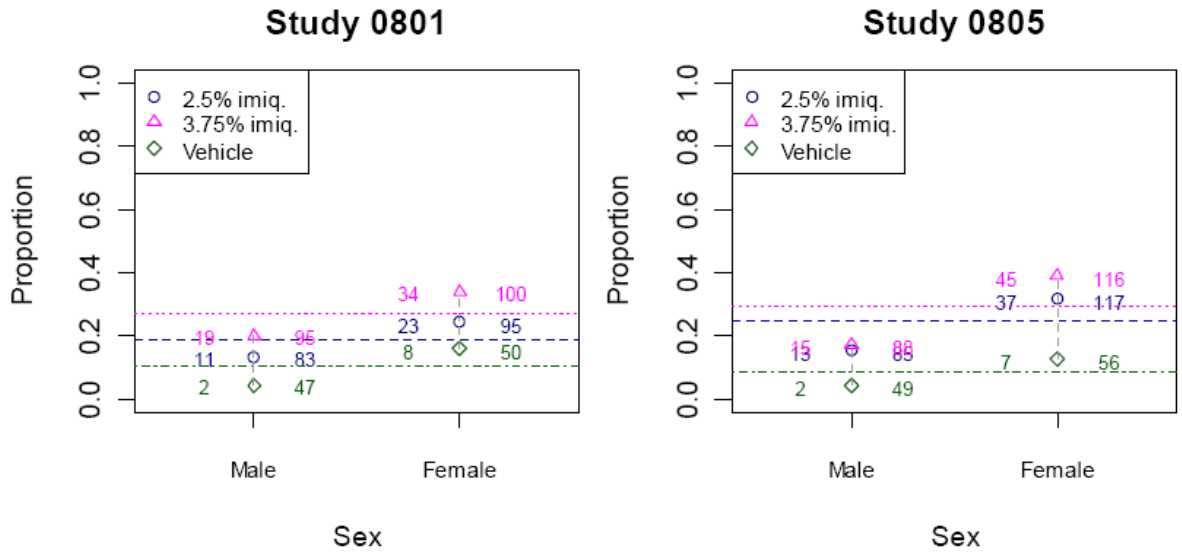
6.1.7 Subpopulations

Gender difference

The efficacy was consistently higher in females then males. This difference was observed in both trials (Figure 13- courtesy of biostatistics reviewer, Kathleen Fritsch, PhD), and across all three arms (see

Figure 10). In addition to higher efficacy overall, females also showed earlier deference in efficacy v. placebo (week 4 for females, week 8 for males).

Figure 13 Complete Clearance Rates by Gender



Comment: Same trend was observed with Aldara® 5% cream.

A summary of complete clearance by anatomic location is provided below:

Table 15 Summary of Subgroup Analyses of the Complete Clearance Rate by Baseline Anatomic Location

Anatomic location	Subpopulation	Complete clearance rate (%) 3.75% imiquimod
Inguinal	male	11
	female	21
Perineal	male	15
	female	41
Perianal	male	28
	female	42
Glans penis	male	33
Penis shaft	male	16
Scrotum	male	9
Foreskin	male	33
Vulva	female	34

Source: ISS- table 5.3.5.3.1-31

Comment: The effect of the anatomic location on treatment effect appeared to be primarily influenced by gender (when same location is present in both genders). The most commonly affected areas (penis shaft for men and vulva for women) showed lower response rates.

Comparison in number of anatomic locations:

Table 16 Summary of Subgroup Analyses of the Complete Clearance Rate by Number of Anatomic Locations

Number of anatomic locations	Subpopulation	Complete clearance rate (%) 3.75% imiquimod	Significance v. vehicle
overall	one	30	yes
	multiple	27	yes
male	one	25	yes
	multiple	11	no
female	one	34	yes
	multiple	38	yes

Source;ISS table 5.3.5.3.1-31

Comment: Only multiple anatomic locations in males treated with imiquimod 3.75% cream did not reach statistical significance v. vehicle treatment in the same locations.

Dichotomized subgroup analysis by age (less/more then 35 years) and by race (white/nonwhite) overall did not influence the superiority of imiquimod 3.75% over vehicle(data reviewed, but not presented).

The comparison of effect in subjects with first episode of EGW v. recurring episode showed that 3.75% imiquimod cream has higher success rate then vehicle in both men and women.

The comparison of effect in subjects with different baseline wart area (≤ 70 mm² v. >70 and ≤150 v. > 150 mm²) and different baseline wart count (more or less then 7 warts) showed that 3.75% imiquimod cream has higher success rate then vehicle (data reviewed, but not presented).

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Applicant submitted two concentrations of imiquimod cream for consideration: 2.5% and 3.75%. As seen in
Figure 8 , 2.5 % concentration did not reach statistical significance compared with vehicle in 801 trial. Further analysis did not reveal a compelling explanation for this finding. Applicant appropriately selected 3.75% concentration that showed consistently higher response rates then vehicle.
.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Subjects who achieved clearance of all warts at any time until Week 16 (end-of-study) were eligible to immediately enter the follow-up period (12 weeks) for determination of recurrence.
Complete clearance rate was achieved by 113 subjects treated with 3.75% imiquimod cream and in 19 subjects treated with vehicle. Please see Table 10. The results from follow-up are presented in Table below (courtesy of biostatistics reviewer, Kathleen Fritsch, PhD):

Table 17 Recurrence Rates for Responding Subjects

Trial		3.75%	Vehicle
0801	Responders	53	10
	Recurrence within 12 weeks	7(13%)	0 (0%)

	No recurrence with 12 weeks follow-up	40(75%)	6 (60%)
	Subjects with< 12 weeks follow-up	6 (11%)	4 (40%)
0805	Responders	60	9
	Recurrence within 12 weeks	10 (17%)	0 (0%)
	No recurrence with 12 weeks follow-up	36 (60%)	7 (78%)
	Subjects with< 12 weeks follow-up	14 (23%)	2 (22%)

Comment: Overall 76/113 of subjects who cleared with imiquimod treatment remained clear (67%) at the end of 12 weeks follow-up in comparison to 13/19 treated with vehicle (68%). In Aldara trials 39/54 in active and 9/11 in vehicle arm remained clear at the end of 12 weeks follow-up (72% and 81% respectively). It is estimated that recurrence rate after treatment of genital warts is 20%-50% (Mayeaux) mostly due to persistent subclinical HPV infection.

