CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204427Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA 204427
Product Name: Kerydin (tavaborole) topical solution, 5%

PMR/PMC Description: Pharmacokinetic/safety study of tavaborole topical solution, 5% in 40 pediatric subjects age 12 to 17 years and 11 months with onychomycosis of the toenails. Pharmacokinetic assessments will be done in at least 16 evaluable subjects under maximal use conditions.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	12/2014
	Study Completion:	12/2018
	Final Report Submission:	06/2019
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other: PREA

Onychomycosis is primarily a disease of adults, and Phase 3 studies were conducted in population 18 years and older as agreed upon during EOP2 Meeting 10/8/2009 and SPA review 9/13/2010.

Kerydin is an NME, and clinical study in relevant pediatric population is required to satisfy PREA requirements. The literature review reveals that disease exists in adolescent population although with significantly lower incidence than in adults. A waiver under 12 years of age is granted since studies in this age group would be impractical due to the low incidence of culture positive onychomycosis in this population.

Adult studies are complete and the application is ready for action. It is recommended to conduct PREA-required study post-approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

PREA-required PK study to collect efficacy and safety data in a population of subjects age 12-18 years.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☒ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

As noted in the agreed to Pediatric Study Plan, a Pharmacokinetic (PK)/safety/tolerability trial in 40 pediatric subjects with toenail onychomycosis ages 12 years to 17 years 11 months will be conducted. PK assessments will be conducted in a subgroup of at least 16 evaluable subjects under maximal use conditions.

Subjects must have a clinical diagnosis of distal subungual onychomycosis affecting at least one great toenail (20% to 60% of the nail after the nail had been trimmed), confirmed by a central mycology laboratory to be positive for KOH wet mount and fungal culture for a dermatophyte. Treatment should consist of daily application of Kerydin for 48 weeks. Safety assessment should consist of adverse events (AEs), application site reactions (ASRs), clinical safety laboratory tests, physical examinations, vital signs, and pregnancy tests for women of childbearing potential.

Subjects included in the PK subgroup should have a disease severity to satisfy maximal use conditions (i.e., subjects with ≥50% involvement of both great toenails and 4 additional affected toenails. Treatment will be applied to all toenails during the PK evaluation period only. Serial PK assessments should be performed after single dose and at steady state. Several trough samples should be obtained to assess the attainment of steady state.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

---

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

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

/s/

CRISTINA Petruccelli Attinello
06/19/2014

TATIANA OUSSOVA
06/19/2014

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 17, 2014
Requesting Office or Division:	Division of Dermatology and Dental Products
Application Type and Number:	NDA 204427
Product Name and Strength:	Kerydin (Tavaborole) Topical Solution, 5%
Submission Date:	July 29, 2013
Applicant/Sponsor Name:	Anacor Pharmaceuticals
OSE RCM #:	2013-2560-1
DMEPA Primary Reviewer:	Carlos M Mena-Grillasca, RPh
DMEPA Team Leader:	Lubna Merchant, MS, PharmD

1 PURPOSE OF MEMO

The Division of Dermatology and Dental Products requested that we review the revised container label, carton labeling (Appendix A), and Full Prescribing Information to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSIONS

The revised container label, carton labeling, and Full Prescribing Information are acceptable from a medication error perspective.

[1] Mena-Grillasca, C. Label, Labeling, and Packaging Review for Kerydin (NDA 204427). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Office of Medication Error Prevention and Risk Management, Division of Medication Error Prevention and Analysis (US); 2014 MAR 11. OSE RCM No. 2013-2560.

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

CARLOS M MENA-GRILLASCA
06/17/2014

LUBNA A MERCHANT
06/17/2014

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: April 16, 2013

TO: Cristina Attinello, Regulatory Project Manager
Milena Lolic, M.D., Medical Officer
David Kettl, M.D., Medical Team Leader
Division of Dermatologic and Dental Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 204427

APPLICANT: Anacor Pharmaceuticals, Inc.

DRUG: Tavaborole Topical Solution, 5%

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of onychomycosis

CONSULTATION REQUEST DATE: October 16, 2013
CLINICAL INSPECTION SUMMARY DATE: May 12, 2014
DIVISION ACTION GOAL DATE: July 11, 2014
PDUFA DATE: July 29, 2014

I. BACKGROUND:

The Applicant submitted this NDA to support the use of Tavaborole Topical Solution, 5%, for the treatment of onychomycosis.

The pivotal studies AN2690-ONYC-301 and AN2690-ONYC-302, both entitled "A Randomized, Double-Blind, Vehicle-Controlled, Multi-Center Study to Evaluate the Efficacy and Safety of AN2690 Topical Solution, 5%, vs. Solution Vehicle in the Treatment of Onychomycosis of the Toenail in Adults" were inspected in support of the indication.

The clinical sites of Drs. Weisfeld and Hudson were selected for inspection. Dr. Weisfeld's site was selected because of large enrollment, a low frequency of adverse events, and the highest treatment efficacy result for the primary endpoint. Dr. Hudson's site was selected for inspection because of its high efficacy result. The sponsor, Anacor Pharmaceuticals Inc., was also inspected since the drug is a New Molecular Entity (NME).

II. RESULTS (by Site):

Name of CI, Location	**Protocol #/ Site #/ # of Subjects (enrolled)**	**Inspection Dates**	**Final Classification**
Max Weisfeld, D.P.M. Hamilton Foot Care 5508 Harford Road Baltimore, MD 21214-2231	AN2690-ONYC-301/ 122/ 37	4-5 Dec 2013	NAI
Charles P. Hudson, M.D. 3501 Washington Avenue Evansville, IN 47714-0538	AN2690-ONYC-302/ 325/ 13	18-19 Dec 2013	NAI
David P. Perry Anacor Pharmaceuticals, Inc. 1020 E. Meadow Circle Palo Alto, CA 94303-4230	AN2690-ONYC-301 and AN2690-ONYC-302	21-29 Jan 2014	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

1. Max Weisfeld, D.P.M.
   Hamilton Foot Care
   5508 Harford Road
   Baltimore, MD 21214-2231

   a. **What was inspected:** At this site for Protocol AN2690-ONYC-301, 92 subjects were screened, 37 subjects were enrolled, and 36 subjects completed the study. All

randomized subjects signed informed consent forms prior to participation in the study. Source documents and case report forms (CRFs) were compared with line listings. Primary and secondary endpoint data were compared with source documents and no discrepancies were noted. Records reviewed included, but were not limited to, protocol deviations, adverse events, IRB approvals, test article accountability, financial interest forms, training documentation, laboratory reports, and monitoring correspondence.

b. General observations/commentary: A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.

c. Assessment of data integrity: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Charles P. Hudson, M.D.
3501 Washington Avenue
Evansville, IN 47714-0538

a. What was inspected: At this site for Protocol AN260-ONYC-302, 82 subjects were screened, 13 subjects were enrolled, and 13 subjects completed the study. Of these 13 subjects, four were treated with the study vehicle and nine were treated with the test article. All screened subjects signed informed consent forms prior to participation in the study. The records of the 13 randomized subjects were reviewed in detail. Source documents, including adverse events, concomitant medications, laboratory results, and efficacy results corresponded with the line listings. Other records reviewed included, but were not limited to, sponsor and IRB correspondence, case report forms (CRFs), and drug accountability documentation.

b. General observations/commentary: A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.

c. Assessment of data integrity: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. David P. Perry
Anacor Pharmaceuticals, Inc.
1020 E. Meadow Circle
Palo Alto, CA 94303-4230

a. What was inspected: This sponsor inspection audited Protocols AN2690-0NYC-301 and AN2690-0NYC-302 and focused on the study activities of Drs. Weisfeld and Hudson. The inspection reviewed the following: corporate history and structure; training program and records; monitoring communications (for 13 sites); site compliance histories; issue resolution; and adverse event (AE) reporting.

b. General observations/commentary: A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.

c. Assessment of data integrity: The studies appear to have been conducted adequately, and the data submitted by the sponsor appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Drs. Weisfeld and Hudson were inspected in support of this NDA. In addition, a sponsor inspection of Anacor Pharmaceuticals, Inc. was conducted. Dr. Weisfeld's and Dr. Hudson's clinical sites were not issued Form FDA 483s, and the final classification of these inspections was No Action Indicated (NAI). The final classification of the inspection of the sponsor, Anacor, was also NAI. The data generated by these clinical sites and submitted by the sponsor appear adequate in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigation

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

/s/

ROY A BLAY
04/23/2014

JANICE K POHLMAN
04/23/2014

KASSA AYALEW
04/23/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	March 14, 2014
To:	Susan Walker, MD Director **Division of Dermatology and Dental Products (DDDP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Puja Shah, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Addendum to Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU) dated March 7, 2014
Drug Name (established name):	KERYDIN (tavaborole)
Dosage Form and Route:	Topical Solution, 5%
Application Type/Number:	NDA 204-427
Applicant:	Anacor Pharmaceuticals, Inc.

1 INTRODUCTION

On July 26, 2013, Anacor Pharmaceuticals, Inc. submitted for the Agency's review a New Drug Application (NDA) 204-427for KERYDIN (tavaborole) Topical Solution, with the proposed indication for the treatment of patients with onychomycosis (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to the requests by the Division of Dermatology and Dental Products (DDDP) on November 6, 2013, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for KERYDIN (tavaborole) Topical Solution.

2 DISCUSSION

On March 10, 2014 DDDP inquired as to whether DMPP thought a MG was needed or if a Patient Information Insert (PPI) would be appropriate. Based on correspondence between DDDP and DMPP, it was determined a PPI would be sufficient and a MG was not warranted because KERYDIN (tavaborole) does not meet criteria for required patient labeling as described in CFR 208.1. Therefore the Applicant's proposed MG has been converted into a PPI.

3 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

4 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI or IFU.

Please let us know if you have any questions.

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

KAREN M DOWDY
03/14/2014

PUJA J SHAH
03/14/2014

BARBARA A FULLER
03/14/2014

LASHAWN M GRIFFITHS
03/14/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 11, 2014
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	NDA 204427
Product Name and Strength:	Kerydin (Tavaborole) Topical Solution, 5%
Product Type:	Single ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Anacor Pharmaceuticals
Submission Date:	1/31/2014
OSE RCM #:	2013-2560
DMEPA Primary Reviewer:	Carlos M Mena-Grillasca, RPh
DMEPA Associate Director:	Lubna Merchant, MS, PharmD

1 REASON FOR REVIEW

This review responds to a request from DDDP to evaluate the proposed container labels and carton labeling for Kerydin for areas of vulnerability that could lead to medication errors. Kerydin is a new molecular entity (NME) currently under review.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	n/a
Previous DMEPA Reviews	n/a
Human Factors Study	n/a
ISMP Newsletters	n/a
Other	n/a
Labels and Labeling	B

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The applicant is proposing to market Kerydin in (b) (4) mL bottles. The product is to be applied once daily to the surface of affected toe nails and it is applied using a dropper; therefore, a (b) (4) mL packaging configuration seems reasonable for a month supply.

We reviewed the container labels and carton labeling and noted that the established name is not commensurate in prominence to the proprietary name. In addition, the route of administration statement "For Topical Use Only" on the carton labeling (b) (4) is difficult to read due to low contrast between the font and the background color and font size. Also, the statement "not for oral, ophthalmic and intravaginal use" is not present on the labels. We note that the precedent with topical products is to include this cautionary statement to prevent wrong route of administration errors, especially considering this type of packaging. Post-marketing experience with other liquid topical products packaged in small bottles which include an applicator tip has shown that wrong route of administration errors to the eye have occurred.

Finally, we note that the applicant did not replace the placeholder "tradename" for the tradename Kerydin on the description statement and on the statement "Use only supply dropper to apply Kerydin".

4 RECOMMENDATIONS FOR THE APPLICANT

DMEPA recommends the following be implemented prior to approval of this Application.

A. Proposed Container Label and Carton Labeling

1. As currently presented the established name is not commensurate in prominence to the proprietary name. Revise the presentation of the established name to ensure that it is at least ½ the size of the proprietary name and commensurate in prominence to the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2).

2. The proposed packaging configuration (with a glass pointed-tip dropper) is similar to ophthalmic solutions and may be a source of wrong route of administration errors. To reinforce the correct route of administration, increase the size of the route of administration statement "For Topical Use Only" and add the statement "Nor for oral, ophthalmic, or intravaginal use" below it using a smaller font.

