

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022496Orig1s000

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 #/Product Name: 022496 Exparel (bupivacaine liposome injectable suspension)

PMR/PMC Description: A multicenter, randomized, double-blind, parallel-group, bupivacaine- and placebo-controlled study to evaluate the safety, efficacy and pharmacokinetic profile of a single intraoperative administration of Exparel for postoperative analgesia in young children 0 to 1 years old undergoing multiple surgical procedures.

PMR/PMC Schedule Milestones: Final Protocol Submission: 08/31/2017
Study/Trial Completion: 02/28/2019
Final Report Submission: 05/31/2019
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

Deferred until additional safety or effectiveness data have been collected.

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.”

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.

A deferred safety and pharmacokinetic study in pediatric patients 0 to 1 years of age.

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)

Continuation of Question 4

- 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
 - 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?

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)

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

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- 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?

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Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
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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.

A deferred safety and pharmacokinetic study in pediatric patients 2 to 5 years of age.

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)

Continuation of Question 4

- 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
 - 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?

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- 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?

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.*

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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.

A deferred safety and pharmacokinetic study in pediatric patients 6 to 11 years of age.

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)

Continuation of Question 4

- 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
 - 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)
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- 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?

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)

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 #/Product Name: 022496 Exparel (bupivacaine liposome injectable suspension)

PMR/PMC Description: A multicenter, randomized, double-blind, parallel-group, bupivacaine- and placebo-controlled study to evaluate the safety, efficacy and pharmacokinetic profile of a single intraoperative administration of Exparel for postoperative analgesia in adolescent subjects 12 to less than 17 years old undergoing multiple surgical procedures

PMR/PMC Schedule Milestones: Final Protocol Submission: 10/31/2012
Study/Trial Completion: 11/30/2013
Final Report Submission: 02/28/2014
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

Studies are ready for approval in adults

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.”

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.

A deferred safety and pharmacokinetic study in pediatric patients 12 to less than 17 years of age.

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)

Continuation of Question 4

- 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
 - 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?

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/

SHARON M TURNER RINEHARDT
10/28/2011

JUDITH A RACOOSIN
10/28/2011

505(b)(2) ASSESSMENT

Application Information		
NDA # 022496	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Exparel Established/Proper Name: bupivacaine liposome injectable suspension Dosage Form: Injection Strengths: 133mg/10mL and 266mg/20mL		
Applicant: Pacira Pharmaceuticals		
Date of Receipt: September 28, 2010		
PDUFA Goal Date: October 28, 2011		Action Goal Date (if different):
Proposed Indication: single-dose infiltration into the surgical site to produce postsurgical analgesia		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. (*If not clearly identified by the applicant, this information can usually be derived from annotated labeling.*)

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Marcaine, NDA 16964	Nonclinical and some clinical pharmacology sections of label, clinical pharmacology data and section of label
Published literature	Nonclinical and some clinical pharmacology sections of label, clinical pharmacology data and section of label

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)
BE Studies

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO”, proceed to question #5.

*If “YES”, list the listed drug(s) identified by name and answer question #4(c).
Marcaine (NDA 16964)*

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Marcaine	16964	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a change in formulation from (bupivacaine) hydrochloride (HCl) to (bupivacaine) (b)(4) liposome.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.

If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
YES NO

If “YES” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “NO” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If “NO”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
YES NO

If “YES” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “NO” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): NDA 18304, Sensorcaine injectable; NDA 18053, Bupivacaine hydrochloride injectable; NDA 18692, Marcaine spinal injectable; and generic injectable product

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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

/s/

SHARON M TURNER RINEHARDT
10/26/2011

R E V I E W ADDENDUM

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

Date: October 20, 2011
From: Arthur B. Shaw, Ph.D., Chemist, Division III, Office of New Drug Quality Assessment
To: NDA 22496
Subject: Review of Vial and Carton

In the draft labeling submitted September 6, 2011 the applicant included the following statement in the package insert:

[REDACTED] (b) (4)

However, the instructions on the vial label state:

[REDACTED] (b) (4)

In an e-mail through the Project Manager Sharon Turner-Rinehardt, dated October 3, 2011 (DARRTS date 10/04/2011), the applicant was asked to explain this discrepancy and to provide the data to support the effect of the temperature on whichever temperature indicator is to be used.

The applicant responded via e-mail to the Project Manager on October 7, 2011. The vial indicator has been modified and the package insert modified accordingly.

The package insert now reads:

"Check the freeze [REDACTED] (b) (4) indicators and discard product if either has been triggered. The freeze indicator turns from green to white when exposed to freezing temperatures. [REDACTED] (b) (4)

The applicant provided copies of the new vial and carton labels. The indicators are included and are readily visible.

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/s/

ARTHUR B SHAW
10/20/2011

PRASAD PERI
10/21/2011
I concur

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

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

MEMORANDUM

Date: September 27, 2011

To: Sharon Turner-Rinehardt – Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: Mathilda Fienkeng – Regulatory Review Officer
Division of Professional Promotion (DPP)

CC: Lisa Hubbard – Professional Group Leader (DPP)
Shenee Toombs – DTC Reviewer
Division of Direct-to-Consumer Promotion (DTCP)

Subject: **DPP draft labeling comments
NDA 022496 EXPAREL™ (bupivacaine extended-release liposome
injection)**

DPP has reviewed the proposed product labeling (PI), and carton and container labels for EXPAREL (bupivacaine extended-release liposome, injection) (Exparel) submitted for DPP review on December 01, 2010. The following comments are provided using the substantially complete version of the labeling sent via email on September 23, 2011, by Sharon Turner-Rinehardt, and the sponsor submitted proposed carton and container labeling of September 9, 2011 (Attachment 1).

DPP's comments are provided directly in the attached marked-up copy of the PI. If you have any questions about DPP's comments, please do not hesitate to contact Mathilda Fienkeng at 301-796-3692 or at Mathilda.fienkeng@fda.hhs.gov.

Carton and Container Label

DPP is concerned about the prominence and disparate font styles of the trade name and established names in the presentations. We recommend revising the proposed established name on the carton labeling to be in accordance with 21 CFR 201.10 (g)(2) which states that, "[t]he established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features."

DPP notes that the carton and container labels present the established drug name as "Bupivacaine Liposome (b) (4) Injectable Suspension" or "bupivacaine liposome (b) (4) injectable suspension". We recommend revising the established name to be consistent with the full PI.

(b) (4)

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/s/

MATHILDA K FIENKENG
09/27/2011

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

Date: June 16, 2011

Application Type/Number: NDA 022496

Through: Zachary Oleszczuk, PharmD, Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Cathy A. Miller, MPH, BSN, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Proprietary Name and Labels and Labeling Review

Drug Name: Exparel (Bupivacaine) Extended-release Liposome Injection
15 mg/mL

Applicant: Pacira Pharmaceuticals, Inc.