6.1.10 Additional Efficacy Issues/Analyses

In regard to high rate of discontinuation in phase 3 trials, applicant submitted additional sensitivity analysis with all missing observations counted as failures, and using observed cases only in the ITT population and in PP population. Overall results are very similar.

Comment: For detailed review, interested reader is referred to Statistical review of NDA 201153 by Kathleen Fritsch, PhD

7 Review of Safety

Safety Summary

The data base for safety evaluation contained 779 subjects (400 randomized to 3.75% cream and 379 to 2.5% cream) in comparison to 202 subjects randomized to vehicle in two phase 3 trials. An additional 18 subjects from PK trial were analyzed as well.
The exposure to the drug was adequate to uncover safety issues. All safety outcomes were analyzed using ITT data sets. It should be noted that 80 subjects from ITT population did not have post-baseline visit (31 from 3.75%, 37 from 2.5% and 12 from vehicle group).
The safety evaluation consisted of adverse events, local skin reactions, vital signs, and laboratory test. Rest periods as the indicators of local tolerance were reported separately. There were no EKG data in this submission.
There was one death reported as the result of accidental gun shot wound.

Serious adverse events (SAEs) were reported by 13 subjects and did not appear to be related to the drug.
Approximately 36% of subjects treated with imiquimod reported adverse events (AE). The most common were application site pain and application site irritation.
Application site reactions were reported by 16% of subjects in 3.75% arm, 15 % of subjects in 2.5% arm and 2.5% in vehicle arm. Pain was the most common reaction occurring in 7% of subjects treated with 3.75% imiquimod and 0.5% in vehicle group.
Severe application site reactions occurred in 2.3% of subjects in 3.75% arm in comparison to 0.5% from vehicle arm.
Systemic AE occurred in 6.5% subjects from 3.75% arm, and 4% from vehicle group. Headache, nausea, and pyrexia were the most common.
The most common local skin reaction (LSR) was erythema (reported in 70% of subjects in 3.75%, and 27% in vehicle group), followed by edema and erosions/ulcerations. In the category of severe LSR, the most common was erosions/ulceration (reported in 11% subjects from 3.75% group). About 1% (8/779) of the subjects randomized to imiquimod cream discontinued due to local skin/application site reaction.
Summary of rest periods showed that about one third (126/400) of subjects in 3.75% arm used rest periods in comparison to 2% (4/202) in vehicle arm.

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).
There are no new safety concerns with imiquimod cream. Safety evaluation supports 3.75% imiquimod cream for approval. Rest periods may be necessary for potential intolerable skin reactions.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data from 3 clinical trials were reviewed and those are: GW01-801, GW01-0805, and GW01-0804 trials.

7.1.2 Categorization of Adverse Events

The applicant 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 applicant and includes paired data from 2 phase 3 trials. Data from pharmacokinetic trial are included in safety analysis by reviewer.
All safety outcomes were analyzed using ITT data sets. It should be noted that 80 subjects did not have post-baseline visit (31 from 3.75%, 37 from 2.5% and 12 from vehicle group)-see Figure 4 and Figure 6.

7.2 Adequacy of Safety Assessments

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

A total of 779 subjects in two pivotal trials were randomized to receive imiquimod cream. Target population demographics were similar.

Table 18 Number of Subjects in Analysis Populations

Trial	3.75%	2.5%	Vehicle	Overall
0801	195	178	97	470
0805	205	201	105	511

Subjects were between the ages of 17-81 (801) and 15-70 (805) and predominately white. Slightly higher proportion of women was enrolled. Data are presented in Tables 19 and 20.

Table 19 Demographic Characteristics of Subjects-801

GW01-0801	3.75 % group	2.5% group	vehicle	overall
Age (mean)	32.5	32.7	30.5	32.2
Sex (male)	48.7 %	46.6%	48.5%	47.9%
Race				
White	75.4%	68.5%	68%	71.3%
Black	21%	26.4%	28.9%	24.7%
Other	3.6%	5.1%	3.1%	4.0%

Table 20 Demographic Characteristics of Subjects-805

GW 01-0805	3.75 % group	2.5% group	vehicle	overall
Age (mean)	32.8	33.1	33.3	33.1
Sex (male)	43.1	42.1	46.7	43.4
Race				
White	69.1%	65.8%	72.4%	68.5%
Black	27%	32.7%	25.7%	29%
Other	4%	1.5%	2%	2.5%

Reviewer's comment: Demographic characteristics between the groups and trials are comparable and reflective of prevalence of this condition in general population. It should be noted that no subjects younger than 15 years were enrolled and that applicant is asking for indication for 12 years and older.

Overall exposure is these trials is affected by several factors including duration of successful treatment (subjects stopped treatment when complete clearance was achieved), unrecorded exposure of subjects that dropped-out (30% of ITT population), rest periods and missed doses. Table 21 is summary of exposure for all subjects with available data.

Table 21 Overall Exposure

	GW01-0801			GW01-0805			Combined		
	3.75 %	2.5%	vehicle	3.75%	2.5%	vehicle	3.75%	2.5%	vehicle
Number of days treated (mean)*	43.1	44.3	50.3	43.7	45.6	51.9	43.3	45	51.2

*Days treated are treatment duration, minus any included rest period days and missed dose days.

Comment: The expected maximum number of days is 56. Exposure is adequate for safety analysis. Differences between imiquimod groups and vehicle may be influenced by efficacy (non responders remained in the trials until the end), however it is not known how many days of treatment had the subset of subjects that dropped out.

7.2.2 Explorations for Dose Response

Applicant did not conduct any phase 2 dose ranging studies, but instead proceeded directly to phase 3.Two different concentrations of cream (2.5 % and 3.75%) were tested in order to select one optimal treatment.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro testing was needed given the applicant'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, skin quality assessments, routine laboratory testing, and monitoring for AE. The methods and tests used as well as the frequency of testing were adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

For the complete analysis of the pharmacokinetic trial GW01-0804, 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 18 subjects with at least 8 EGW or a total area of ≥ 100 mm².
PK parameters for imiquimod and its two metabolites were calculated from the serum samples collected on Days 1, 7, 14, 21, 23 and 24.
The sponsor found that serum concentrations of imiquimod were relatively low. Peak and total serum concentrations increased 2-fold between Day1 and Day 21. (Cmax 0.488+/-0.368 ng/mL). Steady state was achieved by Day 7. Cmax on Day 21 was higher in female subjects (0.676 v. 0.420 ng/mL). The reason may be wider variability in smaller number of subjects (female 4, male 11). 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 because of the low systemic exposure.