B. Proposed Carton Labeling

1. The use of (b) (4) makes the route of administration statement "For Topical Use Only" difficult to read. Relocate the route of administration statements "For Topical Use Only" and "Not for oral, ophthalmic, or intravaginal use" (from comment A.2. above) to a white background area and use color font. (b) (4).

2. Replace the placeholder "tradename" with the proprietary name "Kerydin" on the description statement "Each mL of Kerydin…" and on the statement "Use only supplied dropper to apply Kerydin".

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Kerydin that Anacor Pharmaceuticals submitted on January 31, 2014.

Table 2. Relevant Product Information for Kerydin	
Active Ingredient	Tavaborole
Indication	Treatment of onychomycosis
Route of Administration	Topical
Dosage Form	Solution
Strength	5%
Dose and Frequency	Apply to affected toenail once daily for 48 weeks
How Supplied	(b) (4) mL bottle
Storage	Store at 20–25°C (69–77°F); excursions permitted to 15–30°C (59–86°F).
Container Closure	Amber glass bottle with glass pointed-tip dropper cap.

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following Kerydin labels and labeling submitted by Anacor Pharmaceuticals on January 31, 2014.

- Container label
- Carton labeling

B.2 Label and Labeling Images (not to scale)

Container Label

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

CARLOS M MENA-GRILLASCA
03/11/2014

LUBNA A MERCHANT
03/11/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	March 7, 2014
To:	Susan Walker, MD Director **Division of Dermatology and Dental Products (DDDP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Puja Shah, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	KERYDIN (tavaborole)
Dosage Form and Route:	Topical Solution, 5%
Application Type/Number:	NDA 204-427
Applicant:	Anacor Pharmaceuticals, Inc.

1 INTRODUCTION

On July 26, 2013, Anacor Pharmaceuticals, Inc. submitted for the Agency's review a New Drug Application (NDA) 204-427for KERYDIN (tavaborole) Topical Solution, with the proposed indication for the treatment of patients with onychomycosis (b) (4) .

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to the requests by the Division of Dermatology and Dental Products (DDDP) on November 6, 2013, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for KERYDIN (tavaborole) Topical Solution.

2 MATERIAL REVIEWED

- Draft KERYDIN (tavaborole) Topical Solution Medication Guide (MG) and Instructions for Use (IFU) received on July 29, 2013 and received by DMPP and OPDP on February 18, 2014.
- Draft KERYDIN (tavaborole) Topical Solution Prescribing Information (PI) received on July 29, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 18, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 10 and the IFU document using the Verdana font, size 11.

In our collaborative review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- The enclosed IFU review comments are collaborative DMPP and DMEPA.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG or IFU.

Please let us know if you have any questions.

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

KAREN M DOWDY
03/07/2014

PUJA J SHAH
03/07/2014

BARBARA A FULLER
03/07/2014

LASHAWN M GRIFFITHS
03/07/2014

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 4, 2014

To: Cristina Attinello
Regulatory Project Manager
Division of Dermatology and Dental Products (DDDP)

From: Puja Shah, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Lynn Panholzer, PharmD
Regulatory Review Officer, OPDP

Subject: NDA 204427
KERYDIN (tavaborole) Topical Solution, 5%

Background

This consult review is in response to DDDP's November 6, 2013, request for OPDP's review of the draft package insert (PI), carton/container labeling, and Medication Guide (MG) for KERYDIN (tavaborole) Topical Solution, 5%. OPDP reviewed the substantially complete version of the draft PI provided by the Division of Medical Policy Programs (DMPP) on February 18, 2014. Our comments on the PI are included directly on the attached copy of the labeling.

OPDP is concerned about the lack of prominence of the established name on the carton and container labeling. The KERYDIN tradename is (b) (4) and thus less prominent. We recommend that the applicant revise the established name to reflect comparable prominence as the KERYDIN tradename.

Although, DDDP's consult request did not include the review of the Instruction for Use for KERYDIN (tavaborole) Topical solution, 5%, OPDP received a request from DMPP. Our review of the MG and IFU was conducted jointly with DMPP and will be filed under separate cover

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Puja Shah at 240-402-5040 or puja.shah@fda.hhs.gov

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

PUJA J SHAH
03/04/2014

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	204427
Brand Name	Tavaborole Topical Solution, 5%
Generic Name	AN2690 Topical Solution, 5%
Sponsor	Anacor Pharmaceuticals Inc.
Indication	Treatment of onychomycosis
Dosage Form	Topical Solution
Drug Class	Fungicides/Antidermatophyte Agent
Therapeutic Dosing Regimen	Topical Solution 5% q.d
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Tropical Solution 5% b.i.d.
Submission Number and Date	SDN 001 /29 Jul 2013
Review Division	DDDP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effects of AN2690 (doses of tropical solution, 5% q.d. and tropical solution, 5% b.i.d.) were detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between AN2690 and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that assay sensitivity was established.

In this randomized, single-site, open-label, 4-arm crossover study, 55 healthy subjects received AN2690 tropical solution 5% q.d., AN2690 tropical solution 5% b.i.d., placebo, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for AN2690 (Tropical Solution, 5% q.d. and Tropical Solution, 5% b.i.d.) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
AN2690 Tropical Solution, 5% q.d.	6	0.7	(-2.6, 4.1)
AN2690 Tropical Solution, 5% b i.d.	23	2.8	(-0.5, 6.1)
Moxifloxacin 400 mg*	3	10.6	(6.8, 14.4)

- Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 5.3 ms

The supratherapeutic dose (AN2690 topical solution, 5% twice daily on all 10 toenails and 10 fingernails and approximately 5 mm of skin surrounding all nails) produces mean C_{max} values approximately 10- to 21-fold higher than the mean C_{max} values of the therapeutic dose (AN2690 Topical Solution, 5% QD on all 10 toenails). The rate and extent of exposure following the supratherapeutic multiple topical applications are significantly higher compared to therapeutic multiple topical applications and show that, at these concentrations, there are no detectable prolongations of the QT-interval.

Since AN2690 is to be applied topically, intrinsic and extrinsic factors are not expected to have a major influence on systemic exposures of AN2690. Intrinsic factors (e.g., age, gender, race and hepatic or renal impairment) have not been explored as potential factors of PK variability. For extrinsic factors, no DDI or food effect studies have been conducted.

2 PROPOSED LABEL

2.1 SPONSOR'S PROPOSED LABEL

(b) (4)

2.2 QT-IRT'S PROPSED LABEL

QT-IRT's proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.

At concentrations approximately 12 times the concentrations following the maximum recommended dose, TRADENAME does not prolong QTc to any clinically relevant extent.

3 BACKGROUND

Dermatophytes are a group of fungi that can infect the keratinous layers of the skin, hair, and nails. Very superficial infections by dermatophytes are found only in the stratum

corneum, or the top, scaly part of the skin. Dermatophytes are ubiquitous in our environment, commonly found in the soil. All humans come into contact with dermatophytes in their environment and a notable percentage of the population develops symptomatic disease, leading some to conclude that dermatophytosis is an infectious disease but not a contagious disease.

3.1 PRODUCT INFORMATION

AN2690 Topical Solution, 5%, is under clinical development for the treatment of onychomycosis. AN2690 is a (b) (4) boronic acid molecule (5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole) being developed for topical treatment of onychomycosis.

3.2 MARKET APPROVAL STATUS

AN2690 is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

AN2690 inhibits the hERG current with low affinity (22% inhibition at the only concentration tested: 1μM)

3.4 PREVIOUS CLINICAL EXPERIENCE

There were no reports of sudden cardiac deaths. No clinically relevant ECG abnormalities were reported linked to AN2690 dosing.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of AN2690's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 71,206. The sponsor submitted the study report AN2690-ONYC-102 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Randomized, Crossover Study in Healthy Subjects, of the Effects of AN2690 Topical Solution, 5% on QT/QTc Intervals, with Moxifloxacin Positive Control

4.2.2 Protocol Number

AN2690-ONYC-102

4.2.3 Study Dates

Date first subject enrolled: 18 April 2012
Date last subject completed: 15 August 2012

4.2.4 Objectives

Primary objective: to assess the electrocardiographic (ECG) effects of AN2690 following multiple-dose administration of AN2690 Topical Solution, 5% relative to solution vehicle in healthy adult male and female subjects.

Secondary objective: to assess the safety and tolerability of therapeutic and supratherapeutic doses of AN2690 Topical Solution, 5% when administered for 14 days to healthy adult male and female subjects.

4.2.4.1 Design

This was a Phase 1, single-site, open-label, randomized, 4-arm crossover study to evaluate the effects of AN2690 Topical Solution, 5% in healthy male and female subjects. There was a minimum 7-day washout between treatments.

4.2.4.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.4.3 Blinding

This was an open-label study. Only the central ECG laboratory personnel were blinded to treatment assignment for all subjects.

4.2.5 Treatment Regimen

4.2.5.1 Treatment Arms

Subjects were randomized to one of eight sequences, with the following 4 study treatments:

- Vehicle (V): Solution vehicle for AN2690 once daily (q.d.) on all 10 toenails for 14 days
- Positive Control (PC): Solution vehicle for AN2690 q.d. on all 10 toenails for 14 days, plus a single dose of un-blinded moxifloxacin 400 mg administered orally in the morning on Day 14 under fasted conditions
- Therapeutic Dose (DT): AN2690 Topical Solution, 5% q.d. on all 10 toenails for 14 days
- Supratherapeutic Dose (DS): AN2690 Topical Solution, 5% twice daily (b.i.d., defined as every 12 hours) on all 10 toenails and 10 fingernails and approximately 5 mm of skin surrounding all nails for 14 days.

The random order design of treatment used the following a balanced Williams (double) Latin Square schema subjects randomized in a 1:1:1:1:1:1:1:1 manner to the eight sequences:

Randomization Schema

Sequence Latin Square 1	Treatment Period 1	Treatment Period 2	Treatment Period 3	Treatment Period 4
1	DT	DS	V	PC
2	DS	PC	DT	V
3	V	DT	PC	DS
4	PC	V	DS	DT
Sequence Latin Square 2	**Treatment Period 1**	**Treatment Period 2**	**Treatment Period 3**	**Treatment Period 4**
1	DS	V	DT	PC
2	V	PC	DS	DT
3	DT	DS	PC	V
4	PC	DT	V	DS

DS, Supratherapeutic dose; DT, Therapeutic dose; PC, Positive Control; V, Vehicle.

4.2.5.2 Sponsor's Justification for Doses

The application of AN2690 Topical Solution, 5% QD to 10 toenails (nail plate only) is the maximal clinical intended use of this agent and thus represents the clinical dose. The supratherapeutic dose was determined as application of AN2690 Topical Solution, 5% BID to 10 toenails and 10 fingernails and approximately 5 mm skin surrounding each nail (maximum feasible application).

Each study treatment (except moxifloxacin) was to be administered for 14 consecutive days with study drug administration occurring at the same time (± 1 hour) each day; dosing regimens are shown in Table 3. AN2690 Topical Solution, 5% and solution vehicle for AN2690 were applied topically to toenails, fingernails, and skin surrounding nails, as appropriate for each treatment. Subjects were instructed to take their daily shower in the morning prior to morning application of study drugs to prevent washing off of doses. For fingernail application with the supratherapeutic dose treatment, subjects were instructed to keep hands as still as possible and to not touch any mucous membranes for approximately 30 minutes while the solution dried, followed by washing of hands with water. Subjects could cover their feet after study drug dried to prevent transfer of dried study drug to other areas. In the positive control treatment, a single dose of moxifloxacin 400 mg was administered orally with 240 mL of room-temperature water in the morning on Day 14 following a minimum 8-hour fast.

Source: Clinical Study Report No. 002-CLN CL-006-01, section 9.4.4-9.4.5, page 36-37.

Based on available data, the highest anticipated (worst case scenario) exposure from the highest clinical dose of AN2690 potentially to be used (5% solution applied to ten toenails) would be confidently covered by a supratherapeutic dose of 5% BID solution applied to ten toenails, ten fingernails and 5 mm skin around all nails. The

supratherapeutic dose proposed is projected to yield an average Cmax of ~15 to 30 ng/mL and an average AUC0-24 h of ~125 to 250 ng•hr/mL."

