

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**201153Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 201153, 022483/S-001

SUPPL # NA

HFD # 540

Trade Name Zyclara Cream, 3.75%

Generic Name imiquimod

Applicant Name Graceway Pharmaceuticals, Inc.

Approval Date, If Known 3/24/2011

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

NA

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

NA

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# NDA 022483

Zyclara (imiquimod) Cream, 3.75%

NDA# NDA 020723

Aldara (imiquimod) Cream, 5%

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

GW01-0801 and GW01-0805

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

N/A

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:



Investigation #2

!

YES

!

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form: Cristina Attinello  
Title: Regulatory Health Project Manager  
Date: 3/24/2011

Name of Office/Division Director signing form: Susan J. Walker  
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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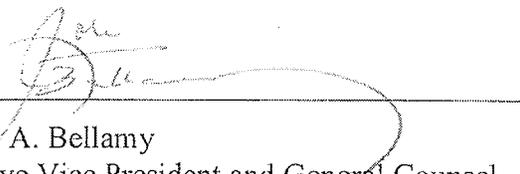
CRISTINA Petruccelli Attinello  
03/24/2011

SUSAN J WALKER  
03/24/2011

1.3.3 Debarment Certification

**DEBARMENT CERTIFICATION**

Graceway Pharmaceuticals, LLC hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal, Food, Drug and Cosmetic Act in connection with this application.



A handwritten signature in dark ink, appearing to read "John A. Bellamy", is written over a horizontal line. The signature is fluid and cursive.

John A. A. Bellamy  
Executive Vice President and General Counsel  
Graceway Pharmaceuticals, LLC

13 Oct 2010

Date

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 201153, 022483/S-001	NDA Supplement # NA	If NDA, Efficacy Supplement Type: NA
Proprietary Name: Zyclara Established/Proper Name: imiquimod Dosage Form: Cream, 3.75%		Applicant: Graceway Pharmaceuticals, LLC Agent for Applicant (if applicable): NA
RPM: Cristina Attinello		Division: Division of Dermatology and Dental Products
<p><b>NDA:</b>                      NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)                      Efficacy Supplement:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b>                      Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> Other (explain)</p> <p><b><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</b></p> <p><input type="checkbox"/> No changes   <input type="checkbox"/> Updated   Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>
<b>❖ Actions</b>		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>12-12-10</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	NA
❖ Application Characteristics <sup>2</sup>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)  Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)  Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p>REMS: <input type="checkbox"/> MedGuide  <input type="checkbox"/> Communication Plan  <input type="checkbox"/> ETASU  <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>2</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes     No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes     No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes     No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes     No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If "No," continue with question (5).*

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>3</sup>	<input checked="" type="checkbox"/> Included
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	AP, 03-24-2011
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	3/22/11
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	06/08/10
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	NA

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 2 7 11

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	3/22/11
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	06/08/10
<ul style="list-style-type: none"> <li>Example of class labeling, if applicable</li> </ul>	NA
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	08/26/10
❖ Proprietary Name <ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>Review(s) (<i>indicate date(s)</i>)</li> </ul>	NA NA
❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )	<input checked="" type="checkbox"/> RPM 10/15/10 <input checked="" type="checkbox"/> DMEPA 10/7/10, 08/19/10 <input checked="" type="checkbox"/> DRISK 11/18/10, 09/16/10 <input checked="" type="checkbox"/> DDMAC 11/5/10, 09/27/10 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews (SEALD) 3/24/11
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	04/28/10
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment ( <i>indicate date</i> )	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>Date reviewed by PeRC <u>09/29/10</u> If PeRC review not necessary, explain: _____</li> <li>Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications ( <i>letters (except action letters), emails, faxes, telecons</i> )	<input checked="" type="checkbox"/> Included

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.  
Version: 2 7 11

❖ Internal memoranda, telecons, etc.	05/21/10
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	11/18/09
• EOP2 meeting ( <i>indicate date of mtg</i> )	01/20/08
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	3/23/11
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	2/2/11
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	2/2/11
• Clinical review(s) ( <i>indicate date for each review</i> )	10/29/10, 4/6/10
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	Clinical Review, 10/29/10 page 13
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	08/02/10 (PMHS)
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement ( <i>indicate date(s) of submission(s)</i> )	
• REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> )	
• Risk management review(s) and recommendations (including those by OSE and CSS) ( <i>indicate date of each review and indicate location/date if incorporated into another review</i> )	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input checked="" type="checkbox"/> None requested

<sup>5</sup> Filing reviews should be filed with the discipline reviews.  
Version: 2 7 11

<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Statistical Review(s) <i>(indicate date for each review)</i>	10/04/10, 4/7/10
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	10/06/10
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	11/5/10, 09/29/10, 4/1/10
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	12/8/10, 09/29/10, 4/6/10
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	9/29/10, page 5
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) ( <i>date completed must be within 2 years of action date</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>6</sup></i> )	Date completed: 05/28/10 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> ) ( <i>original and supplemental BLAs</i> )	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

<sup>6</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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/s/  
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CRISTINA Petruccelli Attinello  
03/30/2011



NDA 201153

**INFORMATION REQUEST**

Graceway Pharmaceuticals, LLC  
Attention: Sean Brennan, Ph.D.  
Sr. Vice President, Regulatory Affairs  
340 Martin Luther King Jr. Blvd.  
Suite 300  
Bristol, TN 37620

Dear Dr. Brennan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyclara (imiquimod) Cream, 3.75%.

We are reviewing the draft labeling for your submission and have the following information request. We request a prompt written response by COB Monday, February 28, 2011 in order to continue our evaluation of your NDA.

Provide a diagrammatic representation of subject accountability for NDA 201153, similar to Figure 1 from section 14.3 External Genital Warts of Aldara labeling.

If you have any questions, call me at (301) 796-3986.

Sincerely,

*{See appended electronic signature page}*

Cristina Attinello, M.P.H.  
Regulatory Project Manager  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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CRISTINA Petruccelli Attinello  
02/24/2011



NDA 201153

**INFORMATION REQUEST**

Graceway Pharmaceuticals, LLC  
Attention: Sean Brennan, PhD  
Sr. Vice President, Regulatory Affairs  
340 Martin Luther King, Jr. Blvd.  
Suite 500  
Bristol, Tennessee 37620

Dear Dr. Brennan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyclara (imiquimod) Cream, 3.75%.