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

Imiquimod is first drug in class known as imidalazoquinolines. 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-aproval reporting data base. The most common adverse events are related to local skin reaction, upper respiratory infections, and flu-like symptoms.
Resiquimod is second generation imidalazoquinoline (b) (4) Oral resiquimod 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 was one death reported during trial 805.The subject was 28 years old man randomized to the 3.75% group who died from gunshot wound on day 40 of the trial.

Comment; Reviewer is in agreement with the investigator's assessment that the event was not related to the treatment.

7.3.2 Nonfatal Serious Adverse Events

There were total of 13 subjects that experienced SAE in reported phase 3 trials. 8 subjects used 3.75% imiquimod, 4 subjects used 2.5% and 1 subject used placebo. PK study did not have any SAE. (modified table 5.3.5.3.2-36)

Table 22 Serious Adverse Events

Treatment	Trial Site/ subject	Adverse event	Onset day	Severity
3.75%	801 19/23	Pelvic mass/acute abdomen	26	Severe
	801 31/27	Choletithiasis	41	Severe
	805 3/14	Pancreatic carcinoma, ovarian cancer, bile duct obstruction, Pneumothorax, catheter induced infection	84	Severe
	805 12/05	Chest pain, anxiety	84	Severe
	805 22/13	Malignant melanoma	55	Mild
	805 34/03	Uncontrolled diabetes mellitus	unknown	Moderate
	805 39/02	Malignant melanoma-right breast Malignant melanoma -right leg	28	Moderate

	805 40/13	Diverticulitis	7	Moderate
2.75%	801 26/41	Iron deficiency anemia	67	Severe
	801 31/004	Migraine Syncope	41 41	severe moderate
	805 19/33	Ovarian cystectomy	30	Moderate
	805 35/04	Suicidal ideation	5	Moderate
vehicle	805 36/21	Arthritis Printzmetal angina	85 106	severe severe

Comment: All narratives were reviewed. Reviewer is in agreement with investigator that events were probably not related to the drug. Selected events will be further presented:

1. Malignant melanoma cases
   - *Subject 22/013- 42 years old American Indian female received 31 packs of imiquimod 3.75% cream during 44 days of treatment and completed the trial on December 29, 2008 (completely cleared). She entered the follow-up for recurrence and on* (b) (6) *underwent a biopsy of skin lesion on her back that was diagnosed as melanoma. No further information about her condition is provided except that she discontinued the follow-up phase on her own request on February 24, 2009.*
     Comment: There is time relationship between imiquimod use and melanoma discovery, however, the site of melanoma is different from application site, and systemic exposure of imiquimod is minimal to be considered cause of malignancy at different site.
   - *Subject 39/002- 44 years old white woman received one dose of 3.75% imoquimod cream on October 6, 2008. She did not apply any further doses and on* (b) (6) *was diagnosed with melanomas of right breast and right leg. Subject discontinued participation in the trial on the same day.*
     Comment: One time exposure to the drug applied on different anatomical site than the melanoma would be very unlikely to cause melanoma. Furthermore time between the application and diagnosis is only (b) (6) *making causality even more unlikely.*
2. Iron deficiency anemia
   - *Subject 26/041-53 African American with previous history of severe anemia received 58 doses of 2.5% imiquimod cream and completed the trial on February 23, 2009. On* (b) (6) *she was hospitalized for anemia with Htc 15.6% (MCV 60). She was pre-syncopal and required transfusion.*
     Comment: Current labeling lists anemia as reported adverse reaction. In this case, subject had previous history of anemia with screening value of Htc 19% and per CFR was not on iron therapy at that time. It is more likely that her anemia worsened because of lack of treatment than because of imiquimod use.
3. Syncope

- Subject 31-004-*47 y/old AA man with h/o migraine and myopia was evaluated in ER on* (b) (6) (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.

4. Suicidal ideation

- *According to CFR, subject 35/004-19 years old Hispanic male, applied first dose of imiquimod 2.5% cream on September 5, 2008 and last on September 7, 2008. Exposure was 16 packets . On* (b) (6) *he was hospitalized for psychiatric/detoxification treatment.*
  Comment: Additional information was requested related to this case as it appeared that overdose might have had occurred. In the response received on July 12, 2010, applicant stated that there was an error in reporting the last day of treatment. Provided information is adequate to dismiss the overdose as potential reason for suicidal ideation. Furthermore, the case is confounded with chemical dependency that may be related to suicide ideation as well.

7.3.3 Dropouts and/or Discontinuations

Total of 794 subjects were screened, and 470 (59.2%) were randomized in 801 trial. Total of 911 subjects were screened, and 511 (56.1%) were randomized in 805 trial. Information about screening failures was provided. The most frequent reason for screening failure was that subjects did not have a clinical diagnosis of EGW with required number of warts (52.5% and 48.5%, respectively).

Following randomization, 147 subjects (31.3%) from 801 trial were discontinued for the reasons presented in the table below:

Table 23 Discontinued Subjects-801

Reason	Treatment group			Total (470)
	3.75 % group (n=195)	2.5% group (n=178)	Vehicle (n=97)	

Safety	3 (10/26,18/20,19/23)	2 (1/25, 16/13)	1 (26/39)	6
Subject's request (not due to AE)	10	8	7	25
Concomitant medication	0	0	0	0
Lost to follow up	39	37	19	95
Lack of efficacy	0	1	0	1
Investigator's request	1	0	0	1
Non compliance	1	4	0	5
Other (not AE)	5	5	4	14
Total (%)	59 (30.3%)	57 (32%)	31 (32%)	147 (31.3%)

In 805 trial 146 subjects (28.6%) were discontinued for the following reasons:

Table 24 Discontinued Subjects-805

Reason	Treatment group			Total (511)
	3.75 % group (n=205)	2.5% group (n=201)	Vehicle (n=105)	
Safety	3 (6/21,31/05,39/2)	5 (3/12,4/22,12/10,18/16,35/4)	0	8
Subject's request (not due to AE)	11	9	4	24
Concomitant medication	0	1	0	1
Lost to follow up	35	40	19	94