Source: Highlights of Clinical Pharmacology Table, Expected High Clinical Exposure Scenario

Reviewer's Comment: Based on prior clinical experience of AN2690, the supra-therapeutic dose selected for the TQT study is reasonable. Moreover, the exposure obtained by the supratherapeutic dose selected (b.i.d. on all 10 toenails and fingernails and 5 mm skin surrounding all nails) is 10- to 21-fold what has been observed in the repeated administration of the therapeutic dose (q.d. on all ten toenails). The doses chosen for the TQT study, for both AN2690 and moxifloxacin, are appropriate.

4.2.5.3 Instructions with Regard to Meals

Subjects fasted from all food and drink except water for at least 8 hours prior to collection of clinical laboratory tests on Day -2 of each treatment period; at end of study or early termination; and prior to dosing with moxifloxacin 400 mg.

Source: Clinical Study Report No. 002-CLN CL-006-01, Section 9.4.7.2, Pg 38

Reviewer's Comments: Since the administration is via topical route, effect of food on AN2690 pharmacokinetics is not anticipated.

4.2.5.4 ECG and PK Assessments

Study Day	-1	14
Intervention	No treatment (Baseline)	Therapeutic Dose: AN2690 Topical Solution, 5% QD on all 10 toenails for 14 days Supratherapeutic Dose: AN2690 Topical Solution, 5% BID on all 10 toenails and 10 fingernails and approximately 5 mm of skin surrounding all nails for 14 days
12-Lead ECGs	On Day -1 of each treatment period at 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, and 23 hours post the baseline zero-hour time point (defined as being 24 hours prior to the first administration of study drug)	On Day 14 of each treatment period at 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, and 23 hours post study drug administration
PK Samples for drug	None collected	PK samples on Day 14 of each treatment period at pre-dose (trough level; approximately 5 minutes pre-dose) and 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, and 23 hours post dose. Post-dose PK samples were to be obtained immediately after 5-minute triplicate ECG extraction time, generally at bedside while subject was still supine.

Reviewer's Comment: The PK and ECG assessments are adequate to capture QT at peak concentrations of AN2690 (median T_{max} ~ 10 hours).

4.2.5.5 Baseline

The Sponsor used QTc pre-dose values on Day -1 as a baseline.

4.2.6 ECG Collection

Intensive 12-Lead Holter monitoring will be used to obtain digital ECGs. Standard 12-Lead ECGs will be obtained while subjects are recumbent.

4.2.7 Sponsor's Results

4.2.7.1 Study Subjects

A total of 55 healthy subjects enrolled, mean BMI was 24 kg/m2 and ranged from 20.2 to 28.4 kg/m2. Forty-five subjects (82%) completed the study and 10 (18%) subjects withdraw prematurely. Reasons for premature discontinuation were protocol non compliance in five subjects, withdrawal of consent unrelated to study treatment in four subjects, and lost to follow-up in one subject. The five cases of protocol noncompliance included positive urine drug screens in two subjects (Subjects S004 and S067) and

behavioral issues/noncompliance with site rules in three subjects (Subjects S050, S072, and S103).

4.2.7.2 Statistical Analyses

4.2.7.2.1 Primary Analysis

The primary endpoint was mean change from baseline, vehicle-corrected (vehicle-adjusted) mean differences between AN2690 and placebo in QTcF. The sponsor used an analysis of covariance model with gender and treatment group as factors and the results are presented in Table 2. This model included gender, period, sequence, time, treatment, and time-by-treatment interaction as fixed effect terms, and baseline as covariate. Subject was included as a random effect. The upper limits of the 2-sided 90% CI for AN2690 (doses of tropical solution 5%, QD and BID) were below 10 ms.

Table 2: Sponsor Results ΔΔQTcF for AN2690 Tropical Solution 5% QD, AN2690 Tropical Solution 5% BID, and Moxifloxacin 400 mg

	AN2690 5% QD (N=49) [a]			AN2690 5% BID (N=50) [b]			Moxifloxacin (N=47) [c]		
Time (hr)	Estimate [d]	Lower Bound [e]	Upper Bound [e]	Estimate [d]	Lower Bound [e]	Upper Bound [e]	Estimate [d]	Lower Bound [e]	Upper Bound [e]
1 hr	-3.25	-6.50	-0.01	0.53	-2.69	3.75	9.79	5.21	14.36
2 hr	-1.69	-4.91	1.54	2.17	-1.05	5.39	9.24	4.63	13.84
3 hr	0.11	-3.12	3.33	2.35	-0.87	5.58	10.21	5.63	14.78
4 hr	-2.00	-5.23	1.23	0.66	-2.56	3.89	8.66	4.09	13.24
5 hr	-1.65	-4.88	1.57	2.48	-0.74	5.71	8.34	3.77	12.92
6 hr	-0.27	-3.49	2.96	1.18	-2.04	4.40	7.97	3.39	12.54
8 hr	-4.07	-7.30	-0.85	-0.32	-3.54	2.90	7.21	2.64	11.79
10 hr	-2.38	-5.60	0.85	3.31	0.09	6.53	6.94	2.37	11.51
12 hr	-3.36	-6.58	-0.13	-0.89	-4.12	2.33	5.08	0.50	9.65
15 hr	-2.92	-6.17	0.32	2.10	-1.15	5.34	5.55	0.91	10.19
18 hr	-6.72	-9.99	-3.45	0.82	-2.45	4.09	3.59	-1.05	8.23
23 hr	-1.86	-5.08	1.37	3.33	0.09	6.58	5.11	0.51	9.72
Time Avg	-2.49	-4.70	-0.28	1.47	-0.73	3.68	7.33	4.19	10.48

BID, twice daily (every 12 hours); ECG, electrocardiogram; QD, once daily; QTcI, ECG interval from the beginning of the Q wave to the end of the T wave corrected for the individual.

Note: p-values for gender effects are: Gender Main Effect = 0.0380.

a Therapeutic dose, AN2690 Topical Solution, 5% once daily to 10 toenails for 14 days.

b Supratherapeutic dose, AN2690 Topical Solution, 5% twice daily (every 12 hours) to 10 toenails, 10 fingernails, and approximately 5 mm skin surrounding all nails for 14 days.

c. Positive control, solution vehicle for AN2690 once daily to 10 toenails for 14 days, plus a single dose of moxifloxacin on Day 14.

d Mixed-Effects General Linear Model is fit for Vehicle-Adjusted change from baseline and includes terms for: treatment, gender, time, period, sequence, and the interactions: treatment by time.

e Lower/upper Bound = lower/upper two-sided 90% model-based confidence limit.

Source: *Clinical Study Report.* No. 002-CLN CL-006-01*, Table 10, Pg 81/125*

Reviewer's Comments: We will provide our independent analysis results in Section 5.2.

4.2.7.2.2 Assay Sensitivity

The sponsor used the same mixed model to analyze the ΔQTcF effect for moxifloxacin. The analysis results were presented in Table 3. The largest unadjusted lower bound 1-sided 95% is 9.27 ms was greater than 5 ms. Thus, assay sensitivity in this thorough QTcF study was established.

Table 3: Sponsor Results ΔΔQTcF for Moxifloxacin 400 mg

Post -dose (Hour)	Mean ΔΔQTcF	Lower Bound 95% CI
2.0	10.60	8.62
3.0	11.25	9.27
4.0	10.29	8.31

CI = Confidence interval.

4.2.7.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc ≤450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms, and changes from baseline QTc ≤30 ms, between 30 and 60 ms, and >60 ms. No subject's absolute QTc > 480 ms and ΔQTc >60 ms.

4.2.7.3 Safety Analysis

No deaths or SAEs were reported. There were no clinically relevant ECG abnormalities reported.

4.2.7.4 Clinical Pharmacology

4.2.7.4.1 Pharmacokinetic Analysis

The PK results of the therapeutic dose (AN2690 Topical Solution, 5% q.d. on all 10 toenails) and supratherapeutic dose (AN2690 Topical Solution, 5% twice daily on all 10 toenails and 10 fingernails and approximately 5 mm of skin surrounding all nails for 14 days) are presented in Table 4 and Figure 1. Following the supratherapeutic dose C_{max} and AUC values in the thorough QT study were 10- to 21-fold and 9- to 22-fold levels seen with the therapeutic dose.

Table 4: Sponsor's Summary of AN2690 Pharmacokinetic Parameters

	Sequence 1 (N=6)		Sequence 2 (N=6-7) [a]		Sequence 3 (N=6)		Sequence 4 (N=6)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Therapeutic Dose								
C_{max}, ng/mL	1.81	0.481	2.04	1.70	1.59	0.879	1.29	0.942
T_{max}, h	16.1	2.45	14.1	4.14	12.9	4.75	10.9	7.57
$AUC_{(0\text{-}last)}$, ng·h/mL	22.5	10.6	27.1	18.0	19.7	11.0	17.8	13.8
Supratherapeutic Dose								
C_{max}, ng/mL	19.8	11.3	24.7	24.1	33.4	15.3	23.3	12.2
T_{max}, h	14.1	6.32	9.96	7.69	14.5	6.20	5.45	5.46
$AUC_{(0\text{-}last)}$, ng·h/mL	251	69.8	273	179	392	197	265	170
Mean C_{max} Ratio [b]	10.9	—	12.1	—	21.0	—	18.1	—
Mean $AUC_{(0\text{-}last)}$ Ratio [c]	11.2	—	10.1	—	19.9	—	14.9	—

Source: (b) (4) Pharmacokinetics Report, Table 3 (Appendix 16.5)

Sequence 1: DT, DS, V, PC; Sequence 2: DS, PC, DT, V; Sequence 3: V, DT, PC, DS; Sequence 4: PC, V, DS, DT.

$AUC_{(0\text{-}last)}$, area under the plasma concentration-time curve from hour 0 to the last measurable concentration; C_{max}, maximum observed plasma concentration; DS, supratherapeutic dose; DT, therapeutic dose; PC, positive control; PK, pharmacokinetic; T_{max}, time to maximum plasma concentration; V, vehicle.

a DT (N=6) and DS (N=7).

b Mean C_{max} Ratio: AN2690 mean C_{max} at supratherapeutic dose/AN2690 mean C_{max} at therapeutic dose.

c Mean $AUC_{(0\text{-}last)}$ Ratio: AN2690 mean $AUC_{(0\text{-}last)}$ at supratherapeutic dose/AN2690 mean $AUC_{(0\text{-}last)}$ at therapeutic dose.

	Sequence 5 (N=6)		Sequence 6 (N=5-6) [a]		Sequence 7 (N=7)		Sequence 8 (N=6-7) [b]	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Therapeutic Dose								
C_{max}, ng/mL	1.97	1.18	1.80	1.12	1.45	0.566	1.11	0.433
T_{max}, h	11.1	5.68	14.1	7.39	14.4	6.60	14.7	6.62
$AUC_{(0\text{-}last)}$, ng·h/mL	24.0	14.8	21.5	18.0	20.9	11.9	11.5	6.90
Supratherapeutic Dose								
C_{max}, ng/mL	18.8	7.93	21.1	15.5	17.0	8.54	21.7	13.6
T_{max}, h	5.10	6.10	10.1	7.77	18.1	15.1	9.77	8.64
$AUC_{(0\text{-}last)}$, ng·h/mL	220	96.6	217	94.3	234	113	256	155
Mean C_{max} Ratio [c]	9.54	-	11.7	-	11.7	-	19.5	-
Mean $AUC_{(0\text{-}last)}$ Ratio [d]	9.17	-	10.1	-	11.2	-	22.3	-

Source: (b) (4) Pharmacokinetics Report, Table 3 (Appendix 16.5)

Sequence 5: DS, V, DT, PC; Sequence 6: V, PC, DS, DT; Sequence 7: DT, DS, PC, V; Sequence 8: PC, DT, V, DS.

$AUC_{(0\text{-}last)}$, area under the plasma concentration-time curve from hour 0 to the last measurable concentration; C_{max}, maximum observed plasma concentration; DS, supratherapeutic dose; DT, therapeutic dose; PC, positive control; PK, pharmacokinetic; T_{max}, time to maximum plasma concentration; V, vehicle.

a DT (N=5) and DS (N=6).