We are reviewing the clinical section of your submission and have the following information request. We request a prompt written response by Wednesday, November 23, 2010, in order to continue our evaluation of your NDA.

Identify the location in your NDA of data that could provide prescribers and patients with comparative safety and efficacy data to inform their selection of the best strength of your imiquimod cream products for the treatment of external genital warts.

If you have any questions, call Barbara Gould, Chief Project Management Staff, at (301) 796-4224.

Sincerely,

*{See appended electronic signature page}*

Barbara Gould, M.B.A.H.C.M.  
Chief, Project Management Staff  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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/s/  
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BARBARA J GOULD  
11/22/2010



NDA 201153

**INFORMATION REQUEST**

Graceway Pharmaceuticals, Inc.  
Attention: Sean Brennan  
Senior Vice President, Regulatory Affairs  
340 Martin Luther King Jr. Blvd  
Bristol, TN 37620

Dear Mr. Brennan:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyclara (imiquimod) Cream, 3.75%.

We are reviewing the label/labeling section of your submission and have the following comments and information requests. We request a prompt written response by Friday, August 27, 2010 in order to continue our evaluation of your NDA.

1. Include NDC number in the carton label just as you have included NDC number in the approved carton label of NDA 022483.
2. Revise carton label so that the dosage form (cream) would be shown in the same line with the drug substance establishment name. You should follow the presentation of the established name and strength of the carton label submitted to NDA 022483 in the amendment dated May 18, 2010.

If you have any questions, call Nichelle Rashid, Regulatory Project Manager, at (301) 796-3904.

Sincerely,

*{See appended electronic signature page}*

Susan J. Walker, M.D., F.A.A.D.  
Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201153	ORIG-1	GRACEWAY PHARMACEUTICA LS LLC	Zyclara (Imiquimod) Cream 3.75%

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/s/

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STANKA KUKICH  
08/18/2010  
Signing for Susan Walker, Division Director



NDA 201153

**INFORMATION REQUEST**

Graceway Pharmaceuticals, LLC  
Attention: Sean Brennan  
Senior Vice President, Regulatory Affairs  
340 Martin Luther King Jr. Blvd.  
Bristol, TN 37620

Dear Ms. Cabrelli:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyclara (imiquimod) Cream, 3.75% for the treatment of external genital warts and perianal warts.

We are reviewing the clinical section of your submission and have the following information request. We request a written response by August 6, 2010.

You requested a partial waiver of studies required under the Pediatric Research Equity Act (PREA) for pediatric patients below the age of 12 years. The waiver request appears reasonable, however it lacks supporting data. Submit sufficient data to support the waiver request (e.g., current published medical literature and/or CDC data on incidence of external genital warts by age group).

If you have any questions, call Nichelle Rashid, Regulatory Project Manager, at (301)796-3904.

Sincerely,

*{See appended electronic signature page}*

Susan J. Walker, M.D., F.A.A.D.  
Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201153	ORIG-1	GRACEWAY PHARMACEUTICA LS LLC	Zyclara (Imiquimod) Cream 3.75%

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/s/

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SUSAN J WALKER  
08/02/2010

## REQUEST FOR CONSULTATION

TO (Office/Division): **Office of Surveillance and Epidemiology/  
Division of Medication Error Prevention and Analysis  
Attention: Janet Anderson**

FROM (Name, Office/Division, and Phone Number of Requestor):

Nichelle Rashid, RPM /DDDP (301) 796-3904  
Milena Lolic (Clinical reviewer) (301) 796-3825  
Jill Lindstrom (Clinical Team leader) (301) 796-0944

DATE  
05/26/10

IND NO.  
NA

NDA NO.  
201153

TYPE OF DOCUMENT  
Original NDA

DATE OF DOCUMENT  
February 8, 2010

NAME OF DRUG  
Zyclara Cream, 3.75%

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG  
Standard

DESIRED COMPLETION DATE  
September 26, 2010

NAME OF FIRM: **Graceway Pharmaceuticals, LLC.**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER             |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING                    |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                         |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE               |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                        |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): NEW NDA |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |   |  |
|---|--|
| <input type="checkbox"/> DISSOLUTION            | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILTY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

#### COMMENTS / SPECIAL INSTRUCTIONS:

Applicant is seeking approval for Zyclara (3.75% imiquimod cream) for external genital warts (EGW) in population 12 years and older.

eCTD application and available on edr site for NDA 201153, Zyclara Cream at the following network location:  
[\\FDSWA150\NONECTD\N201153\N\\_000\2010-02-05](#)

Please review the attached package insert, patient package insert, and carton labeling. The PDUFA date is December 8, 2010.

If you have any questions, please contact me at (301) 796-3904, Milena Lolic (Clinical Reviewer) at (301) 796-3825, and Jill Lindstrom (Clinical Team Leader) at (301) 796-0944.

SIGNATURE OF REQUESTOR <b>Nichelle Rashid</b>	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201153	ORIG-1	GRACEWAY PHARMACEUTICA LS LLC	Zyclara (Imiquimod) Cream 3.75%

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/s/

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NICHELLE E RASHID  
06/08/2010

## REQUEST FOR CONSULTATION

TO (Office/Division): **Office of New Drugs  
Pediatric and Maternal Health Staff  
Attn: Rosemary Addy**

FROM (Name, Office/Division, and Phone Number of Requestor):

**Nichelle Rashid, RPM /DDDP (301) 796-3904  
Milena Lolic (Clinical reviewer) (301) 796-3825  
Jill Lindstrom (Clinical Team leader) (301) 796-0944**

DATE  
**05/26/10**

IND NO.