Lack of efficacy	0	0	0	0
Investigator's request	2	0	1	3
Non compliance	2	3	3	8
Other (not AE)	2	5	1	8
Total	55 (27%)	63 (31.2%)	28 (26.7%)	146 (28.6%)

Reviewer's comments: One subject in 2.5% group (3/12) was recorded twice (safety reason and subject's request) thus the reviewer corrected the applicant's number of safety related discontinued subjects from 4 to 5 and decreased subject's request number from 10 to 9.
Off all randomized subjects approximately 8% discontinued early (80/981) and did not show-up after baseline visit (see Figure 4 and Figure 6). The distribution among treatment arms was comparable (7.7% in 3.75% arm, 7.7% in 2.5% arm and 5.9% in vehicle arm).
In both trials the highest number of subjects did not complete the trial because they were of lost to follow up. No additional information could be extracted from the provided listings. The distribution of lost to follow-up subjects is similar in both trials.
In the category of "subjects' request" no further explanation was given. In category "other" majority were related to subjects' displacement.
Total of 14 subjects were discontinued because of safety reasons: 8 for application site reactions (all active arms), and one for pelvic mass (19/23), gun shot wound (31/5), malignant melanoma(39/2), hypersensitivity 3/12), suicidal ideation (35/4), and bronchitis(26/39). All but one subject were randomized to active treatments.

Reviewer is in agreement with investigator that only application site reactions were related to drug use. In the case of hypersensitivity development of rash coincides with imiqumod treatment but is confounded with Bactrim intake.
Discontinuation rate for application site reactions in active treatment population was approximately 1% (8/779).

7.3.3 Significant Adverse Events

Severe adverse events were rare (total of 45 subjects) and mostly related to application site reactions (25 subjects). Severe adverse events in PK trial were all related to application site reaction (6 erosion and ulcerations, 3 erythema, 2 weeping/exudate , and 1 scabing/crusting).

Table 25 Summary of Severe AE

	Imiquimod Cream		
	3.75% (N=400)	2.5% (N=379)	Placebo (N=202)
Subjects with any severe AE, n (%)	**21 (5.3)**	20 (5.3)	4 (2.0)
General disorders and administration site conditions	**12 (3.0)**	12 (3.2)	1 (0.5)
Application site pain	**6 (1.5)**	5 (1.3)	0
Application site irritation	**2 (0.5)**	3 (0.8)	0
Application site reaction	**1 (0.3)**	3 (0.8)	0
Application site pruritus	**1 (0.3)**	2 (0.5)	0
Application site rash	**2 (0.5)**	0	0
Application site bleeding	**0**	0	1 (0.5)
Application site dermatitis	**0**	1 (0.3)	0
Application site erythema	**0**	1 (0.3)	0
Application site ulcer	**0**	1 (0.3)	0
Application site vesicles	**1 (0.3)**	0	0
Chest pain	**1 (0.3)**	0	0
Influenza like illness	**1 (0.3)**	0	0
Pelvic mass	**1 (0.3)**	0	0
Infections and infestations	**3 (0.8)**	4 (1.1)	0
Nasopharyngitis	**1 (0.3)**	1 (0.3)	0
Application site infection	**0**	1 (0.3)	0
Bronchitis	**0**	1 (0.3)	0
Influenza	**1 (0.3)**	0	0
Pharyngitis streptococcal	**0**	1 (0.3)	0
Vaginal infection	**1 (0.3)**	0	0
Gastrointestinal disorders	**3 (0.8)**	2 (0.5)	1 (0.5)
Acute abdomen	**1 (0.3)**	0	0
Diarrhoea	**0**	1 (0.3)	0
Gastrooesophageal reflux disease	**0**	0	1 (0.5)
Haemorrhoidal haemorrhage	**1 (0.3)**	0	0
Haemorrhoids	**0**	1 (0.3)	0
Proctalgia	**1 (0.3)**	0	0

Reproductive system and breast disorders	**4 (1.0)**	2 (0.5)	0
Scrotal erythema	**2 (0.5)**	1 (0.3)	0
Dysmenorrhoea	**2 (0.5)**	0	0
Vulval ulceration	**0**	1 (0.3)	0
Injury, poisoning and procedural complications	**1 (0.3)**	1 (0.3)	0
Gun shot wound	**1 (0.3)**	0	0
Upper limb fracture	**0**	1 (0.3)	0
Musculoskeletal and connective tissue disorders	**0**	1 (0.3)	1 (0.5)
Arthritis	**0**	0	1 (0.5)
Groin pain	**0**	1 (0.3)	0
Nervous system disorders	**1 (0.3)**	1 (0.3)	0
Headache	**1 (0.3)**	0	0
Migraine	**0**	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders	**1 (0.3)**	0	1 (0.5)
Cough	**0**	0	1 (0.5)
Dyspnoea	**1 (0.3)**	0	0
Sinus congestion	**0**	0	1 (0.5)
Blood and lymphatic system disorders	**0**	1 (0.3)	0
Iron deficiency anaemia	**0**	1 (0.3)	0
Surgical and medical procedures	**1 (0.3)**	0	0
Tooth extraction	**1 (0.3)**	0	0

Source: ISS-Table 5.3.5.3.2-24

Comment: The highest percentage of severe AE(7%) considered to be related to the treatment were severe local reactions. The distribution between active arms was similar (~3% in each), and vehicle arm had 0.5%.

7.3.4 Submission Specific Primary Safety Concerns

Total of 61 subject developed systemic symptoms during the treatment phase (6.2%). Distribution and type of symptoms is presented below (electronically copied from Table 5.3.5.3.2-17)

Table 26 Summary of Systemic Adverse Events

	Imiquimod Cream		
	3.75% (N=400)	2.5% (N=379)	Placebo (N=202)
Subjects with any AE, n (%)	164 (41.0)	156 (41.2)	68 (33.7)
Subjects with any systemic symptom	26 (6.5%)	27 (7.1)	8 (4.0)
Headache	9 (2.3)	8 (2.1)	1 (0.5)
Nausea	7 (1.8)	4 (1.1)	2 (1.0)
Pyrexia	3 (0.8)	2 (0.5)	1 (0.5)
Influenzae	3 (0.8)	4 (1.1)	2 (1.0)
Diarrhoea	2 (0.5)	4 (1.1)	1 (0.5)
Myalgia	2 (0.5)	1 (0.3)	0
Pain	2 (0.5)	2 (0.5)	1 (0.5)
Fatigue	2 (0.5)	0	0
Influenza like illness	1 (0.3)	3 (0.8)	0
Chills	0	2 (0.5)	0
Malaise	0	2 (0.5)	0
Pain in extremity	0	2 (0.5)	0

Comment: These events are considered related to immune activation. Not surprisingly vast majority was noted in active arms.