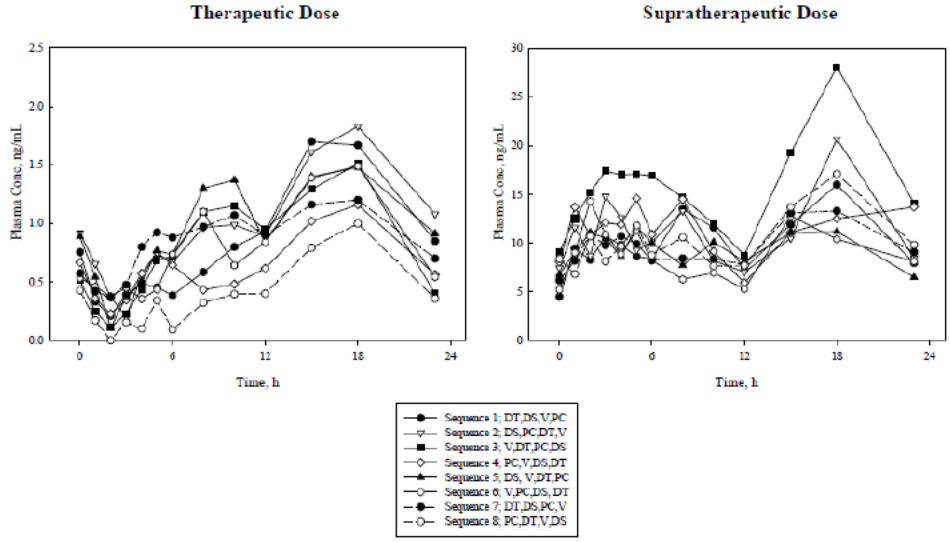
b DT (N=7) and DS (N=6).

c Mean C_{max} Ratio: AN2690 mean C_{max} at supratherapeutic dose/AN2690 mean C_{max} at therapeutic dose.

d Mean $AUC_{(0\text{-}last)}$ Ratio: AN2690 mean $AUC_{(0\text{-}last)}$ at supratherapeutic dose/AN2690 mean $AUC_{(0\text{-}last)}$ at therapeutic dose .

(Source: Sponsor's study report, page 91, Table 13.)

Figure 1: Mean AN2690 Concentration-Time Profiles (Sequences 1 through 8)



Source: (b) (4) Pharmacokinetics Report, Figure 1 (Appendix 16.5)

DS, supratherapeutic dose; DT, therapeutic dose; PC, positive control; PK, pharmacokinetic; V, vehicle.

(Source: Sponsor's study report, page 92, Figure 2.)

4.2.7.4.2 Exposure-Response Analysis

The relationship between ΔΔQTcI and AN2690 concentrations is visualized in Figure 2 and an evident exposure-response relationship is seen. The sponsor reports a significant slope for linear regression of plasma AN2690 concentrations versus ΔΔQTcI to be 0.272 ms/ng/mL (p-value = 0.0242).

Table 5: Concentration-QTc Effect Analysis – Sponsor's Analysis

QT Parameter	Slope of Plasma Conc. Effect on ΔΔQTc [a]	Standard Error of Slope of Plasma Conc. Effect on ΔΔQTc [a]	p-value Slope of Plasma Conc. Effect on ΔΔQTc [a]	Overall Model Fit [a]
QTcI	0.2726	0.1158	0.0242	<0.0001
QTcF	0.2636	0.1211	0.0360	<0.0001
QTcB	0.1674	0.0973	0.0964	<0.0001

QT Parameter	Predicted ΔΔQTc at Average Cmax 22.40 ng/mL	One-sided Upper 95% Confidence Bound of Predicted ΔΔQTc [b]
QTcI	4.12	8.05
QTcF	4.46	8.69
QTcB	3.73	7.07

Source: Table 14.2.3.21

ΔΔQTc, difference between the vehicle-adjusted/corrected change from baseline in QTc interval and plasma concentration of AN2690; C_{max}, maximum observed plasma concentration;
PK-PD, pharmacokinetic-pharmacodynamic; QT, electrocardiogram interval from the beginning of the Q wave to the end of the T wave; QTcB, QT interval corrected using Bazett's formula; QTcF, QT interval corrected using Fridericia's formula; QTcI, QT interval corrected using individual QTc formula.

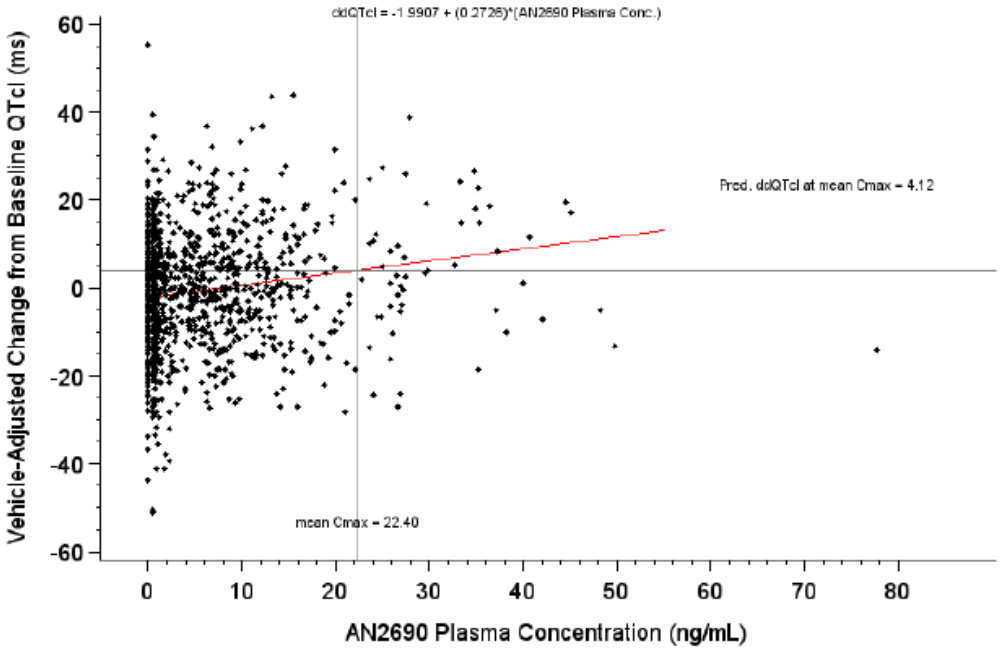
Note: For subject S116: Period 4 data were excluded from all PK/PD analyses due to a dosing error and plasma concentration data from all periods were excluded for calculation of the maximum plasma concentration (C_{max}).

a Linear mixed effects model is fit for vehicle-adjusted change from baseline versus the plasma concentration. Intercept, plasma concentration and subject are included in the model as random effects. The covariance matrix structure is unstructured.

b Upper Bound = upper one-sided 95% linear mixed model based confidence limit.

(Source: Sponsor's clinical study report, page 96, Table 14.)

Figure 2: ΔΔQTcI Vehicle vs. all AN2690 Concentrations – Sponsor's Analysis



Source: Figure 14.3.1

C_{max}, maximum observed plasma concentration; Conc., concentration; dd, ΔΔ;
PK-PD, pharmacokinetic-pharmacodynamic; Pred., predicted; QTcI, individual formula heart rate corrected electrocardiogram interval from the beginning of the Q wave to the end of the T wave.

Note: Subject S116 Period 4 data were excluded from PK-PD analysis due to dosing error.

(Source: Sponsor's study, page 97, Figure 6.)

Reviewer's Comments: The reviewer's analysis is in Section 5.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

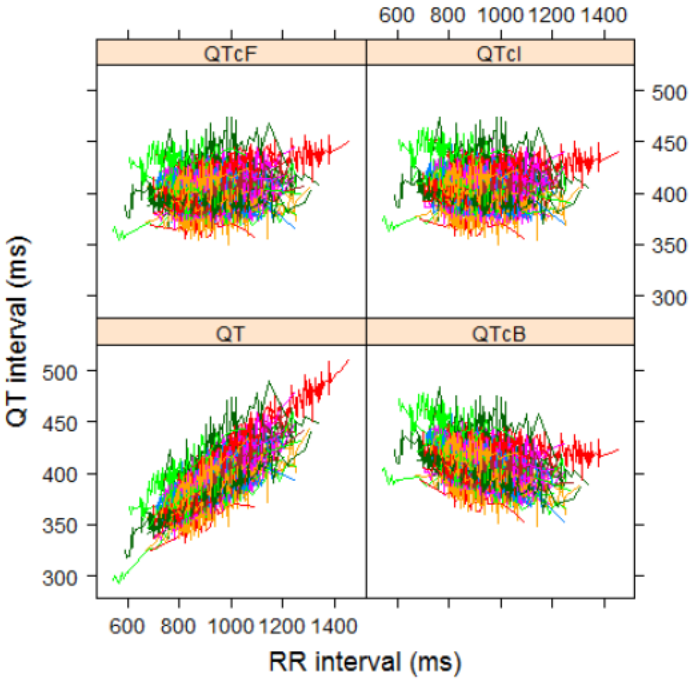
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 6, it appears that QTcF and QTcI are equally better than QTcB. To be consistent with the sponsor's analyses, we choose to present QTcF results.

Table 6: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method					
	QTcB		QTcF		QTcI	
	N	MSSS	N	MSSS	N	MSSS
AN2690 5% QD	51	0.0041	51	0.0022	51	0.0020
AN2690 5% BID	49	0.0040	49	0.0015	49	0.0020
Moxifloxacin	47	0.0057	47	0.0015	47	0.0018
Placebo	49	0.0045	49	0.0026	49	0.0027
All	53	0.0042	53	0.0012	53	0.0015

The QT-RR interval relationship is presented in Figure 3 together with the Bazett's (QTcB), Individual (QTcI) and Fridericia (QTcF) corrections.

Figure 3: QT, QTcB, QTcI and QTcF, vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 Statistical Assessments

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the ΔQTcF effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results

are listed in Table 7. The largest upper bounds of the 2-sided 90% CI for the mean differences between AN2690 tropical solution 5%, QD and placebo, and between AN2690 tropical solution, 5% BID and placebo are 4.1 ms and 6.1 ms, respectively.

Table 7: Analysis Results of ΔQTcF and ΔΔQTcF for AN2690 Tropical Solution, 5% BID, AN2690 Tropical Solution, 5% QD, and Moxifloxacin 400 mg

	Placebo	AN2690 Topical Solution 5% BID				AN2690 Topical Solution 5% QD				Moxifloxacin				
	ΔQTcF	ΔQTcF		ΔΔQTcF		ΔQTcF		ΔΔQTcF		ΔQTcF		ΔΔQTcF		
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	Adj* 90% CI
1	-3.7	51	-2.9	0.8	(-3.0, 4.5)	48	-6.1	-2.4	(-6.2, 1.4)	47	6.7	10.4	(6.6, 14.2)	(5.2, 15.6)
2	-5.0	51	-3.8	1.2	(-2.0, 4.5)	49	-6.4	-1.4	(-4.7, 1.9)	47	4.2	9.2	(5.9, 12.5)	(4.6, 13.7)
3	-5.8	51	-3.8	2.0	(-1.7, 5.8)	49	-6.1	-0.2	(-4.0, 3.6)	47	4.8	10.6	(6.8, 14.4)	(5.3, 15.9)
4	-4.0	51	-3.0	0.9	(-2.5, 4.4)	49	-5.4	-1.5	(-5.0, 2.0)	47	4.7	8.7	(5.2, 12.2)	(3.9, 13.5)
5	-2.9	51	-1.1	1.8	(-1.7, 5.4)	49	-4.2	-1.3	(-4.9, 2.2)	47	5.7	8.6	(5.0, 12.2)	(3.7, 13.5)
6	-3.3	51	-2.5	0.8	(-2.5, 4.1)	49	-2.5	0.7	(-2.6, 4.1)	47	5.0	8.2	(4.9, 11.6)	(3.6, 12.8)
8	-1.3	51	-1.4	-0.2	(-3.5, 3.2)	49	-4.1	-2.8	(-6.2, 0.6)	47	6.2	7.5	(4.1, 10.9)	(2.9, 12.1)
10	-2.8	51	-0.8	2.1	(-1.1, 5.2)	49	-5.0	-2.2	(-5.4, 1.0)	47	4.6	7.4	(4.2, 10.6)	(3.0, 11.8)
12	-3.3	51	-4.5	-1.3	(-4.3, 1.8)	49	-5.9	-2.6	(-5.7, 0.5)	47	2.8	6.0	(2.9, 9.2)	(1.8, 10.3)
15	-3.7	51	-1.3	2.4	(-1.2, 6.0)	49	-5.4	-1.7	(-5.3, 1.9)	46	1.1	4.8	(1.2, 8.5)	(-0.2, 9.8)
18	1.1	51	1.1	-0.0	(-3.6, 3.5)	49	-4.3	-5.4	(-9.1, -1.8)	47	5.2	4.1	(0.4, 7.7)	(-0.9, 9.1)
23	-7.7	51	-4.9	2.8	(-0.5, 6.1)	49	-8.8	-1.1	(-4.4, 2.2)	46	-2.9	4.8	(1.4, 8.2)	(0.2, 9.4)

* Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

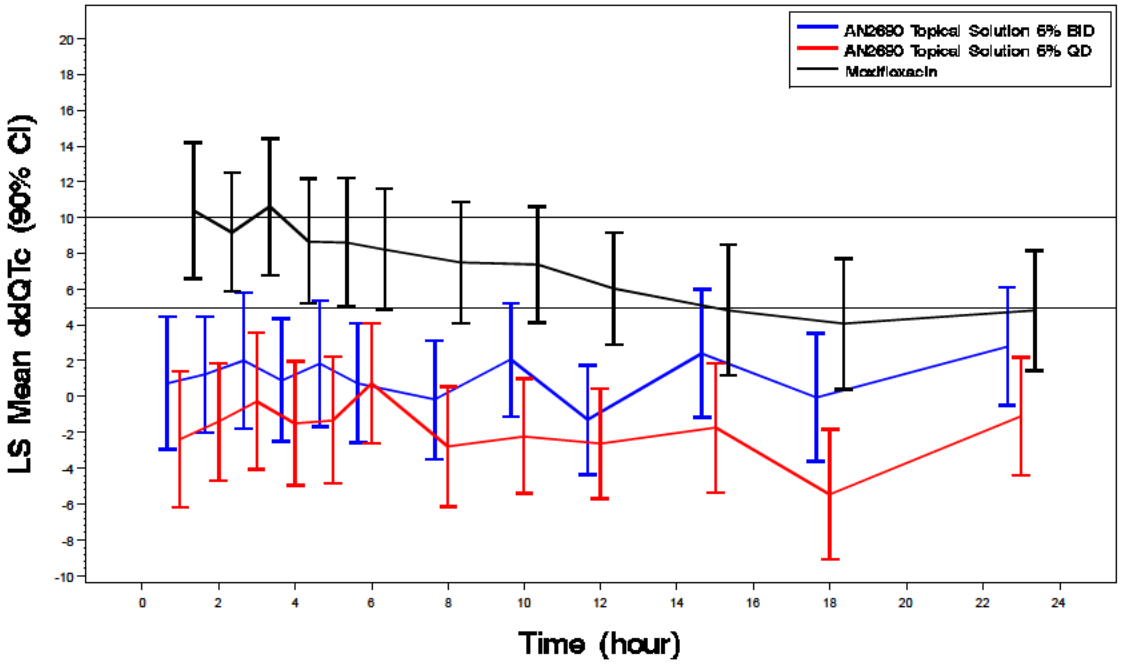
5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 7. The largest unadjusted of the 2-sided 90% lower confidence interval is 6.8 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 5.3 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

5.2.1.3 Graph of ΔΔQTcF Over Time

Figure 4 displays the time profile of ΔΔQTcF for different treatment groups and moxifloxacin 400 mg.

Figure 4: Mean and 90% CI ΔΔQTcF Time Course for AN2690 Tropical Solution ,5% BID, AN2690 Tropical Solution, 5% QD, and Moxifloxacin 400 mg



5.2.1.4 Categorical Analysis

Table 8 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, and between 450 ms and 480 m, and changes from baseline QTc ≤30 ms, between 30 and 60 ms, and >60 ms. No subject's QTcF is above 480 ms. No subject's change from baseline is above 60 ms (see Table 9).

Table 8: Categorical Analysis for QTcF

Treatment Group	Total N	Value<=450 ms	450 ms<Value<=480 ms
AN2690 Topical Solution, 5% BID	52	50 (96.2%)	2 (3.8%)
AN2690 Topical Solution, 5% QD	51	48 (94.1%)	3 (5.9%)
Moxifloxacin	49	45 (91.8%)	4 (8.2%)
Vehicle	50	47 (94.0%)	3 (6.0%)

Table 9: Categorical Analysis for ΔQTcF

Treatment Group	Total N	Value<=30 ms	30 ms<Value<=60 ms
AN2690 Topical Solution 5% BID	52	51 (98.1%)	1 (1.9%)
AN2690 Topical Solution 5% QD	51	50 (98.0%)	1 (2.0%)
Moxifloxacin	49	46 (93.9%)	3 (6.1%)
Vehicle	50	50 (100%)	0 (0.0%)

5.2.2 HR Analysis

The statistical reviewer used mixed model to analyze the ΔHR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 10. The largest upper bounds of the 2-sided 90% CI for the mean differences between AN2690 tropical solution, 5% QD and placebo, and between AN2690 tropical solution, 5% BID and placebo are 4.7 bpm and 4.3 bpm, respectively Table 11 presents the categorical analysis of HR. One subject who experienced HR interval greater than 100 bpm is in AN2690 topical solution, 5% BID group.

Table 10: Analysis Results of ΔHR and ΔΔHR for AN2690 Tropical Solution 5% QD, AN2690 Tropical Solution 5% BID, and Moxifloxacin 400 mg

	placebo	AN2690 Topical Solution 5% BID				AN2690 Topical Solution 5% QD				Moxifloxacin			
	ΔHR	ΔHR		ΔΔHR		ΔHR		ΔΔHR		ΔHR		ΔΔHR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	-0.7	51	-1.2	-0.5	(-2.7, 1.7)	48	0.2	0.9	(-1.3, 3.2)	47	3.7	4.4	(2.2, 6.7)
2	-0.4	51	0.4	0.8	(-1.4, 3.0)	49	1.5	1.9	(-0.3, 4.1)	47	0.2	0.5	(-1.7, 2.8)
3	-1.0	51	0.1	1.0	(-1.0, 3.1)	49	1.2	2.1	(0.0, 4.2)	47	1.7	2.7	(0.6, 4.8)
4	-1.9	51	0.2	2.1	(-0.1, 4.3)	49	0.6	2.5	(0.3, 4.7)	47	2.1	4.0	(1.8, 6.3)
5	-1.5	51	-0.7	0.8	(-1.4, 3.0)	49	0.3	1.8	(-0.4, 4.0)	47	1.1	2.6	(0.4, 4.8)
6	-0.1	51	-0.4	-0.4	(-2.5, 1.7)	49	1.4	1.5	(-0.6, 3.6)	47	0.7	0.8	(-1.4, 2.9)
8	0.2	51	0.1	-0.1	(-2.2, 2.1)	49	1.1	0.9	(-1.3, 3.1)	47	3.6	3.4	(1.2, 5.6)
10	-0.2	51	-0.5	-0.4	(-2.4, 1.7)	49	-0.4	-0.2	(-2.3, 1.9)	47	1.7	1.9	(-0.3, 4.0)
12	1.5	51	0.1	-1.4	(-3.6, 0.8)	49	1.7	0.2	(-2.0, 2.4)	47	1.4	-0.1	(-2.3, 2.2)
15	0.8	51	0.8	-0.1	(-2.3, 2.2)	49	1.3	0.5	(-1.8, 2.7)	46	0.7	-0.2	(-2.5, 2.1)
18	-0.3	51	-0.1	0.2	(-2.2, 2.5)	49	1.0	1.3	(-1.1, 3.6)	47	1.4	1.7	(-0.7, 4.1)
23	4.1	51	4.1	0.0	(-2.2, 2.2)	49	5.2	1.1	(-1.1, 3.4)	46	6.2	2.1	(-0.2, 4.4)

Table 11: Categorical Analysis for HR

Treatment Group	Total N	HR < 100 ms	HR >=100 bpm
AN2690 Topical Solution 5% BID	52	51 (98.1%)	1 (1.9%)
AN2690 Topical Solution 5% QD	51	51 (100%)	0 (0.0%)
Moxifloxacin	49	48 (98.0%)	1 (2.0%)
Vehicle	50	50 (100%)	0 (0.0%)

5.2.3 PR Analysis

The statistical reviewer used mixed model to analyze the ΔPR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 12. The largest upper bounds of the 2-sided 90% CI for the mean differences between AN2690 tropical solution, 5% QD and placebo, and between AN2690 tropical solution. 5% BID and placebo are 4.5 ms and 4.6 ms, respectively. Table 13 presents the categorical analysis of PR. Six subjects who experienced PR interval greater than 200 ms are in both AN2690 topical solution 5%, QD and BID groups.

Table 12: Analysis Results of ΔPR and ΔΔPR for AN2690 Tropical Solution 5% QD, AN2690 Tropical Solution 5% BID, and Moxifloxacin 400 mg

	Placebo	AN2690 Topical Solution 5% BID				AN2690 Topical Solution 5% QD				Moxifloxacin			
	ΔPR	ΔPR		ΔΔPR		ΔPR		ΔΔPR		ΔPR		ΔΔPR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	2.5	51	3.3	0.8	(-2.0, 3.5)	48	3.4	0.9	(-1.9, 3.7)	47	2.5	-0.0	(-2.9, 2.8)
2	3.7	51	3.5	-0.2	(-2.9, 2.5)	49	3.6	-0.2	(-2.9, 2.6)	47	2.2	-1.5	(-4.3, 1.3)
3	2.2	51	4.1	1.9	(-0.8, 4.6)	49	2.4	0.2	(-2.5, 2.9)	47	0.3	-2.0	(-4.7, 0.8)
4	2.7	51	3.2	0.5	(-1.9, 2.9)	49	3.4	0.6	(-1.8, 3.0)	47	0.4	-2.3	(-4.8, 0.1)
5	2.7	51	2.4	-0.3	(-3.0, 2.4)	49	3.9	1.1	(-1.6, 3.8)	47	1.5	-1.3	(-4.0, 1.5)
6	3.4	51	3.4	-0.0	(-2.5, 2.4)	49	2.7	-0.7	(-3.1, 1.7)	47	-0.2	-3.6	(-6.1, -1.2)
8	2.8	51	3.8	1.1	(-1.2, 3.4)	49	3.8	1.0	(-1.3, 3.3)	47	1.6	-1.2	(-3.5, 1.1)
10	4.4	51	2.6	-1.8	(-4.1, 0.5)	49	2.9	-1.6	(-3.9, 0.8)	47	1.0	-3.4	(-5.8, -1.0)
12	2.5	51	2.1	-0.4	(-2.8, 2.1)	49	2.0	-0.5	(-3.0, 2.0)	47	0.8	-1.7	(-4.2, 0.9)
15	0.6	51	1.9	1.3	(-1.2, 3.9)	49	2.2	1.7	(-0.9, 4.2)	46	0.8	0.2	(-2.4, 2.8)
18	1.2	51	2.2	1.0	(-1.5, 3.4)	49	3.2	2.0	(-0.6, 4.5)	47	1.6	0.4	(-2.2, 2.9)
23	0.3	51	0.3	-0.0	(-2.7, 2.7)	49	0.5	0.2	(-2.5, 2.9)	46	1.9	1.6	(-1.2, 4.4)

Table 13: Categorical Analysis of PR

Treatment Group	Total N	PR < 200 ms	PR >=200 ms
AN2690 Topical Solution, 5% BID	52	47 (90.4%)	5 (9.6%)
AN2690 Topical Solution, 5% QD	51	47 (92.2%)	4 (7.8%)
Moxifloxacin	49	44 (89.8%)	5 (10.2%)
Vehicle	50	47 (94.0%)	3 (6.0%)

5.2.4 QRS Analysis

The statistical reviewer used mixed model to analyze the ΔQRS effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 14. The largest upper bounds of the 2-sided 90% CI for the mean differences between AN2690 tropical solution, 5% QD and placebo, and between AN2690 tropical solution, 5% BID and placebo are 1.6 ms and 2.5 ms, respectively. Table 15 presents the categorical analysis of QRS. Two subjects who experienced QRS interval greater than 110 ms are in AN2690 topical solution 5%, BID and QD groups.