OSE RCM #: 2011-308 and 2010-2432

***** This document contains proprietary and confidential information that should not be released to the public.*****

INTRODUCTION

This re-assessment of the proprietary name, Exparel, responds to the anticipated approval of NDA 022496 within 90 days from the date of this review. The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed proprietary name, Exparel, acceptable in OSE Review 2010-2430 dated February 8, 2011 and OSE Review #2008-2006 dated May 15, 2009.

Additionally, this review summarizes DMEPA's evaluation of the proposed labels and labeling for Exparel submitted by the Applicant on September 28, 2010 for areas of vulnerabilities that could lead to medication errors.

1 METHODS AND RESULTS

1.1 PROPRIETARY NAME RISK ASSESSMENT

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources (see Section 4) to identify names with orthographic and/or phonetic similarity to the proposed name that have been approved since the completion of the previous OSE proprietary name review. We use the same search criteria outlined in OSE Review #2008-2006 and #2010-2430, for the proposed proprietary name, Exparel. Since none of the proposed characteristics were altered, we did not evaluate previous names of concern. Our searches of the databases did not yield any new names thought to look or sound similar to Exparel and represent a potential source of drug name confusion.

Additionally, DMEPA searches the USAN stem list to determine if the name contains any USAN stems. DMEPA did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, Exparel, as of May 16, 2011.

1.2 LABELS AND LABELING

The container labels and carton labeling were submitted by the Applicant on September 28, 2010. (See Appendices A and B for images.) DMEPA also evaluated the most current draft package insert labeling submitted on March 2, 2011. Our labels and labeling risk assessment identified the following deficiencies:

- Important administration information contained in the prescribing information Dosage and Administration Sections 2.2. and 2.3 are [REDACTED] (b) (4)
- The prescribing information in highlights section and full prescribing dosage and administration Section 2 contains [REDACTED] (b) (4)
- The NDC numbers [REDACTED] (b) (4)
- The total drug content includes [REDACTED] (b) (4)
- The total drug content is presented [REDACTED] (b) (4)
- The drug concentration [REDACTED] (b) (4)
- The route of administration statement language [REDACTED] (b) (4)
- The proprietary name is presented [REDACTED] (b) (4)

- [REDACTED] (b) (4)

2 DISCUSSION

The following section discuss the deficiencies identified in this review.

2.1 PACKAGE INSERT LABELING

The dosage and administration section of the insert labeling includes important information in Section 2.2 and 2.3 about administration precautions and warnings concerning the non-interchangeability of Exparel with other different Bupivacaine formulations. This information should be included in the highlights section to assure providers get a cursory overview of this information when referencing the prescribing information prior to administration of the drug. Although there is not adequate space to include all of the information in Section 2.2 and 2.3, we believe that abbreviated statements should be added along with a reference to the full prescribing section for further information, to alert providers to read the information thoroughly.

DMEPA also found that the prescribing information includes [REDACTED] (b) (4)

DMEPA is also concerned that [REDACTED] (b) (4)

Lastly, we are concerned that Section 2.1 currently titled “Injection Instructions” may be misleading since this product is administered via infiltration only. Use of a title that more accurately reflects the route of administration (i.e. Infiltration Instructions) may provide clarity to providers during preparation and administration of the product, specifically for those providers who are not yet familiar with this formulation of Bupivacaine.

2.2 CONTAINER LABELS AND CARTON LABELING

The total drug content is currently presented with the established name on the container labels and carton labeling. This is an unconventional presentation and distracts from the clear presentation of the total drug content. Additionally, the total drug content is currently displayed with the same prominence as the concentration on labels and labeling. In accordance with USP, the total drug content should be the primary and most prominent expression on the principal display panel of the label, followed by the strength per milliliter.

¹ ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations. ISMP Medication Safety Alert Newsletter. Volume 8 Issue 24, November 27, 2003.

We also find that the product strength

(b) (4)

DMEPA found that the statement

(b) (4)

The proprietary name is presented with all capital letters, EXPAREL, on container labels and carton labeling. DMEPA recommends the use of mixed upper case/lower case (Exparel) for the presentation of the proprietary names. The presentation of the proprietary name in all capital letters can make it more difficult to clearly read the name on labels and labeling.

Finally, DMEPA finds that there is not adequate differentiation between the sizes. Currently, the two sizes are differentiated only the green versus blue colors in the presentation of the total drug content, and these colors look very similar. We believe that added differentiation is needed to help distinguish the two volumes during drug selection, preparation and administration, and minimize the risk of wrong volume section during the drug use process.

3 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment indicates that the proposed name, Exparel, is not vulnerable to name confusion that could lead to medication errors, nor is the name considered promotional. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proposed proprietary name, Exparel, for this product at this time. DMEPA considers this a final review. However, if approval of the NDA is delayed beyond 90 days from the date of this review, the Division of Anesthesia and Analgesia (DAAP) should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

Our evaluation of the proposed labels and labeling identified areas of needed improvement in order to minimize the potential for medication error. We provide recommendations to the insert labeling in Section 3.1 Comments to the Division for discussion during the labeling meetings. Section 3.2 Comments to the Applicant contains recommendations for revisions to the container labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the applicant with regard to this review. If you have further questions or need clarifications, please contact Danyal Chaudhry, OSE Senior Regulatory Project Manager, at 301-796-3813.

3.1 COMMENTS TO THE DIVISION

A. Highlights of Prescribing Information

1. The Dosage and Administration subsection: Revise the statement that currently appears below the dosing table and relocate it to appear above the dosing table as follows: "Exparel should be administered as an infiltration and injected slowly into soft tissue via local administration. Exparel should not be administered by any other route."
2. Consider adding the following information to the highlights section of the prescribing information to alert practitioners about incompatibilities and lack of bioequivalence between Exparel and other Bupivacaine products:

- Some physiochemical incompatibilities exist between Exparel and several other drugs resulting in a rapid increase in free (unencapsulated) Bupivacaine, altering Exparel characteristics. Therefore, admixing Exparel with other drugs prior to administration is not recommended (See Section 2.2).
 - Different formulations of Bupivacaine are not bioequivalent even if the milligram strength is the same, therefore, it is not possible to convert dosing from any other formulations of Bupivacaine.
3. Consider revising the title of Section 2.1 to read “Infiltration Instructions” rather than “Injection Instructions” to help avert confusion about the route of administration that could lead to wrong route medication errors.
 4. Remove (b) (4) and instead, spell out “greater than or equal to” in the dosing table. (b) (4)

[Redacted]

B. Full Prescribing Information – Dosage and Administration Section 2.1 Injection Instructions

1. Add the following statement to Section 2.1 above the dosing table: “Exparel should be administered as an infiltration and injected slowly into soft tissue via local administration. Exparel should not be administered by any other route.”
2. Consider revising the title of Section 2.1 to read “Infiltration Instructions” rather than “Injection Instructions” to help avert confusion about the route of administration that could lead to wrong route medication errors.
3. Remove (b) (4) and instead, spell out “greater than or equal to” in the dosing table. (b) (4)