In regard to urinary difficulties (see Section 2.6), 2 subjects (0.5%) from 3.75% group (one male and one female) had AE reported dysuria and none from 2.5% or vehicle groups. These events were not severe in intensity and did not meet criteria for SAE.

Application Site Reactions

Application site reactions and local skin reactions are further analyzed by type and severity in the Tables 27 and 28 (modified from sponsor's Tables 5.3.5.3.2-29 and 5.3.5.3.2-27).

Table 27 Summary of Application Site Reactions

Number (%) of subjects with	3.75% (n=400)	2.75% (n=379	Vehicle (n=202)
Any Application Site Reaction	64 (16)	58(15.3)	5(2.5)
Any Severe Application Site Reaction	9 (2.3)	12 (3.2)	1 (0.5)
Application site pain	28 (7)	20 (5.3)	1 (0.5)
Application site irritation	24 (6)	13(3.4)	2 (1)
Application site pruritus	11 (2.8)	17 (4.5)	2 (1)
Application site reaction	4 (1)	5 (1.3)	0
Application site discharge	4 (1)	3 (0.8)	0
Application site rash	4 (1)	3 (0.8)	0
Application site bleeding	4 (1)	3 (0.8)	0

Comment: The most frequent reactions were application site pain, irritation and pruritus and all of them were significantly higher in active groups v. vehicle. Severe reactions were relatively rare. Infection of the site was rare too (<1% per treatment group).
In PK study and irritation and pruritus was reported by one subject (5.6%) each.

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 for each category is presented in Table 28 (modified from sponsor's Table 5.3.5.3.2-27).

Table 28 Frequency Distribution of Post-Baseline LSR

Any reaction n,% **Severe reaction %**	**3.75%** **(n=400)**	**2.5%** **(n=379)**	**Vehicle** **(n=202)**
Any erythema	280 (70)	222(58.5)	55 (27.2)
Severe erythema	36 (9)	36 (9.5)	1 (0.5)
Any edema	163(40.8)	136 (35.8)	16 (7.9)
Severe edema	8 (2)	9 (2.4)	0
Any erosion/ulceration	143(35.6)	116(30.6)	9 (4.5)
Severe erosion/ulc	43 (10.8)	37 (9.7)	1 (0.5)
Any exudate	135(33.8)	106 (27.9)	5 (2.5)
Severe exudate	7 (1.8)	4 (1.1)	0
Any flaking/scaling/dryness	118 (29.5)	77 (20.3)	21(10.4)
Severe flak/dry	0	3 (0.8)	0
Any scabbing/crusting	93 (23.3)	70 (18.5)	8 (3.9)
Severe scab/crus	3 (0.8)	3 (0.8)	0

Comment; The most common LSR was erythema , reported by 70% of subjects, followed by edema(41%). However, when comparing severe LSR, severe erythema comes second (with 9% of all subjects) to erosions/ulcerations that was observed in 11% of subjects.
In PK study (maximal exposure conditions),erythema was observed in 72% of subjects and edema in 94.4 %.Erosion was observed in 6 subjects (33.3%) and ulceration in 5 subjects (27.8%).

Rest periods

Table 29 Summary of Rest Periods

	3.75% **(N=400)**	**2.5%** **(N=379)**	**vehicle** **(N=202)**
Subjects Required Rest Period, n (%)	126 (31.5)	104 (27.4)	4 (2)
Number of Dosing Days Missed Due to Rest Period	126	104	4

Source: (modified from sponsor's Table 5.3 5 3 2-34).

Comment: Approximately one third of imiquimod treated subjects requested rest periods. On average, the rest period lasted 7 days and for the most part, subject requested it after 2 weeks of treatment (coincides with the highest number of local skin reactions).
There was no provision in PK study for taking rest periods. Dosing was interrupted for 2 days for 1 subject due to application site ulcer.

7.4 Supportive Safety Result

7.4.1 Common Adverse Events

About 40% of subjects in active arms and 33.5 % in vehicle arm experienced AE. The most frequent AE are presented in Table 30 (electronically copied Table 5.3.5.3.2-16). Treatment-emergent AE were defined as "AE with the onset between the randomization visit and 30 days after the end of treatment". The summary of those events is presented in Table 31.

Table 30 Adverse Events Occurring in > 1% of Imiquimod –Treated Subjects and at the Greater Frequency than with Vehicle

	Imiquimod Cream		
	3.75% (N=400)	2.5% (N=379)	Placebo (N=202)
Subjects with Any AE, n (%)	**164 (41.0)**	156 (41.2)	68 (33.7)
Number of AEs	**432**	351	118
Application site pain	**28 (7.0)**	20 (5.3)	1 (0.5)
Application site irritation	**24 (6.0)**	13 (3.4)	2 (1.0)
Nasopharyngitis	**16 (4.0)**	21 (5.5)	10 (5.0)
Upper respiratory tract infection	**12 (3.0)**	7 (1.8)	8 (4.0)
Application site pruritus	**11 (2.8)**	17 (4.5)	2 (1.0)
Headache	**9 (2.3)**	8 (2.1)	1 (0.5)
Vaginitis bacterial	**8 (2.0)**	6 (1.6)	2 (1.0)
Nausea	**7 (1.8)**	4 (1.1)	2 (1.0)
Back pain	**7 (1.8)**	4 (1.1)	1 (0.5)
Urinary tract infection	**6 (1.5)**	6 (1.6)	2 (1.0)
Sinusitis	**6 (1.5)**	4 (1.1)	2 (1.0)
Sinus congestion	**6 (1.5)**	1 (0.3)	1 (0.5)
Cough	**5 (1.3)**	5 (1.3)	3 (1.5)
Rash	**5 (1.3)**	2 (0.5)	1 (0.5)
Vomiting	**5 (1.3)**	1 (0.3)	1 (0.5)
Skin laceration	**5 (1.3)**	1 (0.3)	0