NDA NO.  
**201153**

TYPE OF DOCUMENT

DATE OF DOCUMENT  
**February 8, 2010**

NAME OF DRUG  
**Zyclara Cream, 3.75%**

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG  
**Standard**

DESIRED COMPLETION DATE  
**July 2, 2010**

NAME OF FIRM: **Graceway Pharmaceuticals, LLC.**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER             |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING                    |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                         |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE               |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                        |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): NEW NDA |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

#### COMMENTS / SPECIAL INSTRUCTIONS:

#### Background information:

Applicant is seeking approval for Zyclara (3.75% imiquimod cream) for external genital warts (EGW) in population 12 years and older. Pivotal trials submitted in support of Zyclara approval (NDA 201153) have only 3 subjects younger than 18 years (ITT population 981 subjects)

Aldara (5% imiquimod cream) was approved in 1997 for EGW for 18 years and older. In 2002 indication was extended to 12 years and older without additional clinical trials. The differences between these two imiquimod products (Zyclara and Aldara) are:

1. Concentration (3.75% v. 5%)
2. Dosing regimen (daily v. three times per week)

3. Duration of treatment (8 weeks v. 16 weeks)

Systemic exposure in adults is similar (C<sub>max</sub> 0.48 ng/mL for Zyclara v. 0.43 ng/mL for Aldara). Safety review of Zyclara did not reveal any new signal in comparison to Aldara.

Applicant's justification for approval of the Zyclara in population 12 and older includes:

1. Enrollment was open for 12 years and older but without targeting of specific age group as advised by Agency. Applicant is unaware of any clinical factors that would indicate that the effects of treatment of EGW with topical imiquimod would be different for patients age 12-17 years and adults.

Pediatric question:

Has the applicant provided sufficient safety information to support approval of Zyclara 3.75% cream for external genital warts (EGW) in population 12 years and above?

eCTD application and available on edr site for NDA 201153, Zyclara Cream at the following network location:  
**\\FDSWA150\NONECTD\N201153\N\_000\2010-02-05**

If you have any questions, please contact me at (301) 796-3904, Milena Lolic (Clinical Reviewer) at (301) 796-3825, and Jill Lindstrom (Clinical Team Leader) at (301) 796-0944.

SIGNATURE OF REQUESTOR Nichelle Rashid	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201153	ORIG-1	GRACEWAY PHARMACEUTICA LS LLC	Zyclara (Imiquimod) Cream 3.75%

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/s/

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NICHELE E RASHID  
05/27/2010

**REQUEST FOR DDMAC LABELING REVIEW CONSULTATION**

**\*\*Please send immediately following the Filing/Planning meeting\*\***

TO: <b>CDER-DDMAC-RPM</b>	FROM: (Name/Title, Office/Division/Phone number of requestor) Nichelle Rashid, RPM /DDDP (301) 796-3904 Milena Lolic (Clinical reviewer) (301) 796-3825 Jill Lindstrom (Clinical Team leader) (301) 796-0944
------------------------------	---

REQUEST DATE 05/26/10	IND NO. NA	NDA/BLA NO. 201153	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
--------------------------	---------------	-----------------------	---

NAME OF DRUG Zyclara (imiquimod) Cream, 3.75%	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG Standard	DESIRED COMPLETION DATE (Generally 1 week before the wrap up meeting) September 26, 2010
---	------------------------	------------------------------------	--

NAME OF FIRM: Graceway Pharmaceuticals, LLC.	PDUFA Date: December 8, 2010
---	------------------------------

**TYPE OF LABEL TO REVIEW**

<b>TYPE OF LABELING:</b> (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	<b>TYPE OF APPLICATION/SUBMISSION</b> <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	<b>REASON FOR LABELING CONSULT</b> <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION
---	--	---

**EDR link to submission:**  
eCTD application and available on edr site for NDA 201153, Zyclara Cream at the following network location:  
[\\FDSWA150\NONECTD\N201153\N\\_000\2010-02-05](\\FDSWA150\NONECTD\N201153\N_000\2010-02-05)

**Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.**

**COMMENTS/SPECIAL INSTRUCTIONS:**  
  
Mid-Cycle Meeting: 06/08/10  
  
Labeling Meetings: 09/21/10  
10/05/10  
  
Wrap-Up Meeting: 10/19/10

SIGNATURE OF REQUESTER  
Nichelle Rashid

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL <input type="checkbox"/> HAND
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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201153	ORIG-1	GRACEWAY PHARMACEUTICA LS LLC	Zyclara (Imiquimod) Cream 3.75%

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/s/

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NICHELE E RASHID  
06/08/2010

## REQUEST FOR CONSULTATION

TO (Office/Division): **Office of Surveillance and Epidemiology/  
Division of Risk Management  
Attention: Janet Anderson**

FROM (Name, Office/Division, and Phone Number of Requestor):  
**Nichelle Rashid, RPM /DDDP (301) 796-3904  
Milena Lolic (Clinical reviewer) (301) 796-3825  
Jill Lindstrom (Clinical Team leader) (301) 796-0944**

DATE  
**05/26/10**

IND NO.  
**NA**

NDA NO.  
**201153**

TYPE OF DOCUMENT  
**Original NDA**

DATE OF DOCUMENT  
**February 8, 2010**

NAME OF DRUG  
**Zyclara Cream, 3.75%**

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG  
**Standard**

DESIRED COMPLETION DATE  
**September 26, 2010**

NAME OF FIRM: **Graceway Pharmaceuticals, LLC.**

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |   |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER                    |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING                           |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                                |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE                      |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                               |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): <b>NEW NDA</b> |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |   |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |   |  |
|---|--|
| <input type="checkbox"/> DISSOLUTION            | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILTY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES        | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

#### COMMENTS / SPECIAL INSTRUCTIONS:

Applicant is seeking approval for Zyclara (3.75% imiquimod cream) for external genital warts (EGW) in population 12 years and older.

eCTD application and available on edr site for NDA 201153, Zyclara Cream at the following network location:  
[\\FDSWA150\NONECTD\N201153\N\\_000\2010-02-05](#)

Please review the attached package insert and patient package insert. The PDUFA date is December 8, 2010.

If you have any questions, please contact me at (301) 796-3904, Milena Lolic (Clinical Reviewer) at (301) 796-3825, and Jill Lindstrom (Clinical Team Leader) at (301) 796-0944.