Table 14: Analysis Results of ΔQRS and ΔΔQRS for AN2690 Tropical Solution 5% QD, AN2690 Tropical Solution 5% BID, and Moxifloxacin 400 mg

	Placebo	AN2690 Topical Solution 5% BID				AN2690 Topical Solution 5% QD				Moxifloxacin			
	ΔQRS	ΔQRS		ΔΔQRS		ΔQRS		ΔΔQRS		ΔQRS		ΔΔQRS	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	-0.5	51	0.8	1.4	(0.2, 2.5)	48	-0.2	0.3	(-0.9, 1.5)	47	-0.1	0.4	(-0.7, 1.6)
2	0.1	51	0.5	0.3	(-0.8, 1.5)	49	0.2	0.1	(-1.1, 1.3)	47	-0.6	-0.7	(-1.9, 0.5)
3	-0.2	51	0.3	0.4	(-0.7, 1.6)	49	0.3	0.4	(-0.7, 1.6)	47	-0.6	-0.4	(-1.6, 0.8)
4	0.0	51	0.3	0.2	(-0.8, 1.3)	49	0.2	0.2	(-0.9, 1.2)	47	-0.1	-0.1	(-1.2, 1.0)
5	-0.1	51	0.7	0.7	(-0.3, 1.8)	49	-0.5	-0.4	(-1.5, 0.7)	47	-0.3	-0.3	(-1.4, 0.9)
6	0.4	51	0.3	-0.1	(-1.2, 1.0)	49	-0.3	-0.7	(-1.8, 0.4)	47	-0.8	-1.2	(-2.3, -0.1)
8	-0.3	51	-0.1	0.2	(-0.8, 1.2)	49	-1.4	-1.1	(-2.2, -0.1)	47	-1.1	-0.8	(-1.8, 0.3)
10	-0.5	51	0.4	0.8	(-0.2, 1.9)	49	-0.4	0.1	(-0.9, 1.1)	47	-0.8	-0.3	(-1.4, 0.7)
12	-0.4	51	-0.2	0.2	(-0.9, 1.3)	49	-0.6	-0.3	(-1.4, 0.9)	47	-0.2	0.2	(-1.0, 1.3)
15	-0.7	51	-0.6	0.1	(-1.0, 1.2)	49	-0.5	0.2	(-1.0, 1.3)	46	-0.6	0.1	(-1.0, 1.3)
18	-0.5	51	0.2	0.7	(-0.4, 1.7)	49	-0.6	-0.1	(-1.1, 1.0)	47	-0.4	0.1	(-0.9, 1.2)
23	-1.1	51	-0.1	1.1	(-0.1, 2.2)	49	-1.3	-0.2	(-1.4, 1.0)	46	-1.0	0.1	(-1.1, 1.3)

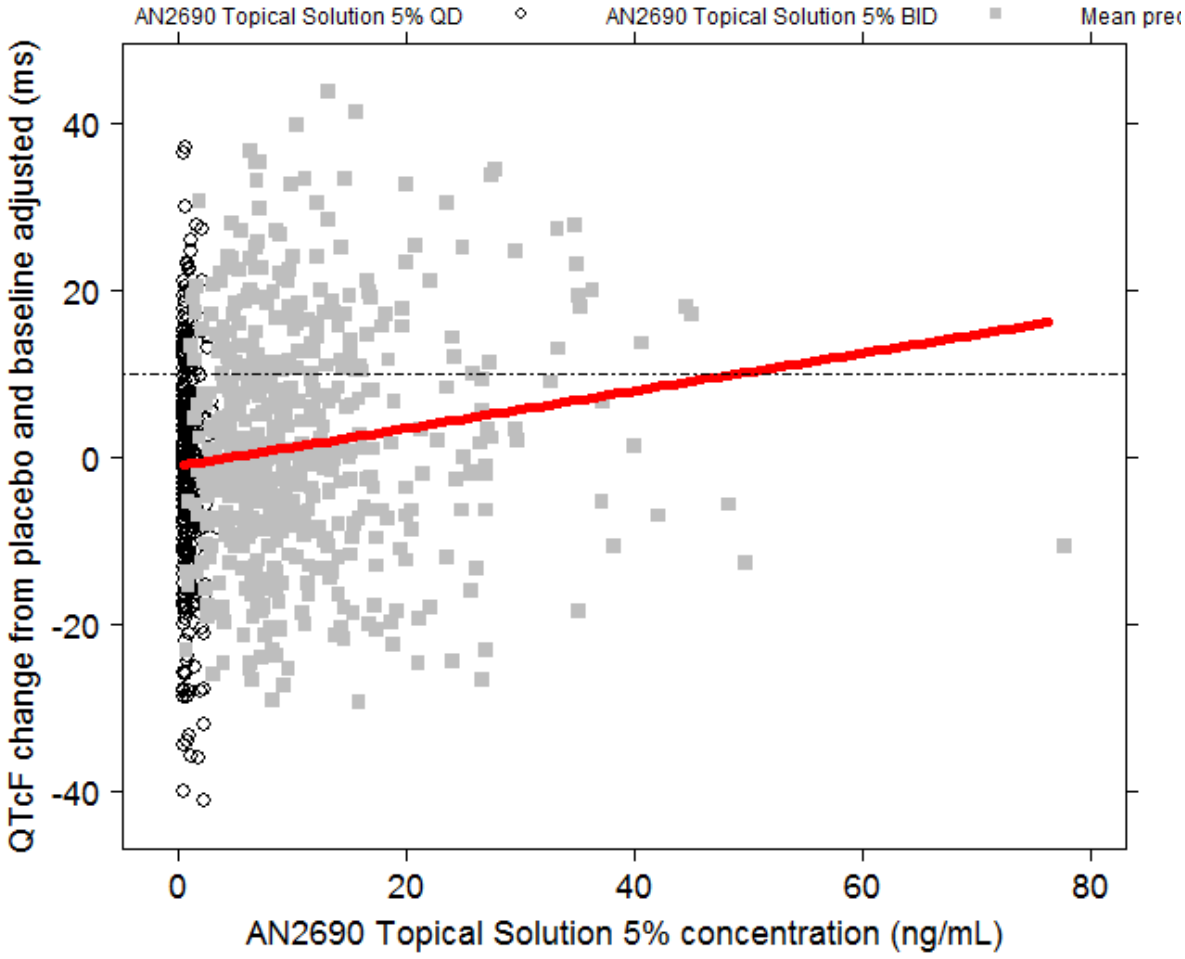
Table 15: Categorical Analysis for QRS

Treatment Group	Total N	QRS < 110 ms	QRS >= 110 ms
AN2690 Topical Solution, 5% BID	52	51 (98.1%)	1 (1.9%)
AN2690 Topical Solution, 5% QD	51	49 (96.1%)	2 (3.9%)
Moxifloxacin	49	47 (95.9%)	2 (4.1%)
Vehicle	50	49 (98.0%)	1 (2.0%)

5.3 Clinical Pharmacology Assessments

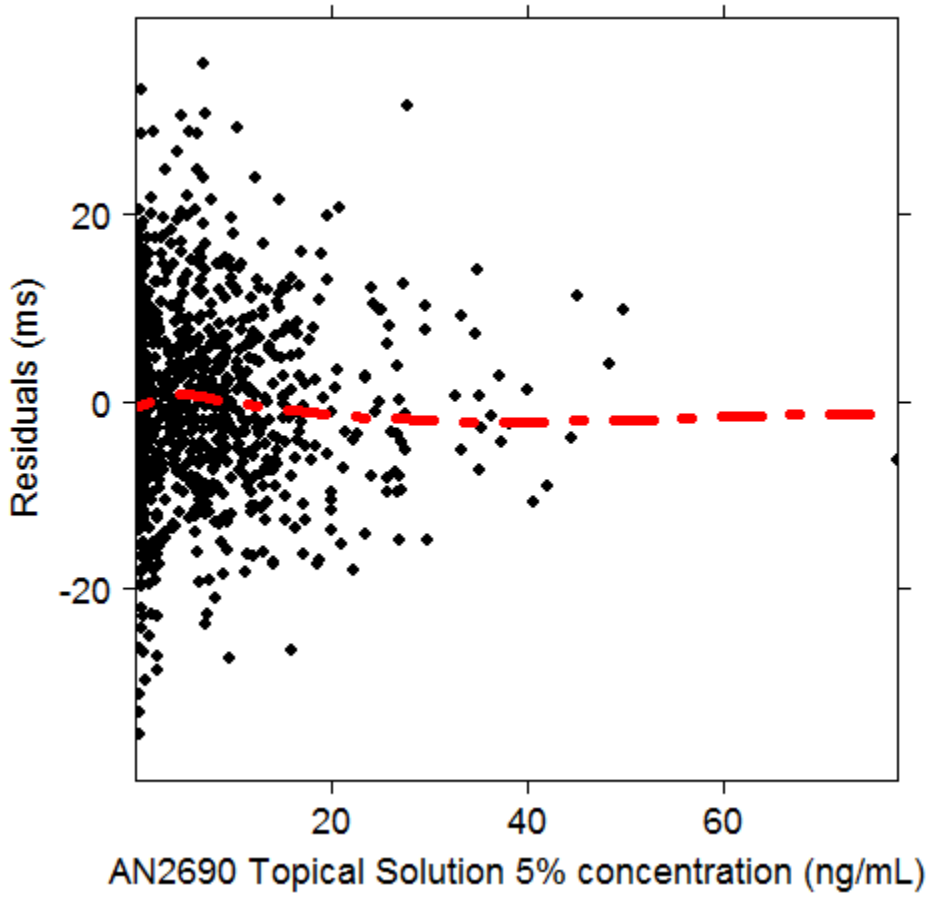
The relationship between ΔΔQTcF and drug concentrations is visualized in Figure 5. Based on graphical evaluation and linear mixed effects modeling, a linear mixed effects model with random intercept and random slope was selected. Independent review yielded a positive and significant relationship between AN2690 plasma concentrations and ΔΔQTcF with a positive slope of 0.23 ms per ng/mL (95% CI: 0.036 – 0.41, p-value = 0.05).

Figure 5: ΔΔQTcF vs. AN2690 concentration



Residuals analysis for the model yielded an adequate fit (Figure 6).

Figure 6: ΔΔQTcF residual vs. AN2690 Concentration –Reviewer's Analysis



The relationship between ΔΔQTcF and AN2690 concentrations was investigated by linear mixed effects modeling. The following three linear models were considered:

Model 1 is a linear model with an intercept

Model 2 is a linear model with mean intercept fixed to 0 (with variability)

Model 3 is a linear model with no intercept

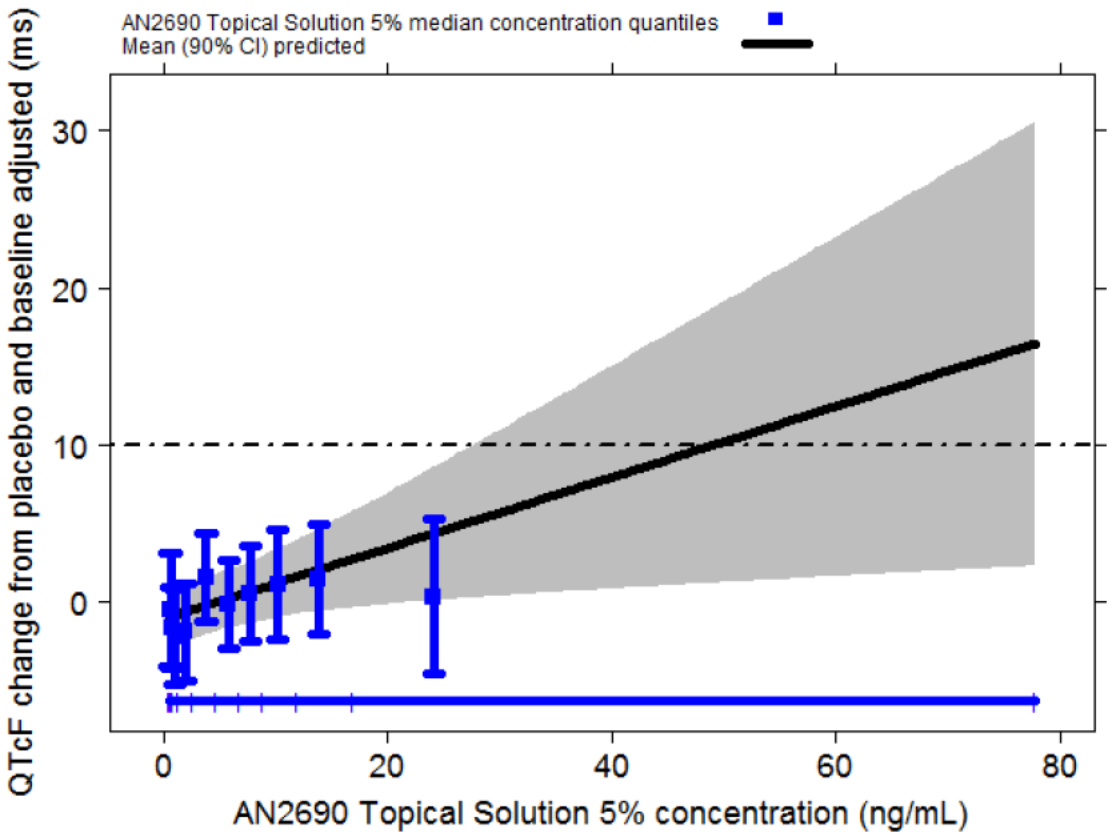
Table 16 summarizes the results of the AN2690 concentration-ΔΔQTcF analyses. Model 1 was used for further analysis since the model with an intercept was found to fit the data best based on model selection criteria (log likelihood and AIC).