Table 31 Treatment-Emergent Adverse Events Occurring in > 1% of the 3.75% Imiquimod –Treated Subjects and at the Greater Frequency than Vehicle

Preferred Term	3.75% (N=400)	2.5% (N=379)	Vehicle (N=202)
Any Adverse Event	144 (36%)	134 (35.3%)	56(27.7%)
Application site pain	28 (7%)	20 (5.3%)	1 (0.5%)
Application site irritation	24 (6%)	13 (3.4%)	2 (1%)
Application site pruritus	11 (2.8%)	17 (4.5%)	2 (1%)
Upper respiratory infection	7 (1.8)	6 (1.6%)	3 (1.5%)
Vaginitis bacterial	6 (1.5%)	3 (0.8%)	2 (1%)
Headache	6 (1.5%)	3 (0.8%)	1 (0.5%)
Rash	5 (1.3%)	1 (0.3%)	1 (0.5%)

Source: ISS 5.3.5.3.2-18

Comment: As expected, application site reactions have higher incidence in the active treatment groups then in vehicle group. In PK study similar frequency and distribution of AEs is noted.10/18 (55.6%) subjects experienced at least one AE. Most frequent were headache and application site reactions [each experienced by 4 subjects (22.2%)].

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 (the highest percentage of subjects was 9.4% in vehicle group).This is not unexpected, as subjects were not requested to fast before providing a blood sample. The significance of similar observation for alanine aminotransferase, cholesterol and urine protein is not clear. However, the rates among active and placebo groups were similar.

7.4.3 Vital Signs

There were no clinically meaningful changes in vital signs. One subject had bradycardia for which treatment was interrupted and medication was prescribed.

7.4.4 Electrocardiograms (ECGs)

There were no ECGs done in pivotal trials. During review of NDA 20-483 question was raised about potential of imiquimod to induce symptomatic arrythmia. Applicant agreed to conduct a post-marketing trial to answer this question.
Overall systemic exposure of topical imiquimod is low and there was no signal of QT prolongation in oral trials (with supratherapeutic imiquimod levels), thus TQT trial is not required.

7.4.5 Special Safety Studies/Clinical Trials

EGW is regarded a chronic condition requiring repeated treatments. Applicant did not conduct long term safety trial as part of this submission. Instead, as previously agreed, provided are results of two long term trials utilizing 5% cream for EGW treatment -1233-IMIQ and 1243-IMIQ (see Section 5.3.2.).
There were no new safety signals detected in 404 subjects during prolonged exposure (more then 6 months) or 1 year follow up (in 100 subjects) in these trials.

Comment: Supportive trials with 5% cream may fulfill the requirement for long term safety for 3.75% cream based upon comparable safety profile, systemic exposure, and adequate number of subjects followed for 6 and 12 months.

7.4.6 Immunogenicity

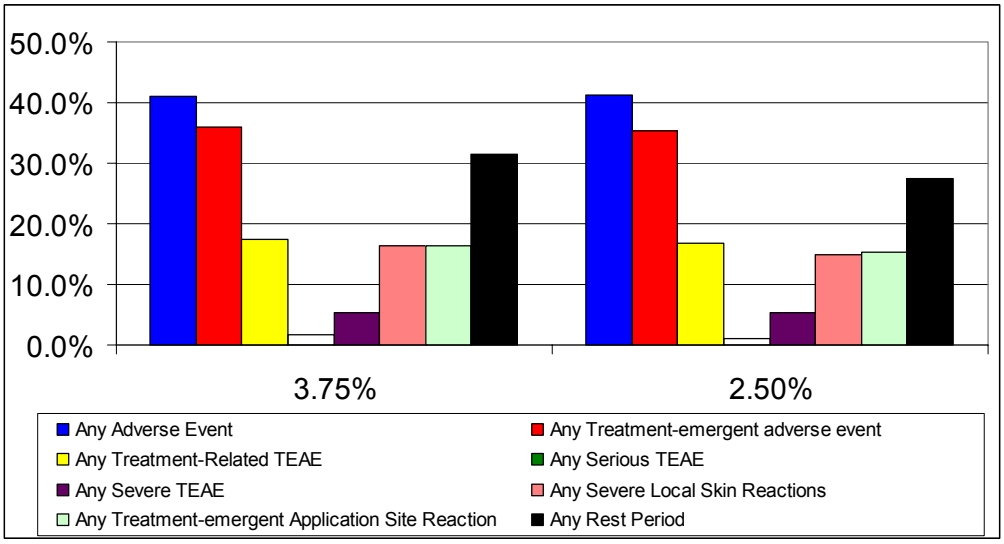
Imiquimod stimulates the immune system. Although not fully understood, this mechanism involves both innate and to less degree acquired aspects of immune response. There was no specific data from this submission that further analyzed different aspects of this quality. Excessive activation of immune system was not observed in this submission which is understandable considering very low systemic exposure.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

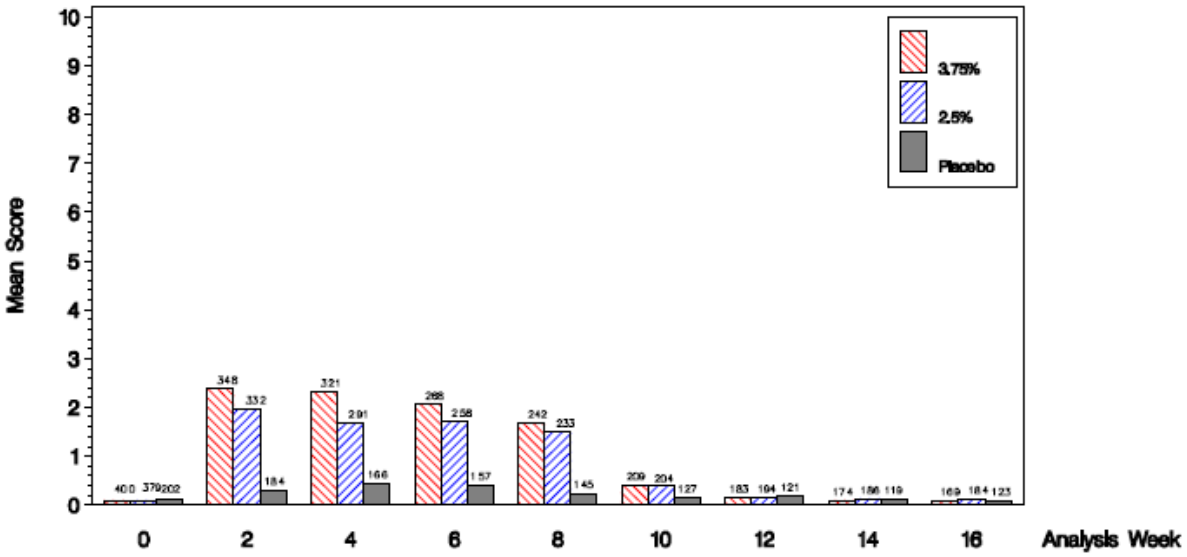
Slightly higher percentage of subjects in 3.75% group reported AE then in 2.5%. This trend was observed across all categories, however the difference in not significant. Data is presented in Figure 14.