[Redacted]

3.2 COMMENTS TO THE APPLICANT

A. Proposed Container Labels and Carton Labeling (All sizes)

1. Revise the expression of the strength on all labels and labeling including deleting (b) (4) and increasing the prominence of the total mg per total volume:

(b) (4)

[Redacted]

2. Revise the route of administration warning statement to read as follows for the container labels and carton labeling: “For Infiltration ONLY. Not for administration by any other route of administration”
 3. Remove the strength statement that reads (b) (4)
- [Redacted]
4. Revise the labels and labeling of the (b) (4) sizes to provide added differentiation between the strengths. Currently, the two sizes are differentiated with colors that look similar (green versus blue). Added differentiation is needed to help distinguish the two different total

drug contents during drug selection, preparation and administration, and to minimize the risk of wrong strength selection during the drug use process. Revise the colors so they are not so similar, and add the selected colors to other elements of the container label and carton labeling to emphasize the differentiation between the two strengths, (b) (4)

5. Consider revising the NDC numbers for the two proposed sizes. (b) (4)

4 REFERENCES

1. Miller, C. OSE Review #2008-2006 Exparel Proprietary Name Review dated May 15, 2009
2. Miller, C. OSE Review #2010-2430 Exparel Proprietary Name Review dated February 8, 2011
3. *Drugs@FDA* (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present.

Drugs@FDA contains official information about FDA approved [brand name](#), [generic drugs](#), [therapeutic biological products](#), [prescription](#) and [over-the-counter](#) human drugs and [discontinued drugs](#) and “[Chemical Type 6](#)” approvals.

4. *USAN Stems* (<http://www.ama-assn.org/ama/pub/category/4782.html>)

USAN Stems List contains all the recognized USAN stems.

5. *Division of Medication Error Prevention and Analysis proprietary name requests*

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

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/s/

CATHY A MILLER
06/16/2011

ZACHARY A OLESZCZUK
06/16/2011

CAROL A HOLQUIST
06/16/2011

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: June 1, 2011

TO: Sharon Turner-Rinehardt, Regulatory Project Manager
Arthur Simone, Medical Officer
Division of Anesthesia, Analgesia, and Addiction Products

FROM: John Lee, Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, MD
Branch Chief, Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-496

APPLICANT: Pacira Pharmaceuticals, Inc.

DRUG: Exparel (bupivacaine extended-release liposome injection)

NME: No

INDICATION: Local injection into surgical wound for postsurgical anesthesia

THERAPEUTIC CLASSIFICATION: Standard

CONSULTATION REQUEST DATE: December 10, 2010

INSPECTION SUMMARY GOAL DATE: July 28, 2011

DAAP ACTION GOAL DATE: July 28, 2011

PDUFA DUE DATE: July 28, 2011

I. BACKGROUND

Postsurgical pain control contributes to improved wound healing, earlier patient mobilization, shortened hospital stay, and reduced healthcare cost. Currently available systemic analgesics have considerable drawbacks; for example, opioids have significant adverse effects, including respiratory depression, hypotension, nausea, vomiting, central nervous system depression, pruritus, and constipation.

Bupivacaine is a long-acting local anesthetic commonly used for postsurgical analgesia. However, its duration of local analgesia is limited, usually to no more than 12 hours. While many delivery systems have been developed to extend the duration of analgesia, they typically require an indwelling catheter, all with the associated inconvenience and risks of infection. The formulation of bupivacaine presented in this NDA (Exparel) may be given conveniently as a single injection after or during surgery to provide adequate, continuous, and extended pain relief with minimal breakthrough pain, and to reduce the need for supplemental opioids.

Of two placebo-controlled pivotal phase 3 studies that support the effectiveness of Exparel for local surgical wound analgesia, SKY042-C-316 (Study C-316) was the major study (multicenter, randomized, double-blind, parallel-group, placebo-controlled) supporting NDA 22-496 that included an evaluation of the highest dose proposed for regulatory approval (300 mg). A single dose of the study medication (local intraoperative injection) was compared with placebo for extended (days) postsurgical pain control after hemorrhoidectomy in adults. Compared with placebo, Exparel was associated with a statistically significant reduction in pain through 72 hours (area under the curve, pain intensity versus time; $p < 0.0001$), with a similar adverse event profile and without an appreciable adverse effect on wound healing.

Among the clinical sites that participated in Study C-316 (conducted in Georgia, Poland, and Serbia), 4 sites in Georgia with the largest treatment effect were selected for clinical inspection; the efficacy and safety data from the 4 sites were considered critical to the approvability of the NDA as proposed by the applicant.

II. INSPECTION RESULTS

Four clinical study sites in Georgia were inspected in support of this NDA review, as summarized in the table below:

Key to Classification:

NAI = no deviation from regulations

VAI = deviation from regulations

OAI = significant deviation from regulations and/or data unreliable

Pending:

Preliminary classification based on communication with the field investigator; final establishment inspection report has not been received from the field office and DSI's complete review of the report remains pending as of this inspection summary

	Clinical Investigator Site	Protocol (Site / Subjects)	Inspection Date	Classification
1	Baadur Mosidze, MD JSK K. Eristavi National Center of Cinical and Experimental Surgery 5 Chachava str. 0159 Tbilisi, Republic of Georgia	SKY-0402-C-316 Site 10 40 subjects	Mar 4 - 10 2011	pending NAI
2	Gia Mukhashavria, MD Society with Limited Responsibility Proctology Center 29 Vazha-Pshavela ave, 0160 Tbilisi, Republic of Georgia	SKY-0402-C-316 Site 11 2 subjects	Mar 1 - 3 2011	pending NAI
3	Rema Gvamichava, MD Chemotherapy and Immunotherapy Clinic – Medulla 6 Jikia str. 0186 Tbilisi, Republic of Georgia	SKY-0402-C-316 Site 12 14 subjects	Mar 11 - 15 2011	pending NAI
4	Erckle Tchubabria, MD Purulent Surgery Dept of Tbilisi State Medical University Alexandre Aladashvili University Clinic #1 103 Uznadze str. 0102 Tbilisi, Republic of Georgia	SKY-0402-C-316 Site 13 16 subjects	Mar 16 - 17 2011	pending NAI

1. Baadur Mosidze (Site 10)

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, adverse event reporting, adherence to protocol and applicable regulations
- Data verification: primary efficacy endpoint, adverse events, concomitant medications, protocol deviations, randomization, and subject discontinuations
- Subjects: 51 subjects were screened, 40 enrolled in study, and 40 completed the study. Complete records were reviewed for 18 subjects.

b. General observations and comments:

- No significant deficiencies were observed and a Form FDA 483 was not issued. IRB oversight and study monitoring appeared to be adequate.
- Primary efficacy endpoint data were verifiable, as compared among source documents, case report forms, and data listings. There was no evidence of adverse event underreporting.
- The study appeared to be well-performed at this site by the PI and the study team. Study records appeared to be complete, including source data; only a few minor, non-significant discrepancies were detected. All subjects appeared to have been consented properly.

c. Assessment of data integrity: No significant regulatory violations were noted in the conduct of the study at this site. Data from this study site appear reliable.