SIGNATURE OF REQUESTOR <b>Nichelle Rashid</b>	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201153	ORIG-1	GRACEWAY PHARMACEUTICA LS LLC	Zyclara (Imiquimod) Cream 3.75%

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/s/

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NICHELLE E RASHID  
06/08/2010

## MEMORANDUM OF TELECON

DATE: May 21, 2010 2:40 pm

APPLICATION NUMBER: NDA 201153 Zyclara (imiquimod) Cream, 3.75%

BETWEEN:

Name: Sean Brennan, Sr. Vice President, Regulatory Affairs  
Phone: (423) 274-5210  
Representing: Graceway Pharmaceuticals, LLC

AND

Name: Margo Owens, Project Management Team Leader  
Nichelle Rashid, Regulatory Health Project Manager  
Division of Dermatology and Dental Products, HFD-540

SUBJECT: Requested Information

Background: On February 5, 2010, the sponsor submitted an original NDA for Zyclara for external genital warts and perianal warts.

Call: The Agency requested that the sponsor submit revised labeling to reflect both indications, external genital warts and perianal warts and actinic keratoses. The Agency also requested that a companion efficacy supplement (without a fee) be submitted to NDA 22483, Zyclara Cream, 3.75% to combine the two indications in one label. The sponsor was advised to indicate that the clinical information will be cross reference to NDA 201153 in the cover letter. The sponsor inquired about the possibility of converting the new NDA to a labeling supplement. The Agency acknowledged that there were administrative issues with the database that prevent the conversion of the submission. The Agency requested that the sponsor submit revised labeling by first week of June.

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Margo Owens  
Project Management Team Leader  
Division of Dermatology & Dental Products

ADDENDUM:

The sponsor submitted revised labeling on June 8, 2010.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201153	ORIG-1	GRACEWAY PHARMACEUTICA LS LLC	Zyclara (Imiquimod) Cream 3.75%

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/s/

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MARGO L OWENS  
06/22/2010



NDA 201153

**FILING COMMUNICATION**

Graceway Pharmaceuticals, LLC  
Attention: Sean Brennan, Ph.D.  
Vice President, Regulatory Affairs  
340 Martin Luther King Jr. Blvd.  
Bristol, TN 37620

Dear Dr. Brennan:

Please refer to your new drug application (NDA) dated February 5, 2010, received February 8, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Zyclara (imiquimod) Cream, 3.75%.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is December 8, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

**REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

If you have any questions, call Kelisha C. Turner, Regulatory Project Manager, at (301) 796-0766.

Sincerely,

*{See appended electronic signature page}*

Stanka Kukich, M.D.  
Deputy Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-201153

-----  
ORIG-1

-----  
GRACEWAY  
PHARMACEUTICA  
LS LLC

-----  
Zyclara (Imiquimod) Cream  
3.75%

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/s/  
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STANKA KUKICH  
04/23/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 30,432

**MEETING MINUTES**

Graceway Pharmaceuticals, LLC  
Attention: Sean Brennan, Ph.D.  
Senior Vice President, Regulatory Affairs  
340 Martin Luther King Jr. Blvd.  
Bristol, TN 37620

Dear Dr. Brennan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for imiquimod.

We also refer to the meeting between representatives of your firm and the FDA on November 18, 2009. The purpose of the meeting was to discuss the content and format of the proposed application.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Kelisha Turner, Regulatory Project Manager at (301) 796-0766.

Sincerely,

*{See appended electronic signature page}*

Jill Lindstrom, M.D.  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** November 18, 2009; 9:00am  
**Meeting Location:** WO Bldg. 22, Rm 1415

**Application Number:** IND 30,432  
**Product Name:** imiquimod  
**Indication:** External Genital Warts  
**Sponsor/Applicant Name:** Graceway Pharmaceuticals, LLC

**Meeting Chair:** Jill Lindstrom, M.D.  
**Meeting Recorder:** Kelisha C. Turner

### FDA ATTENDEES

Julie Beitz, M.D., Director, ODE III  
Jill Lindstrom, M.D., Clinical Team Leader, DDDP  
Milena Lolic, M.D., Clinical Reviewer, DDDP  
Barbara Hill, Ph.D., Pharmacology Supervisor, DDDP  
Jerry Wang, Ph.D., Pharmacology Reviewer, DDDP  
Mohamed Alosch, Ph.D., Biostatistics Team Leader, DB III  
Kathleen Fritsch, Ph.D., Biostatistics Reviewer, DB III  
Abimbola Adebawale, Ph.D., Clinical Pharmacology Reviewer, DCP 3  
Shulin Ding, Ph.D., Pharmaceutical Assessment Lead, DPA II, Branch III  
Nam Kim, Director, ORP  
Zei-Pao Huang, M.S., Supervisory Program Analyst, DRRS  
Erin McCray, Computer Scientist, DRRS  
Valerie Gooding, Regulatory Information Specialist, DRRS  
Barbara Gould, M.B.A.H.C.M., Chief, Project Management Staff, DDDP  
Kelisha C. Turner, Regulatory Health Project Manager, DDDP

### SPONSOR ATTENDEES

Jefferson Gregory, JD, Chief Executive Officer  
James Lee, M.D., Ph.D., Chief Medical Officer  
Michael Nordsiek, Executive Vice President, Product Development  
John A. A. Bellamy, JD, Executive Vice President and General Counsel  
Sean Brennan, Ph.D., Senior Vice President, Regulatory Affairs  
Sharon Levy, M.D., Senior Vice President, Clinical Research  
Robert Babilon, Senior Director, Product Development  
James Kulp, Senior Director, Clinical Research  
Tiepu Liu, Senior Director, Biostatistics  
Jason Wu, M.D., Senior Director, Clinical Research

Michael Adams, Pharm.D., Consultant – Pharmacokinetics  
Dror Rom, Ph.D., Consultant - Biostatistics

## **DISCUSSION**

### **Regulatory**

#### **Question 1:**

Does the Agency agree that this marketing application may be provided as a supplement to NDA 22-483?

#### **Response:**

No, you cannot submit your application as a supplement to a non-approved NDA.

#### **Meeting Discussion:**

The sponsor stated that they intend to submit an original NDA.

#### **Question 2:**

Does that Agency agree to the proposed hybrid eCTD format? Does the Agency have any questions concerning the format of this submission?