Table 16: Exposure-response Analysis of AN2690 Associated ΔΔQTcI Prolongation

Parameter	Estimate	p-value	Interindividual Variablility (CV%)
*Model 1: Δ Δ QTcF = Intercept + slope * AN2690 Topical Solution 5% Concentration*			
Intercept (ms)	-1.03 (-2.97; 0.90)	0.4	6.92
Slope (ms per ng/mL)	0.23 (0.04; 0.42)	0.05	0.59
Residual Variability (ms)	10.49		
*Model 2: Δ Δ QTcF = Intercept + slope * AN2690 Topical Solution 5% Concentration (Fixed Intercept)*			
Intercept (ms)	0		6.99
Slope (ms per ng/mL)	0.19 (0.0098; 0.37)	0.08	0.59
Residual Variability (ms)	10.49		
*Model 3: Δ Δ QTcF = slope * AN2690 Topical Solution 5% Concentration (No Intercept)*			
Slope (ms per ng/mL)	0.13 (-0.08; 0.33)	0.3	0.74
Residual Variability (ms)	11.54		

The goodness-of-fit plot in Figure 7 shows the observed median-quantile AN2690 concentrations and associated mean (90% CI) ΔΔQTcF (90% CI) together with the mean(90% CI) predicted ΔΔQTcF.

Figure 7: Observed Median-Quantile AN2690 Concentrations and Associated Mean (90% CI) ΔQTcF (color dots) Together with the Mean (90% CI) Predicted ΔQTcF (black line with shaded grey area) - Reviewer's Analysis

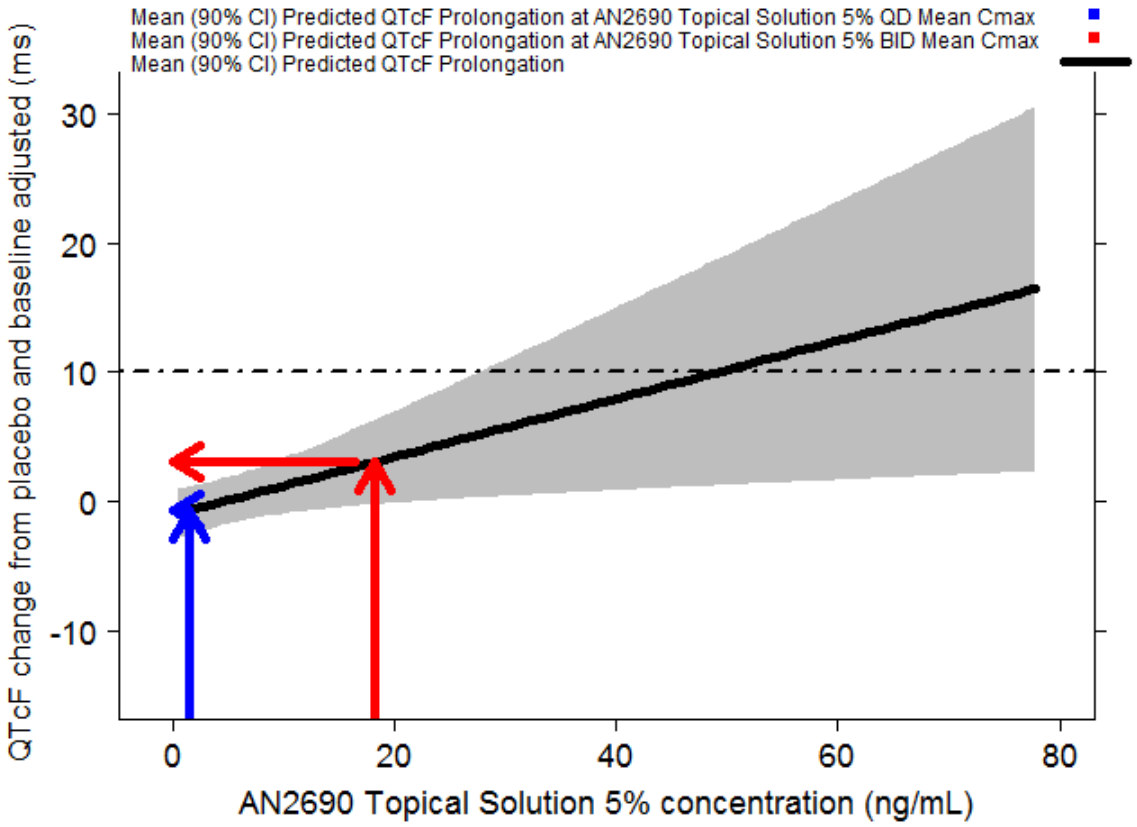


The predicted ΔΔQTcF at the mean C_{max} AN2690 concentrations can be found in Table 17 and Figure 8.

Table 17: Predicted ΔΔQTcI Interval at Mean C_{max} AN2690 Concentration Using Model 1

Treatment	C_{max} (ng/mL)	Predicted ΔΔQTcF (ms)	90% Confidence Interval
AN2690 Topical Solution 5% QD	1.44	-0.71	(-2.56; 1.14)
AN2690 Topical Solution 5% BID	18.2	3.05	(-0.22; 6.32)

Figure 8: ΔΔQTcI vs. AN2690 Peak Concentration, linear model prediction - Reviewer's Analysis



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines (i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 97% of the ECGs were annotated in the primary lead II, with less than 1% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

Six subjects had PR > 200 ms, no post-baseline value exceeded 218 ms. Two subjects had a QRS > 110 ms at baseline.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	AN2690 Topical Solution, 5% applied daily	
Maximum tolerated dose	Not identified	
Principal adverse events	*Most common adverse events*: Application site reaction, contact dermatitis *Dose limiting adverse events*: None identified	
Maximum dose tested *Specify dosing regimen*	Single Dose	For studies with PK: 002-CLN PK-004-01: 7.5% solution to ten toenails and 5 mm skin around each toenail on Day 1 002-CLN PK-003-01: 5% solution to ten toenails and 2 mm skin around each toenail on Day 1
	Multiple Dose	002-CLN PK-004-01: 7.5% solution to ten toenails and 5 mm skin around each toenail for 28 days 002-CLN PK-003-01: 5% solution to ten toenails and 2 mm skin around each toenail QD for 14 days (Days 5 to 18)
Exposures Achieved at Maximum Tested Dose *Mean (%CV) C_{max}, AUC*	Single Dose	002-CLN PK-004-01: No PK analysis conducted due to lack of quantifiable concentration data (LLOQ=5 ng/mL) 002-CLN PK-003-01: C_{max} (ng/mL): **3.54 (64)** AUC_{last} (ng·hr/mL): **44.4 (57)** (LLOQ=0.5 ng/mL)

	Multiple Dose	002-CLN PK-004-01: No PK analysis conducted due to lack of quantifiable concentration data (LLOQ=5 ng/mL) 002-CLN PK-003-01: C_{max} (ng/mL): **5.17 (67)** AUC_{last} (ng·hr/mL): **148 (63)**

Range of linear PK *Specify dosing regimen*	Not determined	
Accumulation at steady state *Mean (%CV)*	002-CLN PK-003-01: The accumulation ratio [mean (%CV)] after reaching steady state was **2.22 (64)** from 5% solution to ten toenails and 2 mm skin around each toenail QD for 14 days (Days 5 to 18)	
Metabolites	002-CLN PK-005-01: Single topical application of 5% of ^{14}C-AN2690 (100 µCi) to ten toenails and 5 mm skin around each toenail 002-CLN PK-003-01: 5% solution to ten toenails and 2 mm skin around each toenail QD for 14 days (Days 5 to 18) Findings in these two studies show that the biotransformation of AN2690 in humans occurs primarily by the oxidative oxoborole ring cleavage to form 5-fluoro-2-hydroxybenzyl alcohol (M6) that was further oxidized to form 5-fluoro-2-hydroxybenzoic acid (M6a) or conjugated to form M6-sulfate (M5), which were detected in urine only at steady-state. These metabolites were inactive.	
Absorption	Absolute/ Relative Bioavailability	Absolute bioavailability has not been determined (a clinical intravenous AN2690 dosage form is not available). No studies have been conducted to compare topical administration to an oral dosage form. 002-CLN PK-005-01: Absorption was estimated to be approximately **18%** of the topical dose, defined by the recovery of ^{14}C-AN2690- derived radioactivity in urine.
	Tmax *Median (range)*	002-CLN PK-003-01: **8.03 h (0.467-24.0 h)** for parent Not determined for metabolites
Distribution	Vd/F or Vd *Mean (%CV)*	Not determined

	% bound *Mean (%CV)*	002-NCL PK-048-01 *In vitro* human plasma protein binding: **45.8-76.9% (0-3)** at 0.001–85 µg/mL

Elimination	Route	002-CLN PK-005-01: Excretion of drug-derived radioactivity was primarily in the urine, which accounted for approximately **18%** of the nominally applied dose.
	Terminal t½ *Mean (%CV)*	002-CLN PK-003-01: **28.5 h (37)** for parent [data from 10 of 21 subjects] Not determined for metabolites
	CL/F or CL	Not determined
Intrinsic Factors	Age	Not determined.
	Sex	Not determined.
	Race	Not determined.
	Hepatic & Renal Impairment	Not determined.
Extrinsic Factors	Drug Interactions	002-NCL PK-053-01 and 002-NCL PK-046-01: Using the estimated K_i value, the likelihood for in vivo drug interactions of AN2690 would be remote ([I/]K_i ratio < 0.1) as long as the total plasma C_{max} concentration of AN2690 remains ≤5 µM (≤760 ng/mL). Based on data gathered to date, no DDI is expected. No DDI studies have been conducted.
	Food Effects	To be applied topically; hence, not applicable.
Expected High Clinical Exposure Scenario	Based on available data, the highest anticipated (worst case scenario) exposure from the highest clinical dose of AN2690 potentially to be used (5% solution applied to ten toenails) would be confidently covered by a supratherapeutic dose of 5% solution applied to ten toenails, ten fingernails and 5 mm skin around all nails. The supratherapeutic dose proposed is projected to yield an average C_{max} of **~15 to 30 ng/mL** and an average $AUC_{0\text{-}24\ h}$ of **~125 to 250 ng·hr/mL**.	