2. Gia Mukhashavria (Site 11)

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, adverse event reporting, adherence to protocol and applicable regulations
- Data verification: primary efficacy endpoint, adverse events, concomitant medications, protocol deviations, randomization, and subject discontinuations
- Subjects: 3 subjects were screened, 2 enrolled in study, and 2 completed the study. Complete records were reviewed for 2 subjects.

b. General observations and comments:

- No significant deficiencies were observed and a Form FDA 483 was not issued. IRB oversight and study monitoring appeared to be adequate.
- Primary efficacy endpoint data were verifiable, as compared among source documents, case report forms, and data listings. There was no evidence of adverse event underreporting.
- The study appeared to be well-performed at this site by the PI and the study team. Study records appeared to be complete, including source data; no discrepancies were detected. All subjects appeared to have been consented properly.

c. Assessment of data integrity: No significant regulatory violations were noted in the conduct of the study at this site. Data from this study site appear reliable.

3. Rema Gvamichava (Site 12)

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, adverse event reporting, adherence to protocol and applicable regulations

- Data verification: primary efficacy endpoint, adverse events, concomitant medications, protocol deviations, randomization, and subject discontinuations
 - Subjects: 19 subjects were screened, 14 enrolled in study, and 14 completed the study. Complete records were reviewed for 14 subjects.
- b. General observations and comments:
- No significant deficiencies were observed and a Form FDA 483 was not issued. IRB oversight and study monitoring appeared to be adequate.
 - Primary efficacy endpoint data were verifiable, as compared among source documents, case report forms, and data listings. There was no evidence of adverse event underreporting.
 - The study appeared to be well-performed at this site by the PI and the study team. Study records appeared to be complete, including source data; no discrepancies were detected. All subjects appeared to have been consented properly.
- c. Assessment of data integrity: No significant regulatory violations were noted in the conduct of the study at this site. Data from this study site appear reliable.

4. Erckle Tchubabria (Site 13)

- a. What was inspected:
- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring, IRB oversight, adverse event reporting, adherence to protocol and applicable regulations
 - Data verification: primary efficacy endpoint, adverse events, concomitant medications, protocol deviations, randomization, and subject discontinuations
 - Subjects: 19 subjects were screened, 16 enrolled in study, and 16 completed the study. Complete records were reviewed for 16 subjects.
- b. General observations and comments:
- No significant deficiencies were observed and a Form FDA 483 was not issued. IRB oversight and study monitoring appeared to be adequate.
 - Primary efficacy endpoint data were verifiable, as compared among source documents, case report forms, and data listings. There was no evidence of adverse event underreporting.
 - The study appeared to be well-performed at this site by the PI and the study team. Study records appeared to be complete, including source data; no discrepancies were detected. All subjects appeared to have been consented properly.
- c. Assessment of data integrity: No significant regulatory violations were noted in the conduct of the study at this site. Data from this study site appear reliable.

Note: Observations noted above for all four sites are based on preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In support of this NDA review, the conduct of Study SKY-0402-C-316 was inspected at four clinical sites in Republic of Georgia. No significant deficiencies were noted and a Form FDA 483 was not issued at any of the inspected study sites. At all four sites inspected, the study appeared to have been conducted in accordance with the study protocol and applicable good clinical practice regulations, including data collection and assurance of subject safety and welfare. The study data appear reliable with respect to the study protocol as written and submitted in the NDA.

Note: For all four inspections, the final EIR from the field has not been received at DSI and the final classification remains pending. The observations noted above are based on preliminary communications with the field investigator. An addendum to this clinical inspection summary will be forwarded to DAAP if the final classification changes from the pending classification or if additional observations of clinical or regulatory significance are discovered after receipt and review of the EIRs.

{See appended electronic signature page}

John Lee, MD
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, MD
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

JONG-HOON LEE
06/01/2011

TEJASHRI S PUROHIT-SHETH
06/01/2011

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

NDA	22496
Generic Name	Bupivacaine HCl
Sponsor	Pacira Pharmaceuticals
Indication	For Single-Dose Local Administration Into The Surgical Wound To Produce Postsurgical Analgesia
Dosage Form	Liposome Injection
Drug Class	Analgesic
Therapeutic Dosing Regimen	(b) (4)
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	Not determined
Application Submission Date	28 Sep 2010
Review Classification	QT Study
Date Consult Received	17 Dec 2010
Clinical Division	DAAP

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No apparent QT prolongation effect of bupivacaine (SKY0402) (300, 450, 600, and 750 mg) was detected in two QT studies (Study SKY0402-C-105 and Study SKY0402-C-107). Bupivacaine appears to be associated with concentration-dependent QTc interval shortening. Similar negative concentration-QT relationships were observed in all tested dose groups across two QT studies (Figure 7 and Figure 8). As shown in Study SKY0402-C-107, the smallest lower bounds of the 2-sided 90% confidence intervals (CI) for the mean differences between SKY0402 (600 and 750 mg) and placebo, per ICH E14 analysis, were -9.1 and -11.9 ms, respectively. The detected QTc interval shortening is not considered as clinically meaningful.

The QT effect following the administration of SKY0402 was evaluated in two QT studies - Study SKY0402-C-105 and Study SKY0402-C-107. Study SKY0402-C-107 is an extension of Study SKY0402-C-105. The overall findings were summarized as follows:

- No apparent QT prolongation effect of 300 mg and 450 mg SKY0402 was detected in Study SKY0402-C-105. Study SKY0402-C-105 was a single center, randomized, 2-stage (placebo/moxifloxacin stage and bupivacaine stage), double-blind, placebo (to moxifloxacin)- and positive-controlled, five-way cross-over trial. A total of 48 healthy subjects received SKY0402 300 mg, SKY0402 450 mg, placebo, and a single oral dose of 400 mg moxifloxacin. The study results for the largest upper bounds of placebo-adjusted, baseline-corrected QTcI ($\Delta\Delta\text{QTcI}$) were summarized in Table 1.
- No apparent QT prolongation effect of 600 mg and 750 mg SKY0402 was detected in Study SKY0402-C-107. Study SKY0402-C-107 was a phase I, single center, sequential dose and open-label study. A total of 16 healthy subjects, who were previously enrolled in Study SKY0402-C-107, received SKY0402 600 mg and 750 mg. The study results for the largest upper bounds of $\Delta\Delta\text{QTcI}$ were summarized in Table 1.
- Conclusions on the QT prolongation effect of SKY0402 up to 750 mg based on Study SKY0402-C-105 and Study SKY0402-C-107 are drawn without assay sensitivity being demonstrated in either of the two QT studies. 1.) Study SKY0402-C-107 did not include a positive control arm (e.g., 400 mg moxifloxacin) to demonstrate assay sensitivity. 2.) Assay sensitivity was not established in the second stage of Study SKY0402-C-105, where the QT effect of SKY0402 was assessed. Even though assay sensitivity in the first stage of Study SKY0402-C-105 was established, as evident by the 24-hour moxifloxacin ECG profile (Figure 4) and the largest lower bound of the two-sided 90% CI of $\Delta\Delta\text{QTcI}$ greater than 5 ms, using the first stage assay sensitivity to claim assay sensitivity in the second stage is not valid. The conclusions on “no apparent QT prolongation effect” are drawn mainly because SKY0402 shortens QT interval in a concentration-dependent manner. To establish assay sensitivity using 400 mg moxifloxacin is only important to quantify small increases in QT interval. Because QT prolongation is not anticipated for drugs shorten QT interval, to demonstrate assay sensitivity is not critical in the QT studies.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds $\Delta\Delta\text{QTcI}$ for SKY0402 (300mg, 450 mg, 600 mg and 750 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (h)	$\Delta\Delta\text{QTcI}$ (ms)	90% CI (ms)
SKY0402 300 mg	96	1.1	(-1.3, 3.5)
SKY0402 450 mg	0	1.4	(-0.9, 3.6)
SKY0402 600 mg	0	3.6	(-0.9, 8.1)
SKY0402 750 mg	0.5	-1.2	(-6.4, 3.9)
Moxifloxacin 400 mg	3	11.0	(9.0, 12.9) *

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 8.1 ms.

Using 750 mg as suprathereapeutic dose yields 40% increase in maximum exposure. In patients with moderate hepatic impairment, the C_{max} increases by 50-60%. The suprathereapeutic dose tested in the trial is slightly (10~ 20%) lower than the maximum exposure achieved in patients with moderate hepatic impairment. Because bupivacaine demonstrates concentration-dependent QTc interval shortening, the maximum exposure in patients with moderate hepatic impairment is unlikely to be associated with meaningful QTc interval prolongation. Because bupivacaine is administered directly into the surgical wound, inadvertent intra-vascular drug administration is possible. However, intravascular administration of bupivacaine changes the intended route of administration. Exposure increase due to overdose or change in route of administration does not need to be covered / investigated by using suprathereapeutic exposure in a TQT study.

2 PROPOSED LABEL

QT-IRT recommends that following language in the label. Our recommendations are suggestions only. We defer final labeling decisions to the review division.

Section 12.2

The effect of bupivacaine 300 mg, 450 mg, 600 mg, and 750 mg on QTc interval was evaluated in two QT studies. The first QT study was a randomized, 2-stage (placebo/moxifloxacin stage and bupivacaine stage), double-blind, placebo (to moxifloxacin)- and positive-controlled, five-way cross-over trial conducted in 48 healthy subjects receiving 300 mg and 450 mg bupivacaine. The second QT study was a sequential dose and open-label study including 16 healthy subjects previously enrolled in the first QT study. No apparent QTc interval prolongation was detected. Bupivacaine appears to be associated with concentration-dependent QTc interval shortening. Suprathereapeutic dose tested in the trial yielded about 40% increase in maximum exposure. In patients with moderate hepatic impairment, the C_{max} increases by 50-60%. The suprathereapeutic dose tested in the trial is slightly (10~ 20%) lower than the maximum exposure achieved in patients with moderate hepatic impairment. Because bupivacaine demonstrates concentration-dependent QTc interval shortening, the maximum exposure in patients with moderate hepatic impairment is unlikely to be associated with meaningful QTc interval prolongation.

3 BACKGROUND

3.1 PRODUCT INFORMATION

SKY0402 consists of microscopic spherical, multivesicular liposomes (DepoFoam® drug delivery system), which is composed of a honeycomb-like structure of numerous non-concentric internal aqueous chambers containing bupivacaine.

3.2 MARKET APPROVAL STATUS

SKY0402's active ingredient (bupivacaine) and inactive ingredient (DepoFoam) are each contained, though separately, in previously approved United States (US) Food and Drug Administration (FDA)-approved products:

1. Bupivacaine HCl has been marketed in the US for over 30 years as Marcaine® (NDA 16-964).
2. DepoFoam is a liposomal extended-release formulation contained in the marketed products DepoCyt® (NDA 21-041, 1999) and DepoDur® (NDA 21-671, 2004). The

form of DepoFoam used in each of the three products – DepoCyt, DepoDur, and SKY0402 – has a slightly different mixture of lipid components. However, unlike the other two products, SKY0402 employs a novel lipid excipient (dierucoylphosphatidylcholine [DEPC]) in its formulation.

3.3 PRECLINICAL INFORMATION

Safety pharmacology studies as per S7A and B guidance were not submitted to this NDA.

3.4 PREVIOUS CLINICAL EXPERIENCE

From NDA, eCTD 2.5.5 and ISS

“In the All Wound Infiltration Studies pool, a total of 823 subjects received SKY0402, which exceeds the minimum of 500 subjects requested by the FDA (see FDA correspondence dated February 9, 2006 and September 27, 2006). There were adequate numbers in the ≥ 65 years of age category (171 subjects), in the ≥ 75 years of age category (47 subjects), and the ASA Class 3-4 category (135 subjects), which fulfills the expectations of the FDA (see FDA correspondence dated February 9, 2006 and September 27, 2006) of evaluating the study drug in >125 subjects per group. These sample sizes are sufficient to allow a meaningful assessment of SKY0402 safety in these subgroups. Clinical experience with SKY0402 has not identified differences in efficacy or safety between elderly and younger patients.”

(b) (4)

“As shown in Table 2, in the SKY0402 All Doses group, the TEAEs reported with an incidence $\geq 2\%$ were nausea (30.5%), constipation (17.1%), vomiting (12.3%), pyrexia (9.2%), dizziness (6.1%), edema peripheral (5.0%), anemia (4.7%), hypotension (4.6%), pruritus (4.0%), tachycardia (3.6%), headache (3.3%), insomnia (3.3%), anemia postoperative (3.2%), muscle spasms (2.8%), hemorrhagic anemia (2.7%), somnolence (2.2%), and procedural pain (2.2%).”