#### **Response:**

No we do not agree. eCTD format is the agency's standard accepted format and the preferred format for submitting electronic submissions to applications. You may request a waiver for the new application, if unable to submit your application in eCTD format. A waiver is issued per application and not for all the company's applications.

Additional general comments regarding electronic submission:

If you are allowed to submit in non-eCTD format, you must follow the guidance and specifications listed below. If the electronic submission received does not conform to guidance and specifications and impacts the review, electronically submitted components may need to be resubmitted, or the submission could be rejected. Also, future waiver requests may be denied.

- Regulatory Submission in Electronic Format: New Drug Application Guidance  
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163187.pdf>
- CDER study data specification: :  
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163561.pdf>

- Final Guidance for Industry: Providing Regulatory Submissions in Electronic Format-- Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications [PDF] (June 2008)
- Portable Document Format Specifications [PDF] (6/4/2008)

If and when you are ready to submit an eCTD application, an eCTD sample is required from you before submitting an actual eCTD application. The following link provides information on how to submit a sample.

Submit a Sample eCTD to the FDA:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

If you have any questions with submitting eCTD and non-eCTD applications, you may contact [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)

### **Meeting Discussion:**

The sponsor stated that they will be requesting a waiver for a hybrid eCTD for the original NDA.

The Agency stated that NDA 22-483 submitted in a hybrid eCTD format was very difficult to navigate using links within the submission.

The Agency clarified that if a hybrid eCTD is submitted, then each submission needs a cover letter and sequential number and all files should be in PDF format unless requested by the Agency.

### **Question 3:**

Does the Agency agree to the proposed format for the CTD table of contents? Does the Agency have any questions regarding the proposed table of contents?

### **Response:**

Yes, the proposed format is acceptable. You should check the most recent FDA specifications available at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm> before submission.

### **Question 4:**

Does the Agency agree with proposal to update the Zyclara labeling with EGW information?

**Response:**

No. Zyclara is not approved (see response to Question 1). Content of an NDA includes draft labeling; therefore, draft labeling for the proposed EGW indication should be provided in the new marketing application. Content and format of new drug applications are described in 21CFR 314.50.

**Question 5:**

Does the Agency have any additional comments regarding the proposed package insert?

**Response:**

See response to Question 4.

**Question 6:**

Does the Agency agree with the 4-month Safety Update Report proposal?

**Response:**

You should provide a safety update 120 days after NDA submission, and you may include a cross reference to the periodic AE reports for other imiquimod products if the time of those reports closely coincides with the 120 day safety report. The acceptability of your proposed timeline will be dependent on the date of submission of your application.

**Meeting Discussion:**

The Agency stated that a 2 month interval was acceptable between the 120 day safety update and periodic safety report.

**Question 7:**

Does that Agency agree that it is reasonable to include in the NDA a request for a waiver of pediatric studies for patients below the age of 12 years old?

**Response:**

Yes, it is reasonable to request a waiver of pediatric studies for patients below the age of 12 years old for EGW indication. You should provide the rationale with supporting data for the requested waiver in your NDA.

**Question 8:**

Does the Agency agree that, since QT/QTc information has been provided in the original NDA 22-483 submission, and since systemic exposure in patients with EGW is comparable to that of

subjects with AK (PK study GW01-0706), no further information needs to be provided in this supplement to address the potential for QT/QTc prolongation?

**Response:**

No, we do not agree. See Complete Response letter dated October 16, 2009 for NDA 22-483.

**Meeting Discussion:**

The sponsor stated that they intend to submit the study report from R-837-009 and pharmacokinetic data from different studies for EGW.

The Agency responded that the adequacy of this data to address the potential for QT/QTc prolongation will be a review issue. The Agency inquired as to the timing of the QT/QTc protocol and conduct of the study. The sponsor responded that they intend to submit the protocol expeditiously and submit the study report before the end of 2010. The Agency anticipated that QT-IRT comments will be provided by 90 days.

**Question 9:**

Does the Agency have any additional comments or questions regarding this proposed marketing application?

**Response:**

Case-narratives should follow established clinical way of presenting cases: e.g. adverse event in one sentence, past medical history, concomitant medications, imiquimod exposure data, detailed event description, discussion on causality, outcome.

Submit electronic datasets for clinical studies in SAS transport form. The data sets should include demographic and baseline data as well as efficacy and safety data. Please note the following:

1. The data base for the Phase 3 studies should include analysis datasets with derived variables suitable for conducting primary and secondary efficacy analyses. The analysis datasets should include the treatment assignments. If imputations are used in the analysis datasets, these should be clearly identified.
2. The database for the Phase 3 studies should include datasets containing 'raw' variables from the CRF.
3. The submission should include adequate documentation for the data sets (define.pdf) including definitions of each variable in the data set, algorithms for derived variables and decodes for any factor variables so that all categories are well-defined in the documentation. The documentation should indicate which variables are derived.

- 4.I If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.

In addition to the electronic data sets, the NDA submission should include the following items for the Phase 3 studies:

- a. Study protocols including the statistical analysis plan, protocol amendments and their dates, and an annotated copy of the Case Report Form.
- b. The generated treatment assignment lists and the actual treatment allocations (along with date of enrollment) from the trials.

**Meeting Discussion:**

The sponsor asked if the raw data needed to be submitted in SDTM format. The Agency responded that SDTM format is encouraged, but not required.

Additional Comments on Studies 0801 and 0805:

Studies 0801 and 0805 appear to have had a high rate of study discontinuations (~30%). While the protocols included a primary method of handling missing data, in light of the high rate of missingness, please include in the application a full discussion of the impact of missing data on the studies' conclusions and include additional sensitivity analyses using alternate scientific methods such as multiple imputation.

**Meeting Discussion:**

The Agency recommended that the sponsor investigate whether their drop out is related to treatment, lesion counts prior to drop out, or any other factors. The sponsor should then consider such factors, if any, in their approach for handling missing data.

The sponsor stated that they will conduct additional sensitivity analyses for missing data and include these analyses in a separate document.

The Agency noted that one study did not demonstrate statistical significance for the 2.5% concentration. The Agency requested that the EGW NDA include a full discussion of the results including examination by center and subgroups.