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

/s/

MOH JEE NG
11/08/2013

QIANYU DANG
11/08/2013

SATJIT S BRAR
11/08/2013

KEVIN M KRUDYS
11/12/2013

MONICA L FISZMAN
11/12/2013

NORMAN L STOCKBRIDGE
11/12/2013

DGCPC/OSI CONSULT: Request for Clinical Inspections

Date: 10/16/2013

To: Kassa Ayalew, M.D., Acting Branch Chief, GCPAB
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB
CDEROCDSIPMOs@fda.hhs.gov
Roy A Blay, Ph.D.
Division of Good Clinical Practice Compliance Assessment Branch
Office of Scientific Investigations
Office of Compliance/CDER

Through: Milena Lolic, M.D., Medical Officer, DDDP
David Kettl, M.D.,Team Leader, DDDP

From: Cristina Attinello, M.P.H., RPM, DDDP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 204427
IND#: IND 071206
Applicant: Anacor Pharmaceuticals Inc.
Phone: (650) 543-7576
Email: info@anacor.com
Regulatory Point of Contact: Carmen R. Rodriguez, M.Sc. VP, Regulatory Affairs and Quality
Regulatory Point of Contact Phone: (650) 543-7576
Regulatory Point of Contact Email: crodriguez@anacor.com

Drug Proprietary Name:
Generic Drug Name: (tavaborole) Topical Solution, 5%
NME or Original BLA (Yes/No): Yes
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): onychomycosis

PDUFA: 07/29/2014
Action Goal Date: 07/11/2014
Inspection Summary Goal Date: 05/12/2014

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Site #	Protocol ID	Number of Subjects	Indication
Hudson, Charles 3501 Washington Ave Evansville, IN 47714 USA United States phone:1-812-474-1234 fax:1-812-402-3636 email:hudsonderm@aol.com	325	AN2690-ONYC-302	13	A Randomized, Double-Blind, Vehicle-Controlled, Multi-Center Study to Evaluate the Efficacy and Safety of AN2690 Topical Solution, 5%, vs. Solution Vehicle in the Treatment of Onychomycosis of the Toe
Weisfeld, Max 5508 Harford Road Baltimore, MD 21214 USA United States phone:1-410-426-5508 fax:1-410-426-4066 email:maxweisfeld@aol.com	122	AN2690-ONYC-301	37	A Randomized, Double-Blind, Vehicle-Controlled, Multi-Center Study to Evaluate the Efficacy and Safety of AN2690 Topical Solution, 5%, vs. Solution Vehicle in the Treatment of Onychomycosis of the Toe

III. Site Selection/Rationale

Site Information

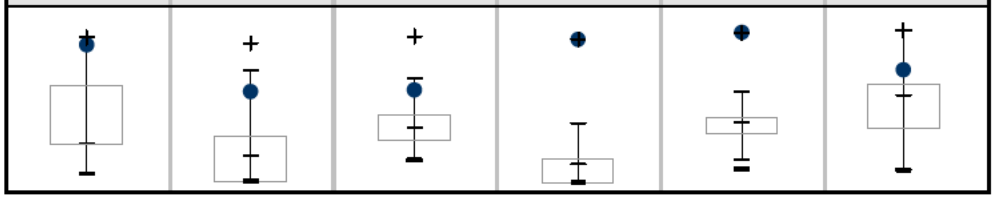
STUDY:	AN2690-ONYC-301	SITEID:	122

NAME	Weisfeld, Max
LOCATION	5508 Harford Road Baltimore, MD, USA 21214
PHONE/FAX	1-410-426-5508 / 1-410-426-4066
EMAIL	maxweisfeld@aol.com

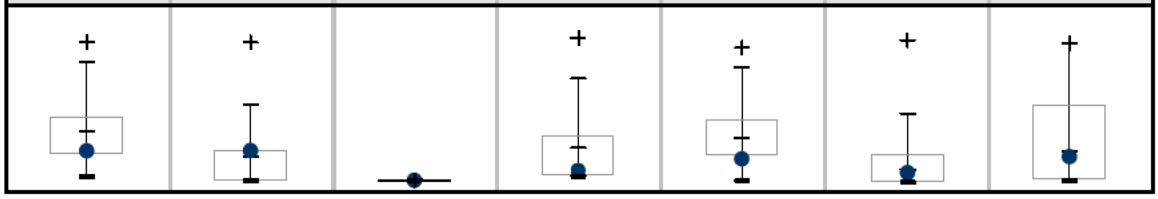
RANK	2	FINLDISC	0	COMPLAINT	0
SITE RISK	12.1	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	39	0.25	0.50	6.00	6.00	55%
Study Rate	17	0.05	0.06	0.79	0.70	31%
Min	2	0.00	-0.10	0.00	-2.10	4%
Site	37	0.16	0.24	6.00	6.00	40%



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	5.8	0.3	0%	60%	2.0	12.0	29
Study Rate	2.0	0.0	0%	13%	0.6	1.1	6
Min	0.0	0.0	0%	0%	0.0	0.0	0
Site	1.1	0.1	0%	3%	0.3	0.8	5



Site Memo

Second highest enroller with low adverse events, highest treatment efficacy result for primary endpoint

Site Information

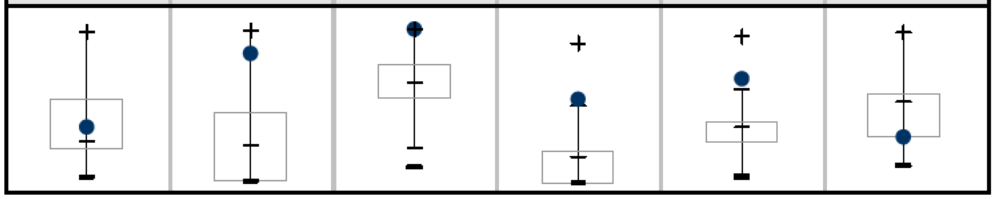
STUDY:	AN2690-ONYC-302	SITEID:	325

NAME	Hudson, Charles
LOCATION	3501 Washington Ave Evansville, IN, USA 47714
PHONE/FAX	1-812-474-1234 / 1-812-402-3636
EMAIL	hudsonderm@aol.com

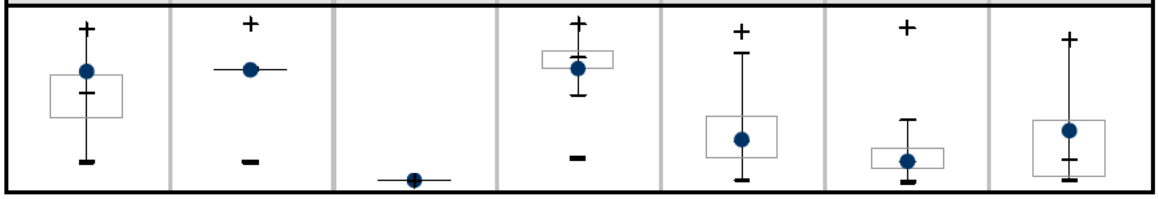
RANK	12	FINLDISC	0	COMPLAINT	0
SITE RISK	7.9	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	36	0.27	0.33	5.00	5.00	54%
Study Rate	14	0.06	0.07	0.93	0.72	29%
Min	1	0.00	-0.33	0.00	-1.67	6%
Site	13	0.23	0.33	3.00	3.00	16%



	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	3.5	0.5	0%	50%	2.3	9.3	34
Study Rate	1.3	0.0	0%	13%	0.6	1.2	5
Min	-1.0	-1.0	-100%	-100%	0.0	0.0	0
Site	2.1	0.0	0%	0%	0.6	1.3	12



Site Memo

High efficacy

Domestic Inspections:

Reasons for inspections:

- ✓ Enrollment of large numbers of study subjects
- ✓ High treatment responders (specify):
- ____ Significant primary efficacy results pertinent to decision-making
- ____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- ____ Other (specify):

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

/s/

CRISTINA Petruccelli Attinello
10/16/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA 204427	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: tavaborole Dosage Form: Topical Solution Strengths: 5%		
Applicant: Anacor Pharmaceutical Inc. Agent for Applicant (if applicable):		
Date of Application: 26 Jul 2013 Date of Receipt: 29 Jul 2013 Date clock started after UN:		
PDUFA Goal Date: 29 Jul 2014	Action Goal Date (if different):	
Filing Date: 27 Sep 2013	Date of Filing Meeting: 04 Sep 2013	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1 NME		
Proposed indication(s)/Proposed change(s): Treatment of onychomycosis (b) (4)		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 071206	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	✓			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	✓			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	✓			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		✓		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	✓			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☐ Paid ☐ Exempt (orphan, government) ☒ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			✓	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***				
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** *http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm* **If yes**, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***		✓		

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		✓		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		✓		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	✓			
Index: Does the submission contain an accurate comprehensive index?	✓			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	✓			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	✓			
Are all establishments and their registration numbers listed on the form/attached to the form?	✓			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	✓			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	✓			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	✓			

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] 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." Applicant may not use wording such as, "To the best of my knowledge…"*	✓			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	✓			
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			✓	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be*	✓			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	✓			
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			✓	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	✓			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		✓		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***		✓		
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***			✓	
Prescription Labeling			☐ **Not applicable**	
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL	✓			

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

format? ***If no, request applicant to submit SPL before the filing date.***				
Is the PI submitted in PLR format?[4]		✓		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***		✓		
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	✓			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	✓			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	✓			
OTC Labeling	**☒ Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)		✓		

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If yes, specify consult(s) and date(s) sent:				
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 28 Oct 2009 ***If yes, distribute minutes before filing meeting***	✓			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 29 May 2013 ***If yes, distribute minutes before filing meeting***	✓			
Any Special Protocol Assessments (SPAs)? **Date(s):** 13 Sep 2010 ***If yes, distribute letter and/or relevant minutes before filing meeting***	✓			

ATTACHMENT

MEMO OF FILING MEETING

DATE: 04 Sep 2013

NDA 204427

PROPRIETARY NAME: Pending

ESTABLISHED/PROPER NAME: tavaborole

DOSAGE FORM/STRENGTH: Topical Solution, 5%

APPLICANT: Anacor Pharmaceutical Inc

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of onychomycosis (b) (4)

BACKGROUND:
Tavaborole Topical Solution, 5% is an anti-fungal agent. This application provides for the use of Tavaborole Topical Solution, 5% for the treatment of patients with onychomycosis (b) (4) This complete application is subject to "The Program" under PDUFA V agreement.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:		
	CPMS/TL:	Barbara Gould	Y
Cross-Discipline Team Leader (CDTL)	David Kettl		Y
Clinical	Reviewer:	Milena Lolic	Y
	TL:	David Kettl	Y
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Kerian Grande Roche	Y
	TL:	Kerry Snow	N

Clinical Pharmacology	Reviewer:	An-Chi (Angie) Lu	Y
	TL:	Doanh (Donny) Tran	Y
Biostatistics	Reviewer:	Kathleen Fritsch	Y
	TL:	Mohamed Alosh	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Linda Pellicore	Y
	TL:	Barbara Hill	Y
Statistics (carcinogenicity)	Reviewer:	Steven Thomson	N
	TL:	Karl Lin	N
Product Quality (CMC)	Reviewer:	Gene Holbert	Y
	TL:	Shulin Ding	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Erika Pfeiler	N
	TL:	John Metcalfe	N
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Christina Capacci-Daniel	Y
	TL:	Don Henry	N
OSE/DMEPA (proprietary name)	Reviewer:	Carlos Mena-Grillasca	Y
	TL:	Luba Merchant	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Roy Blay	
	TL:	Janice Polman	
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Julie Beitz Susan Walker Maria Walsh		
Other attendees	Stanka Kukich Stother Dixon Olga Simakova Giuseppe Randazzo Michelle Eby		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: The application did not raise significant safety or efficacy issues
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☐ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS	☐ Not Applicable ☒ FILE

Comments:	☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☐ YES ☒ NO ☒ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☐ YES ☒ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO

• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Julie Beitz, MD

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): 12/27/2013

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter

☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

BARBARA J GOULD
09/11/2013

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 204427

Application Type: New NDA

Name of Drug: (tavaborole) Topical Solution, 5%

Applicant: Anacor Pharmaceuticals, Inc.

Submission Date: 26 Jul 2013

Receipt Date: 29 Jul 2013

1.0 Regulatory History and Applicant's Main Proposals

This application provides for the use of (Tavaborole) Topical Solution, 5% for the treatment of patients with onychomycosis (b) (4). The safety and efficacy of tavaborole was studied in tow double-blind vehicle-controlled, clinical Phase 3 studies. This application is reviewed under the "The Program" PDUFA V.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

NO 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *References to the specific section or subsection in the FPI needs to added for all items in "DOSAGE AND ADMINISTRATION" and "DOSAGE FORMS AND STRENGTHS" in the Highlights.*

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment: *The name of the drug product in should be in UPPER CASE*

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES

21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

N/A 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

NO 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *The title of section 17 should be "PATIENT COUNSELING INFORMATION" without the word "AND" inserted. This should be corrected in both TOC of and FPI.*

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

NO 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment: *The cross reference in section 12.1 should be corrected to read [see CLINICAL PHARMACOLOGY (12.4)]*.

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

YES 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

NO 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment: *The statement should be modified to refer to "clinical trials" instead of "clinical studies"*

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

NO 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment: *The words "approved patient labeling" should not be capitalized in the labeling, and the overall statement should not be italicized.*

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

/s/

BARBARA J GOULD
09/10/2013