“In the bupivacaine HCl group, the TEAEs reported with an incidence $\geq 2\%$ were nausea (38.7%), constipation (22.9%), vomiting (12.3%), anemia (7.4%), pruritus (7.4%), pyrexia (7.0%), headache (5.2%), insomnia (4.7%), dizziness (4.2%), anemia postoperative (4.2%), edema peripheral (4.2%), hypotension (4.2%), tachycardia (3.9%), procedural pain (3.9%), muscle spasms (3.7%), hemorrhagic anemia (3.4%), pain in extremity (2.5%), hypoesthesia (2.2%), and back pain (2.2%).”

“In the All Wound Infiltration Studies pool, most TEAEs were mild or moderate in severity. The overall incidence of severe TEAEs was 5.1% in the SKY0402 All Doses group, 6.7% in the bupivacaine HCl group, and 3.2% in the placebo group (ISS Section 5.2.2.1.1). The incidence of mild or moderate TEAEs was similar between the SKY0402 All Doses group (39.9% and 16.8%, respectively) and the bupivacaine HCl group (41.9% and 26.2%, respectively), and lowest in the placebo group (28.4% and 11.6%, respectively).”

“Across all studies, there were two deaths reported. Both deaths occurred in Study SKY0402-C-208. Subject 208-032-7002, who received 600 mg SKY0402, died due to hemorrhagic cystitis. The Investigator assessed the death as unrelated to study drug. Subject 208-005-3030, who received 150 mg bupivacaine HCl, died due to a massive pulmonary embolus. The Investigator assessed the death as unlikely related to the study drug (ISS Section 5.3.2.1). A by-subject summary of all serious adverse events (SAEs) in the All Studies pool is presented in ISS

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Table 2: Common Treatment-Emergent Adverse Events (Incidence ≥2%): All Parallel Group Wound Infiltration Studies – SKY0402 Doses Combined and All Doses Groups

System Organ Class Preferred Term	SKY0402		(b) (4)	Bupivacaine HCl		Placebo	
	120 mg (N=97) n (%)	300 mg (N=258) n (%)		Doses Combined [1] (N=568) n (%)	All Doses [2] (N=783) n (%)		(N=406) n (%)
ANY TEAE	54 (55.7)	85 (32.9)		309 (54.4)	410 (52.4)	270 (66.5)	74 (38.9)
GASTROINTESTINAL DISORDERS	41 (42.3)	70 (27.1)		242 (42.6)	316 (40.4)	200 (49.3)	52 (27.4)
NAUSEA	39 (40.2)	48 (18.6)		191 (33.6)	239 (30.5)	157 (38.7)	37 (19.5)
CONSTIPATION	2 (2.1)	29 (11.2)		92 (16.2)	134 (17.1)	93 (22.9)	3 (1.6)
VOMITING	27 (27.8)	20 (7.8)		78 (13.7)	96 (12.3)	50 (12.3)	21 (11.1)
DYSPEPSIA	0 (0.0)	0 (0.0)		5 (0.9)	7 (0.9)	4 (1.0)	1 (0.5)
ANAL HAEMORRHAGE	0 (0.0)	3 (1.2)		3 (0.5)	3 (0.4)	0 (0.0)	4 (2.1)
PAINFUL DEFAECATION	0 (0.0)	2 (0.8)		2 (0.4)	2 (0.3)	1 (0.2)	5 (2.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (4.1)	26 (10.1)		74 (13.0)	104 (13.3)	49 (12.1)	2 (1.1)
PYREXIA	2 (2.1)	21 (8.1)		48 (8.5)	72 (9.2)	30 (7.4)	1 (0.5)
OEDEMA PERIPHERAL	0 (0.0)	7 (2.7)		29 (5.1)	39 (5.0)	17 (4.2)	0 (0.0)
CHILLS	0 (0.0)	3 (1.2)		12 (2.1)	13 (1.7)	8 (2.0)	1 (0.5)
ASTHENIA	0 (0.0)	2 (0.8)		7 (1.2)	9 (1.1)	5 (1.2)	0 (0.0)
FEELING HOT	2 (2.1)	0 (0.0)		3 (0.5)	3 (0.4)	0 (0.0)	0 (0.0)
NERVOUS SYSTEM DISORDERS	20 (20.6)	12 (4.7)		64 (11.3)	100 (12.8)	50 (12.3)	31 (16.3)
DIZZINESS	11 (11.3)	6 (2.3)		33 (5.8)	48 (6.1)	17 (4.2)	25 (13.2)
HEADACHE	5 (5.2)	4 (1.6)		13 (2.3)	26 (3.3)	21 (5.2)	8 (4.2)
SOMNOLENCE	5 (5.2)	2 (0.8)		8 (1.4)	17 (2.2)	2 (0.5)	1 (0.5)
HYPOAESTHESIA	0 (0.0)	1 (0.4)		8 (1.4)	12 (1.5)	9 (2.2)	1 (0.5)
LETHARGY	0 (0.0)	2 (0.8)		9 (1.6)	11 (1.4)	0 (0.0)	0 (0.0)
SYNCOPE	2 (2.1)	0 (0.0)		2 (0.4)	2 (0.3)	4 (1.0)	0 (0.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0 (0.0)	4 (1.6)		54 (9.5)	58 (7.4)	44 (10.8)	0 (0.0)
ANAEMIA	0 (0.0)	2 (0.8)		35 (6.2)	37 (4.7)	30 (7.4)	0 (0.0)
HAEMORRHAGIC ANAEMIA	0 (0.0)	2 (0.8)		19 (3.3)	21 (2.7)	14 (3.4)	0 (0.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (2.1)	7 (2.7)		35 (6.2)	46 (5.9)	34 (8.4)	3 (1.6)
MUSCLE SPASMS	1 (1.0)	2 (0.8)		18 (3.2)	22 (2.8)	15 (3.7)	2 (1.1)