**Chemistry, Manufacturing and Controls (CMC)**

**Question 1:**

[Redacted content]

(b) (4)

**Response:**

(b) (4)

**Meeting Discussion:**

The sponsor stated that they plan (b) (4) sachets presentation with this original NDA submission. They plan to submit complete CMC information to support (b) (4) however, they plan to cross reference NDA 22-483 for the sachet. The Agency responded that they cannot cross reference an unapproved NDA; and therefore they would need to submit complete CMC information. The Agency further commented that clinical input would be important in the approvability of (b) (4) since clinical studies were conducted using sachet presentation.

**Pharmacology/Toxicology**

There was no pharmacology/toxicology questions submitted in the briefing package. However, you stated in the meeting package under item 10: (b) (4)  
(b) (4) This approach is not acceptable. You should provide nonclinical information in the NDA submission. A comprehensive summary of nonclinical information with corresponding cross-reference information for the pivotal nonclinical studies contained in previous IND/NDAs should be provided in the NDA submission.

**Meeting Discussion:**

The sponsor asked if a similar presentation of the Pharmacology/Toxicology information in NDA 22-483 would be acceptable for the EGW NDA. The Agency responded that this would be acceptable.

**Clinical Pharmacology/Biopharmaceutics**

**Question 1:**

Does the Agency agree that study GW01-0804 as conducted is adequate to support the submission of a 3.75% imiquimod formulation for the treatment of EGW? (section 9.3.5)

**Response:**

The summary data and description of study GW01-0804 appears to be consistent with the advice given in the previous sponsor-FDA communications. Ultimate acceptability of the study/data itself is a review issue.

## **Clinical/Biostatistics**

### **Question 1:**

Does the Agency agree that there is adequate information for the filing for approval of an NDA for a 3.75% imiquimod cream product, applied daily for up to 8 weeks?

### **Response:**

It appears that you may have adequate information for filing, however approval will be a review issue.

### **Question 2:**

Does the Agency agree with the plans for presentation and analysis of these efficacy and safety results, as described in the Clinical/Statistical section and **Appendix 7** Mock Tables for the ISS and ISE of this briefing package?

### **Response:**

The plans for the integrated analyses of Studies 0801 and 0805 are acceptable. See also the response to Clin/Stat Question 3.

### **Question 3:**

Does the Agency agree that 1233-IMI and 1243-IMI, which will be submitted as full study reports within Module 5, may be then summarized only within Module 2.5 Clinical Overview, with no information required to be included within Module 2.7 Summary of Clinical Safety or the ISS?

### **Response:**

If you want to submit data from 1233 and 1243 studies in support of imiquimod 3.75% safety, then the findings should be included in the Summary of Clinical Safety and the ISS.

### **Question 4:**

Does the Agency agree that clinical studies 1233-IMI and 1243-IMI of the 5% imiquimod product are sufficient to address the requirement for long-term safety information for the treatment of EGW with 3.75% imiquimod cream?

### **Response:**

If you intend to use data obtained with another formulation, e.g. imiquimod 5%, you will need to explain why data obtained with that formulation is relevant to your proposed product. You are referred to the ICH E1A guidance for articulation of long term safety data needs.

### **General Administrative Comments**

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND or NDA might identify additional comments or information requests.
2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21 CFR 54 and 21CFR 314.50(k).
3. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.
4. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.
5. You are reminded that effective June 30, 2006 all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for additional details).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-30432	GI-1	GRACEWAY PHARMACEUTICA LS LLC	ALDARA (IMIQUMOD) CREAM

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/s/  
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JILL A LINDSTROM  
12/15/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 30432

Graceway Pharmaceuticals  
Attention: Sean Brennan, Ph.D., VP, Regulatory Affairs  
340 Martin Luther King Jr. Blvd  
Bristol, Tennessee 37620

Dear Dr. Brennan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for imiquimod for treatment of external genital warts.

We also refer to the telecon between representatives of your firm and the FDA on May 20, 2008. Graceway's stated purpose of the meeting was to obtain agreement that the proposed development program designed to demonstrate that imiquimod is superior to placebo would meet the regulatory standards for filing a marketing application. The purpose of the meeting derived from the April 7, 2008 meeting briefing document, as understood by FDA attendees, was to discuss the data that would be obtained from the conduct of trials of previously agreed-upon design, and the basis on which a regulatory decision would ultimately be made. This correspondence will address both the discussion points (minutes of the discussion) and the question you posed regarding filing. The attachment to this correspondence documents attendee information.

Discussion:

Division representatives noted that imiquimod currently is approved in a 5% strength to be used in a 4-month treatment regimen for external genital warts. Without comparative data, it will not be possible to adequately label the product for a second strength/regimen in a way that supports the decisions healthcare practitioners must make regarding the appropriate treatment regimen for their patients. Graceway clarified that they intend to [REDACTED] (b) (4) support safety and efficacy of the product through two placebo (vehicle) controlled superiority trials.

Conclusion on the question of whether the application would be filed based solely on placebo controlled trials (i.e., without comparability information between the current and proposed treatment regimens) could not be reached due to the difference in understanding regarding the purpose of the discussion. The division agreed to consider the filing question and schedule a follow-up discussion as soon as possible.

The filing question:

The division believes that the following addresses the question and that further discussion will not be necessary.

The division agrees that an NDA that depends on the proposed placebo-controlled superiority studies to support safety and efficacy can be filed. However, whether the application is ultimately approvable is a review issue. Assuming positive and significant study outcomes as well as a better or unchanged safety profile, the application should include information to demonstrate why the results for the proposed imiquimod treatment regimen represent an appropriate labeling change for the product. Graceway assumes a risk that in the face of equivocal or borderline significance this may not be possible without comparative data between the regimens. In addition, it would not possible to label the product for multiple treatment regimens without adequate data to convey information supporting the treatment decisions healthcare practitioners would have to make.

Please notify us of any significant differences in understanding regarding the meeting outcomes. If you have any questions, call me at (301) NUMBER.