Figure 14 Dose Dependency for Adverse Events



7.5.2 Time Dependency for Adverse Events

Figure 15 Time Dependency for Local Skin Reactions



Local adverse events peaked between Week 2 and 4 and continue to decrease more rapidly towards the end of the treatment. (electronically copied Figure 5.3.5.3.2-3). In the post-treatment period most of the reactions resolved.

7.5.3 Drug-Demographic Interactions

There is little difference in incidence of adverse events when analyzed by age, number of treated areas or EGW count. AE seems to be more likely in subjects with >35 years and with multiple anatomic areas involved. Geriatric population could not be adequately evaluated because of limited data (only 5 subjects over 65 years of age were exposed to imiquimod 3.75% cream). Reader is referred to Table 32 (modified from applicant's Table 5.3.5.3.2-40).

Table 32 Number (%) of Subjects with Adverse Events by Subpopulation

	Imiquimod Cream		
	3.75%	2.5%	Placebo
Age ≤35	90/265 (34.0)	83/240 (34.6)	37/138 (26.8)
Age >35	54/135 (40.0)	51/139 (36.7)	19/64 (29.7)
One anatomic area	65/192 (33.9)	65/179 (36.3)	26/104 (25.0)
Multiple anatomic areas	79/208 (38.0)	69/200 (34.5)	30/98 (30.6)
Baseline EGW Count ≤7	85/230 (37.0)	66/215 (30.7)	32/112 (28.6)
Baseline EGW Count >7	59/170 (34.7)	68/164 (41.5)	24/90 (26.7)

Comment: It appears that there is small increase in AE when multiple areas are treated. However, same trend was observed in vehicle group.

Comparison of AE between genders is presented in Tables 33 and 34 (electronically copied from ISS Tables 5.3.5.3.2-19 and 20).Slightly higher percentage of women compared to men reported AE during the trial and that is true for every treatment group including vehicle. Again seen, application site pain, application site irritation, and nasopharyngitis were reported by the largest percentage of subjects in both genders.

Table 33 Number (%) of Males with Adverse Events

	Imiquimod Cream		
	3.75% (N=183)	2.5% (N=168)	Placebo (N=96)
Male subjects with any AE, n (%)	**59 (32.2)**	46 (27.4)	17 (17.7)
Application site irritation	**12 (6.6)**	2 (1.2)	1 (1.0)
Application site pain	**11 (6.0)**	9 (5.4)	1 (1.0)
Nasopharyngitis	**4 (2.2)**	1 (0.6)	3 (3.1)
Application site pruritus	**4 (2.2)**	3 (1.8)	0
Upper respiratory tract infection	**4 (2.2)**	3 (1.8)	0
Pruritus genital	**3 (1.6)**	2 (1.2)	0
Rash	**3 (1.6)**	0	0
Scrotal pain	**3 (1.6)**	0	0
Scrotal erythema	**2 (1.1)**	5 (3.0)	0
Application site reaction	**2 (1.1)**	3 (1.8)	0
Scrotal ulcer	**2 (1.1)**	3 (1.8)	0
Influenza	**2 (1.1)**	1 (0.6)	1 (1.0)
Scrotal oedema	**2 (1.1)**	2 (1.2)	0
Secretion discharge	**2 (1.1)**	2 (1.2)	0
Application site rash	**2 (1.1)**	1 (0.6)	0
Pyrexia	**2 (1.1)**	1 (0.6)	0
Sinus congestion	**2 (1.1)**	1 (0.6)	0
Anxiety	**2 (1.1)**	0	0
Application site cellulitis	**2 (1.1)**	0	0
Application site excoriation	**2 (1.1)**	0	0
Chest pain	**2 (1.1)**	0	0
Sinusitis	**2 (1.1)**	0	0
Skin exfoliation	**2 (1.1)**	0	0
Tinea cruris	**2 (1.1)**	0	0

Table 34 Number (%) of Females with Adverse Events

	Imiquimod Cream		
	3.75% (N=217)	2.5% (N=211)	Placebo (N=106)
Female subjects with any AE, n (%)	**85 (39.2)**	88 (41.7)	39 (36.8)
Application site pain	**17 (7.8)**	11 (5.2)	0
Application site irritation	**12 (5.5)**	11 (5.2)	1 (0.9)
Nasopharyngitis	**7 (3.2)**	13 (6.2)	6 (5.7)
Application site pruritus	**7 (3.2)**	14 (6.6)	2 (1.9)
Vaginitis bacterial	**6 (2.8)**	3 (1.4)	2 (1.9)
Headache	**6 (2.8)**	3 (1.4)	0
Urinary tract infection	**4 (1.8)**	5 (2.4)	2 (1.9)
Back pain	**4 (1.8)**	3 (1.4)	1 (0.9)
Upper respiratory tract infection	**3 (1.4)**	3 (1.4)	3 (2.8)
Nausea	**3 (1.4)**	2 (0.9)	2 (1.9)
Application site erythema	**3 (1.4)**	3 (1.4)	0
Application site bleeding	**3 (1.4)**	1 (0.5)	1 (0.9)
Application site discharge	**3 (1.4)**	1 (0.5)	0
Application site oedema	**3 (1.4)**	1 (0.5)	0

In regard to LSR, there was no significant difference in overall distribution of AE or in intensity. Women tend to have reactions earlier (week 2) then men (week 4).
Rest periods were taken by women earlier and more frequently then men.

7.5.4 Drug-Disease Interactions

These trials do not provide sufficient data to examine drug-disease reactions.