System Organ Class Preferred Term	SKY0402		(b) (4)	Bupivacaine HCl		Placebo	
	120 mg (N=97) n (%)	300 mg (N=258) n (%)		Doses Combined [1] (N=568) n (%)	All Doses [2] (N=783) n (%)		(N=406) n (%)
BACK PAIN	0 (0.0)	4 (1.6)		9 (1.6)	13 (1.7)	9 (2.2)	1 (0.5)
PAIN IN EXTREMITY	1 (1.0)	1 (0.4)		8 (1.4)	11 (1.4)	10 (2.5)	0 (0.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	9 (9.3)	9 (3.5)		41 (7.2)	46 (5.9)	36 (8.9)	7 (3.7)
PRURITUS	3 (3.1)	8 (3.1)		27 (4.8)	31 (4.0)	30 (7.4)	1 (0.5)
ERYTHEMA	1 (1.0)	0 (0.0)		8 (1.4)	9 (1.1)	2 (0.5)	0 (0.0)
PRURITUS GENERALISED	5 (5.2)	1 (0.4)		6 (1.1)	6 (0.8)	4 (1.0)	6 (3.2)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (2.1)	8 (3.1)		33 (5.8)	45 (5.7)	34 (8.4)	0 (0.0)
ANAEMIA POSTOPERATIVE	0 (0.0)	4 (1.6)		16 (2.8)	25 (3.2)	17 (4.2)	0 (0.0)
PROCEDURAL PAIN	0 (0.0)	4 (1.6)		14 (2.5)	17 (2.2)	16 (3.9)	0 (0.0)
POST PROCEDURAL SWELLING	2 (2.1)	0 (0.0)		4 (0.7)	4 (0.5)	1 (0.2)	0 (0.0)
PSYCHIATRIC DISORDERS	0 (0.0)	6 (2.3)		36 (6.3)	42 (5.4)	23 (5.7)	0 (0.0)
INSOMNIA	0 (0.0)	5 (1.9)		22 (3.9)	26 (3.3)	19 (4.7)	0 (0.0)
ANXIETY	0 (0.0)	1 (0.4)		12 (2.1)	14 (1.8)	2 (0.5)	0 (0.0)
CONFUSIONAL STATE	0 (0.0)	0 (0.0)		5 (0.9)	5 (0.6)	3 (0.7)	0 (0.0)
VASCULAR DISORDERS	1 (1.0)	7 (2.7)		24 (4.2)	36 (4.6)	17 (4.2)	1 (0.5)
HYPOTENSION	1 (1.0)	7 (2.7)		24 (4.2)	36 (4.6)	17 (4.2)	1 (0.5)
CARDIAC DISORDERS	0 (0.0)	5 (1.9)		22 (3.9)	28 (3.6)	16 (3.9)	0 (0.0)
TACHYCARDIA	0 (0.0)	5 (1.9)		22 (3.9)	28 (3.6)	16 (3.9)	0 (0.0)
INVESTIGATIONS	5 (5.2)	2 (0.8)		19 (3.3)	20 (2.6)	2 (0.5)	3 (1.6)
BLOOD GLUCOSE INCREASED	0 (0.0)	1 (0.4)		7 (1.2)	8 (1.0)	0 (0.0)	0 (0.0)
HAEMOGLOBIN DECREASED	0 (0.0)	0 (0.0)		6 (1.1)	6 (0.8)	2 (0.5)	0 (0.0)
ALANINE AMINOTRANSFERASE INCREASED	3 (3.1)	1 (0.4)		4 (0.7)	4 (0.5)	0 (0.0)	3 (1.6)
ASPARTATE AMINOTRANSFERASE INCREASED	3 (3.1)	0 (0.0)		3 (0.5)	3 (0.4)	0 (0.0)	2 (1.1)
BLOOD CREATININE INCREASED	2 (2.1)	0 (0.0)		2 (0.4)	2 (0.3)	0 (0.0)	0 (0.0)
RENAL AND URINARY DISORDERS	0 (0.0)	7 (2.7)		12 (2.1)	14 (1.8)	6 (1.5)	0 (0.0)
URINARY RETENTION	0 (0.0)	7 (2.7)		12 (2.1)	14 (1.8)	6 (1.5)	0 (0.0)
METABOLISM AND NUTRITION DISORDERS	2 (2.1)	0 (0.0)		11 (1.9)	12 (1.5)	8 (2.0)	2 (1.1)
DECREASED APPETITE	2 (2.1)	0 (0.0)		6 (1.1)	6 (0.8)	5 (1.2)	2 (1.1)

System Organ Class Preferred Term	SKY0402		(b) (4)	Doses Combined [1] (N=568) n (%)	All Doses [2] (N=783) n (%)	Bupivacaine HCl (N=406) n (%)	Placebo (N=190) n (%)
	120 mg (N=97) n (%)	300 mg (N=258) n (%)					
HYPONATRAEMIA	0 (0.0)	0 (0.0)		5 (0.9)	6 (0.8)	3 (0.7)	0 (0.0)
INFECTIONS AND INFESTATIONS	2 (2.1)	0 (0.0)		7 (1.2)	7 (0.9)	2 (0.5)	2 (1.1)
CELLULITIS	0 (0.0)	0 (0.0)		5 (0.9)	5 (0.6)	2 (0.5)	1 (0.5)
FUNGAL INFECTION	2 (2.1)	0 (0.0)		2 (0.4)	2 (0.3)	0 (0.0)	1 (0.5)

Source: ISS Appendix 18.2, Table 4.15

TEAE = treatment-emergent adverse event.

All parallel group wound infiltration studies include SKY0402 C-317, (b) (4) SKY0402-C-316, SIMPLE Hemorrhoidectomy 312, SKY0402-C-207, SKY0402-C-209, SKY0402-C-201, and (b) (4).

Bupivacaine HCl includes 75 mg, 100 mg, 105 mg, 150 mg, and 200 mg.

At each level of summation (overall, system organ class, preferred term), subjects are only counted once.

Preferred terms are included where at least 2% of subjects reported the event in any treatment group.

[1] Doses Combined includes 120 mg, 300 mg, and (b) (4) SKY0402.

[2] All Doses includes all doses of SKY0402 used in any study.

“Appendix 18.2, Table 4.12. The overall incidence of SAEs in the Safety Population was 25/1307 subjects (1.9%) in the SKY0402 All Doses group, 24/622 subjects (3.9%) in the bupivacaine HCl group, and 2/239 subjects (0.8%) in the placebo group (ISS Section 5.2.4.3 and Section 5.3.2.3).”

“The incidence of SAEs was higher in the combined SKY0402 >300-750 mg dose group (17/339 subjects, 5.0%) than in the combined SKY0402 ≤300 mg dose group (8/1014 subjects, 0.8%). However, the higher incidence of SAEs in the higher SKY0402 dose group is confounded by the preponderance of subjects who underwent more intensive surgical procedures, in (b) (4) in the >300-750 mg SKY0402 group where SAEs are more likely while the control groups contained subjects from all studies including the less intense surgeries where SAEs are less likely. Moreover, a higher rate of SAEs also would be anticipated as greater numbers of ASA Class 3-4 subjects were enrolled in the studies with the more intensive surgeries than the studies with the lower dose groups.”

“Serious AEs reported by more than one subject in the pooled SKY0402 dose groups were cellulitis (three subjects, 0.2%), congestive cardiac failure (two subjects, 0.2%), and sedation (two subjects, 0.2%). In the bupivacaine HCl group, SAEs reported by more than one subject were atrial fibrillation (two subjects, 0.3%), hypoglycemia (two subjects, 0.3%), and deep vein thrombosis (two subjects, 0.3%).”

“**Cardiac Disorders.** An association has been suggested between bupivacaine use at very high concentrations and cardiovascular changes. There are several publications that describe a cardiotoxic threshold for bupivacaine; virtually all of the published thresholds for bupivacaine cardiotoxicity are above 4 mg/L.”