Sincerely,

*{See appended electronic signature page}*

Susan Walker, M.D.  
Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure - Meeting Attendee List

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** May 20, 2008  
**TIME:** 11:00- 11:45 a.m.  
**LOCATION:** N/A- telecon  
**APPLICATION:** IND 30432  
**DRUG NAME:** Imiquimod  
**TYPE OF MEETING:** Guidance

**MEETING CHAIR:** Stanka Kukich, M.D.  
Deputy Director

**MEETING RECORDER:** Bronwyn Collier

**FDA ATTENDEES:**

Division of Dermatology and Dental Products

Stanka Kukich M.D., Deputy Director

Jill Lindstrom M.D., Clinical Team Leader

Brenda Carr M.D., Medical Officer

Division of Clinical Pharmacology III

Tapash Ghosh Ph.D., Clinical Pharmacology Reviewer

Division of Biostatistics III

Mohamed Alesh Ph.D., Statistical Team Leader

Kathleen Fritsch Ph.D., Statistical Reviewer

Office of Drug Evaluation III

Bronwyn Collier, Associate Director for Regulatory Affairs

**EXTERNAL CONSTITUENT ATTENDEES:**

Graceway Pharmaceuticals, LLC

Jefferson Gregory, Chairman and CEO

John Bellamy, EVP and General Counsel

Mike Nordsiek, EVP, Product Development

Jim Lee M.D., VP, Clinical Development

Sean Brennan Ph.D., VP, Regulatory Affairs

Sharon Levy M.D., VP, Clinical Development

T.C. Meng M.D., Executive Director, Medical Affairs

Jason Wu M.D., Clinical Development

Jim Kulp, Senior Director, Clinical Development

Alicia Cabrelli, Senior Manager, Regulatory Affairs

Linked Applications

Sponsor Name

Drug Name

ND 30432

GRACEWAY  
PHARMACEUTICALS  
LLC

ALDARA (IMIQUMOD) CREAM

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

/s/

BRONWYN E COLLIER on behalf of SUSAN J WALKER  
05/23/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 30,432

Graceway Pharmaceuticals, LLC  
Attention: Alicia M. Cabrelli  
Sr. Manager, Regulatory Affairs  
222 Valley Creek Boulevard, Suite 300  
Exton, PA 19341

Dear Ms. Cabrelli:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Imiqimod Cream <sup>(b) (4)</sup> and 3.75%.

We also refer to the meeting between representatives of your firm and the FDA on January 20, 2008. The purpose of the meeting was to discuss the development of new <sup>(b) (4)</sup> and 3.75% strengths of imiquimod cream for the treatment of external genital warts.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Margo Owens, Regulatory Project Manager, at (301) 796-2110.

Sincerely,

*(See appended electronic signature page)*

Stanka Kukich, M.D.  
Deputy Director  
Division of Dermatology and Dental  
Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

## MEMORANDUM OF MEETING MINUTES



**Meeting Date:** January 20, 2008      **Time:** 3:00 P.M.  
**Location:** WO Room 1315      **Meeting ID:** 23053  
**Topic:** IND 30,432, imiquimod cream (b) (4) 3.75% for the  
treatment of external genital warts  
**Subject:** End of Phase 2 meeting  
**Sponsor:** Graceway Pharmaceuticals, LLC  
**Meeting Chair:** Stanka Kukich, M.D./Deputy Division Director, DDDP  
**Meeting Recorder:** Margo Owens/Regulatory Project Manager, DDDP

### FDA Attendees:

Stanka Kukich, M.D./Deputy Division Director, DDDP  
Jill Lindstrom, M.D./Team Leader, Clinical, DDDP  
Brenda Carr, M.D./Clinical Reviewer, DDDP  
Bogdan Kurtyka, CMC Reviewer, ONDQA  
Lydia Velazquez, Pharm.D./Team Leader, Clinical Pharmacology, DPEIII  
Tapash Ghosh, Ph.D./Clinical Pharmacology Reviewer, DPEIII  
Mohamed Alish, Ph.D./Team Leader, Biostatistics, DBIII  
Clara Kim, Ph.D./Biostatistics Reviewer, DBIII  
Margo Owens/Regulatory Project Manager, DDDP

### Sponsor Attendees:

#### **Graceway Pharmaceuticals, LLC**

Michael Nordsiek, Executive Vice President, Product Development  
Robert Babilon, Senior Director, Product Development  
Sharon Levy, M.D., Vice President, Clinical Research  
James Kulp, Senior Director, Clinical Research  
Jason Wu, M.D., Senior Director, Clinical Research  
James Lee, M.D., Chief Medical Officer  
Sean Brennan, Vice President, Regulatory Affairs  
Michael Adams, Consultant, Pharmacokinetics  
Dror Rom, Consultant Biostatistics  
Marie Kuker, Consultant, Regulatory Affairs  
John Bellamy, Executive Vice President and General Counsel  
Jefferson Gregory, CEO and Chairman

### **Purpose:**

The sponsor requests input from the Agency on the development of a new dosing regimen for imiquimod cream for the treatment of external genital warts. The pre-meeting briefing document (submitted January 18, 2008) provides background and questions for discussion.

**Chemistry, Manufacturing and Controls:**

There are no CMC questions presented in this briefing document.

**Pharmacology/Toxicology:**

There are no Pharmacology/Toxicology questions presented in this briefing document.

**Clinical Pharmacology/Biopharmaceutics:**

**Question:**

Does the Agency agree that protocol GW01-0706 is adequate to support a marketing application for imiquimod cream (b) (4) 3.75% for the treatment of patients with AK, BCC and EGW?

**Response:**

No. Protocol GW01-0706 will not support the requirements for external genital warts (EGW) due to differences in the disease states, dosing regimens and site of application.

Therefore, for the purpose of this IND for EGW, as mentioned in the guidance meeting minutes between the Agency and the Sponsor (dated July 27, 2007), we recommend that you conduct a pharmacokinetic study in patients with EGW using the to-be-marketed formulation under maximal use condition.

**Meeting Discussion:**

The sponsor agreed to conduct the pharmacokinetic study in EGW patients with the highest strength of 3.75%. They were advised to maintain a record of the amount of drug product used and the surface area involved. They will use similar enrollment criteria to the pivotal trials but will set a lower limit for the amount of area of involvement to capture subjects with the upper end of disease severity.