7.5.5 Drug-Drug Interactions

These trials do not provide sufficient data to examine imiquimod cream interactions with other drugs.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There is no signal regarding carcinogenicity in post-marketing data base for 5% imiquimod.

7.6.2 Human Reproduction and Pregnancy Data

Imiquimod is category C pregnancy risk based upon pre-clinical data included in NDA 22-723. No trials with imiquimod were conducted in pregnant women.

Subjects were required to maintain pregnancy control measures during the phase 3 trials. Urine pregnancy tests were performed at the screening, baseline, and end-of study visits, as well as follow-up periods for women of child-bearing potential.

Eleven pregnancies were reported during the trial, 3 in the 3.75% imiquimod group, 5 in the 2.5% imiquimod group, and 3 in the placebo group and are presented in the table below:

Table 35 Pregnancies during the Trial

Treatment group	Trial Site/ subject	Pregnancy outcome	comment
3.75%	801 26/55	to be determined	+ test at week 12
	805 4/17	to be determined	+ test at week 18
	805 34/14	to be determined	+ test at week 8
2.5%	801 9/37	to be determined	Last dose taken prior to pregnancy
	801 26/038	to be determined	+ test at week 16
	805 28/14	to be determined	- test at week 8, then lost contact
	805 39/01	Delivery	healthy infant
	805 40/14	to be determined	+ test on day 26, discontinued medication on day 28
vehicle	801 3/02	Terminated	+ test at week 8
	801 04/49	to be determined	+ test on day 23, discontinued medication on day 23
	805 5/05	to be determined	+ test on week 12

According to the available data, all the treatments were already completed or terminated about the time when pregnancy was discovered. One pregnancy was terminated and one ended with delivery of healthy baby.
Comment: The outcome of all pregnancies was provided in 120 –day safety report (see Section 7.7).

7.6.3 Pediatrics and Assessment of Effects on Growth

External genital warts is disease of sexually active individuals, thus per the exclusion criteria subjects less then 12 years of age were not eligible to participate in trials. Applicant submitted a request for partial waiver of pediatric studies for children < 12 years of age which was granted by Pediatric Review Committee on September 29, 2010. 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.

As stated, trials were open to subjects 12 years and older, and the applicant is seeking approval for “12 years and older”. However, the vast majority of treated subjects were

18 years and older. Indeed, there were only three subjects between ages 15 and 17 and no subjects below age 15 that were enrolled. Thus, safety and efficacy of imiquimod 3.75% cream for the adolescent population with EGW (from 12-17 years) is available from 3 subjects only. From the efficacy stand-point all three subjects achieved complete clearance. One subject (from 2.5% group) had no AE and no LSR reported, and the other two subjects (both from 3.75% group) had moderate LSR and non related AE.
Information request was sent to the applicant requesting justification for age indication and clarification on the available data to support it. Response was received on July 12, 2010, containing a summary of the relevant data for 3 adolescent subjects and:

- safety summary from molluscum contagiosum trials with imiquimod 5% cream conducted in subjects 2-12 of age (total of 559 subjects treated with imiquimod 5% cream). Review of the safety revealed that LSR remained the most frequent AEs. Systemic exposures from pharmacokinetic trial for molluscum indication were higher (0.29-1.06 ng/mL) then for either imiquimod 5% for EGW (0.4ng/mL) or for imiquimod 3.75% for EGW (0.26-0.85 ng/mL).
- literature review. Total of 14 subjects were described that used 5% cream for EGW, however 13 were younger then 12 years, and one was 17 years old. There were no new safety signals from these reports.

Applicant concluded that they are "unaware of any clinical factors that would indicate that the effects of treatment of EGWs with topical imiquimod would be different for patients between age 12-15 years versus those older than 15 years of age, or between those age 12-17 years and adults**."**
Pediatric consult was obtained regarding the need to further study safety of imiquimod 3.75% cream in adolescents. The reviewer concluded that "Adult safety data from clinical trials for several indications for Aldara® and Zyclara™ can provide supportive data for a pediatric safety database....Safety cannot be extrapolated from adults to pediatric patients; however, safety information in adults can support a finding of safety in pediatric patients. Additional support for the safety of Zyclara™ in adolescents is the fact that the product is topical and has a low systemic absorption...
Given the additional supportive safety information from experience with use of Aldara® in the pediatric population, one would expect the safety of Zyclara to be similar in adolescents as in adults and additional studies in adolescents are not needed."

Comment: Reviewer agrees that available safety data for ages 2-12 and 18 and older treated with imiquimod 5% provide sufficient reassurance. There is no reason to assume that age group 12-18 would experience new or more severe adverse reactions based on their age only.

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7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of overdose occurred in any of the submitted trials. 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.

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7.7 Additional Submissions / Safety Issues

120 day safety data were submitted on June 7, 2010. Follow-up information on 11 subjects who became pregnant during phase three trials was provided: two subjects had their pregnancies terminated (both in vehicle group- 801-3/02 and 805-5/05), 4 subjects had uneventful deliveries of healthy babies (one from vehicle group 801-4/49, and three from 2.5% group 801-9/37, 801-26/038 and 805-39/01) and 5 subjects were lost to follow up with unknown outcome (three from 3.75% group: 801-26/55,805-4/17 and 805-34/13 and two from 2.5% group: 805-28/14 and 805-40/14).

Comment: This report does not raise any new safety concerns.

8 Postmarket Experience

3.75% imiquimod cream is marketed for AK in Canada since December 2009 and in the US since March 2010. The time frame is too short to reflect on post marketing data for imiquimod 3.75% cream. However, data were provided for Aldara® cream (imiqimod 5%) in the Periodic Safety Update Report (PSUR) submitted on April 27, 2010 and cross-referenced to this submission. PSUR, which covers period from February 2009-February 2010, is reviewed separately and only conclusions will be provided here:

- no deaths were reported,
- 19 events were serious and 700 non-serious,
- there were no new major safety findings,
- application site reactions remained the most common adverse event observed since imiquimod 5% cream was approved,
- information derived from this report is expected to change the labeling of Aldara® in such way that hypertrophic scaring will be added in the Post-marketing experience section.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

Agreement on labeling is ongoing at the time of close of this review.

9.3 Advisory Committee Meeting

No Advisory Committee was convened for this application.

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/s/

MILENA M LOLIC
10/29/2010

JILL A LINDSTROM
10/29/2010