**Clinical/Biostatistics:**

**Introductory Statement**

We acknowledge that the sponsor “plans to proceed with two Phase 3 studies with a dose response element, with a substantial number of patients, in order to establish an adequate risk/benefit profile for each formulation.” The Agency further acknowledges the sponsor’s rationale for so proceeding (p. 28): “Graceway agrees that the decision to select a dose for approval should be based on clinical data; with the narrow dose range under investigation, however, a Phase 2 study with limited enrollment would likely not provide the extensive data to conclusively select one dose over the other.”

The responses and comments below are provided in the context of the Agency’s recommendations that the sponsor conduct Phase 2 dose-ranging studies before proceeding to Phase 3 studies (please see the minutes from the July 27, 2007 Guidance meeting).

**Question #2:** Does the Agency agree that the clinical program as described is appropriate and adequate to support a marketing application for (b) (4) 3.75% imiquimod cream in treatment of EGW?

**Question #3:** Does the Agency agree that the proposed Phase 3 study designs, as described in the complete protocols, support a marketing application for EGW?

Combined Response to Questions #2 and #3:

The sponsor proposes to conduct two Phase 3 trials:

- a randomized, double-blind, placebo-controlled study in which the 2.5% and 3.75% products would be compared to placebo; this study would also include an assessment for recurrence (GW01-0801).

-  (b) (4)

Elements of the study designs for the proposed Phase 3 program, as presented in the briefing package, may be adequate to support a marketing application for  (b) (4) 3.75% product. However, the extent to which the proposed program would adequately address

 (b) (4)

Meeting Discussion:

 (b) (4)

Meeting Discussion:

 (b) (4)

The sponsor stated that shorter dosing duration might be considered a favorable element of the risk-benefit calculus. The sponsor was advised that efficacy, safety and duration of treatment are all considered in the risk-benefit analysis and would be weighted from most important to least important in that order.

Question #4: Does the Agency agree that the defined subject population is appropriate?

Response: The proposed subject population may be generally acceptable; however, the sponsor is requested to provide the rationale for limiting the wart area to up to (b) (4)

Meeting Discussion:

The sponsor was advised that limitation of area of involvement of warts to be enrolled would impact the indication garnered should one of the new products be approved. The sponsor was advised that the breakpoint of (b) (4) is an arbitrary and artificial clinical distinction; the sponsor was encouraged to enroll all comers.

Question #5: Does the Agency agree with the proposed efficacy and safety endpoints and the statistical methods as described in the complete protocols?

Response: The proposed primary endpoint of the proportion of subjects achieving complete clearance of all warts (baseline and new) at efficacy assessment is acceptable (at 8 weeks post-treatment for the new products; at end of treatment, i.e. 16 weeks for the approved product). The proposed safety assessments appear to be acceptable.

The Agency acknowledges the sponsor's response regarding secondary endpoints. However, it should be noted that the protocol should pre-specify a multiplicity adjustment method to control the type I error rate.

The sponsor stated that centers with less than six subjects will be pooled with others centers. Six subjects per center implies approximately two subjects per treatment arm per center. To reduce the problems in the analysis of small centers, the Division recommends the sponsor to plan to enroll at least six subjects per treatment arm per center. The algorithm to pool centers if actual enrollment does not meet the above criterion should be specified in detail. The protocol should include methods on how to evaluate the treatment-by-center interaction for the primary efficacy analysis. The Division recommends the treatment-by-center interaction effect to be tested at a significance level of 0.10 for each comparison. If the interaction is significant, the protocol should pre-specify a sensitivity analysis to ensure that the efficacy results are not driven by extreme centers (e.g. evaluating efficacy after deleting extreme centers).

Question #6: Does the Agency agree that a prospective long-term clinical study is not required to address the assessment of safety?

Response: EGW is potentially a chronic indication, and long-term safety should be addressed. Information from previously-conducted studies may fulfill long-term safety data needs outlined in the ICH E1A Guideline.

Question #7: Does the Agency agree that the assessment of recurrence in one study (GW01-0801) is adequate to address the Agency's request for recurrence data?

Response: Please see the combined response to questions #2 and #3.

Question #8:

(b) (4)

(b) (4)

Response: Please see the combined response to questions #2 and #3.

Question #9: Does the Agency have any additional comments regarding the described clinical plan for the development of a low strength imiquimod cream for the treatment of EGW?

Response:

1. It is recommended that all females have Pap smears (or appropriate cervical screening) done, and that the protocol provide for disposition of subjects with abnormal results.

Meeting Discussion:

The sponsor inquired as to the rationale for recommending pap smears or cervical screening and the Agency stated that it is for reasons of safety.

2. The sponsor's sample size calculation was based on treatment effect estimates of (b) (4) for the 3.75% and placebo arms, respectively. However, the sponsor did not provide where these estimates were obtained. (b) (4) taken into account in the sample size calculation. The sponsor may be taking a risk of under powering the study by not using reliable treatment effect estimates when calculating the sample size.
3. The protocol should specify what would be done if both concentrations (b) (4) and 3.75%, are statistically significant compared to vehicle.

Administrative Comments:

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.
2. Please refer to the Guidance for Industry: Special Protocol Assessment and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT (SPA)**. Please clearly identify this submission as an SPA in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical or carcinogenicity) and include a reference to this End-of-Phase 2 meeting. Ten desk copies (or alternatively, an electronic copy) of this SPA should be submitted directly to the project manager.
3. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
4. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens to contain and assessment of the safety and effectiveness of the

pediatric patients unless this requirement is waived or deferred.

5. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

6. In response to a final rule published February 11, 1998, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this demographic analysis.

7. In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). Please plan to address this issue early in development.

8. We remind you that effective June 30, 2006, all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for additional details).

9. You are encouraged to request a Pre-NDA Meeting at the appropriate time.

Minutes Preparer: \_\_\_\_\_  
Margo Owens/Regulatory Project Manager DDDP

Chair Concurrence: \_\_\_\_\_  
Stanka Kukich, M.D./Deputy Division Director, DDDP

Linked Applications

Sponsor Name

Drug Name

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IND 30432

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GRACEWAY  
PHARMACEUTICALS  
LLC

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ALDARA (IMIQUMOD) CREAM

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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STANKA KUKICH  
02/29/2008