“Cardiac disorders were similar between the SKY0402 All Doses group (53/823 subjects, 6.4%) and the bupivacaine HCl group (26/446 subjects, 5.8%) (Table 3, ISS Section 5.2.1.1.1). There were no TEAEs within the Cardiac Disorders SOC in the placebo group. The incidence of TEAEs was higher in the combined SKY0402 >300 mg -750 mg dose group (30/278 subjects, 10.8%) than in the combined SKY0402 ≤300 mg SKY0402 dose group (23/545 subjects, 4.2%). Although the incidence of TEAEs in the Cardiac Disorders SOC was higher in the >300-750 mg group compared to the bupivacaine HCl group, this is confounded by the preponderance of subjects who underwent more intensive surgical procedures, in (b) (4) the >300-750 mg SKY0402 group where incidental cardiovascular findings are more likely while the control groups contained subjects from all studies including the less intense surgeries where incidental cardiovascular events are less likely.”

“In summary, the overall incidence and types of TEAEs within the Cardiac Disorders SOC were similar between the pooled active treatment groups. There were no TEAEs within the Cardiac

Disorders SOC in the placebo group. SKY0402 did not demonstrate a detectable cardiovascular toxicity signal.”

Table 3: Incidence of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term: All Wound Infiltration Studies – SKY0402 Doses Combined and All Doses Group

System Organ Class Preferred Term	SKY0402			Bupivacaine HCl	Placebo
	≤300 mg (N=545) n (%)	>300-750 mg (N=278) n (%)	All Doses (N=823) n (%)	(N=446) n (%)	(N=190) n (%)
CARDIAC DISORDERS	23 (4.2)	30 (10.8)	53 (6.4)	26 (5.8)	0 (0.0)
TACHYCARDIA	13 (2.4)	19 (6.8)	32 (3.9)	20 (4.5)	0 (0.0)
BRADYCARDIA	8 (1.5)	5 (1.8)	13 (1.6)	4 (0.9)	0 (0.0)
ATRIAL FIBRILLATION	1 (0.2)	1 (0.4)	2 (0.2)	2 (0.4)	0 (0.0)
CARDIAC FAILURE CONGESTIVE	0 (0.0)	2 (0.7)	2 (0.2)	0 (0.0)	0 (0.0)
PALPITATIONS	1 (0.2)	1 (0.4)	2 (0.2)	1 (0.2)	0 (0.0)
ANGINA PECTORIS	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
DIASTOLIC DYSFUNCTION	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
MYOCARDIAL INFARCTION	0 (0.0)	1 (0.4)	1 (0.1)	0 (0.0)	0 (0.0)
SINUS BRADYCARDIA	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
SUPRAVENTRICULAR EXTRASISTOLES	0 (0.0)	1 (0.4)	1 (0.1)	0 (0.0)	0 (0.0)
VENTRICULAR EXTRASISTOLES	0 (0.0)	1 (0.4)	1 (0.1)	0 (0.0)	0 (0.0)
VENTRICULAR TACHYCARDIA	0 (0.0)	1 (0.4)	1 (0.1)	0 (0.0)	0 (0.0)
ARRHYTHMIA	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
CARDIOMEGALY	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
VASCULAR DISORDERS	27 (5.0)	25 (9.0)	52 (6.3)	32 (7.2)	8 (4.2)
HYPOTENSION	17 (3.1)	19 (6.8)	36 (4.4)	17 (3.8)	1 (0.5)
HYPERTENSION	5 (0.9)	2 (0.7)	7 (0.9)	8 (1.8)	0 (0.0)
HAEMATOMA	1 (0.2)	1 (0.4)	2 (0.2)	1 (0.2)	0 (0.0)
FLUSHING	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
HAEMORRHAGE	0 (0.0)	1 (0.4)	1 (0.1)	0 (0.0)	0 (0.0)
HOT FLUSH	1 (0.2)	0 (0.0)	1 (0.1)	2 (0.4)	2 (1.1)
PALLOR	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
PHLEBITIS SUPERFICIAL	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
THROMBOPHLEBITIS	0 (0.0)	1 (0.4)	1 (0.1)	0 (0.0)	1 (0.5)
THROMBOSIS	0 (0.0)	1 (0.4)	1 (0.1)	0 (0.0)	0 (0.0)
DEEP VEIN THROMBOSIS	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.9)	1 (0.5)
ORTHOSTATIC HYPOTENSION	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
PERIPHERAL COLDNESS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
VASODILATATION	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)

Source: ISS, Table 29.

“**Heart rate changes:** There were seven SKY0402-treated subjects across all studies that had cardiac disorders that were assessed as related to study drug: these were five AEs of bradycardia and two AEs of tachycardia. There was no apparent relationship to dose of SKY0402. None of the cardiac AEs were considered SAEs and all were mild or moderate in severity. All AEs recovered or resolved. One subject underwent a VQ scan to rule out pulmonary embolus. None of the subjects in the bupivacaine HCl or placebo groups reported cardiac disorders related to treatment.”

“Adverse drug reactions of HR changes (both bradycardia and tachycardia) in subjects who received SKY0402 >300 mg in all wound infiltration studies where plasma bupivacaine concentrations were collected were reviewed; are listed below.

- 201-036-1100: Bradycardia ($C_{max} < 1000$; no details provided on this case)

- 208-032-4009: Tachycardia ($C_{max} < 1000$; associated with fever)
- 208-032-4047: Tachycardia ($C_{max} < 1000$; associated with fever)
- 208-032-7002: Tachycardia ($C_{max} < 1000$; associated with acute blood loss)
- 208-032-7005: Tachycardia ($C_{max} > 1000$; associated with fever)
- 208-032-7007: Bradycardia ($C_{max} < 1000$; associated with urinary retention)
- 208-032-7012: Tachycardia ($C_{max} > 1000$; associated with acute blood loss)
- 208-032-7032: Tachycardia ($C_{max} > 1000$; associated with acute blood loss)
- 208-032-7034: Tachycardia ($C_{max} < 1000$; associated with acute blood loss)
- 208-032-7102: Tachycardia ($C_{max} > 1000$; associated with acute blood loss)
- 208-032-7104: Bradycardia ($C_{max} > 1000$; associated with nausea)
- 208-132-7030: Tachycardia ($C_{max} > 1000$; no other symptoms/findings)

“As 50% of these occurred in subjects who had C_{max} above 1000 and 50% occurred in subjects who had C_{max} below 1000, these did not appear to be related to a C_{max} cut point of greater or less than 1000. With the exception of one case, (Subject 208-132-7030) these bradycardic or tachycardic instances were always associated with clinical events/conditions to account for the HR change.”

“Additionally, the AE profile in all subjects who had C_{max} above 1000 was reviewed, and no consistent cardiac or CNS profile emerged. In summary, the AE database shows no clear signal of any clinically important cardiac related AEs related to the use of SKY0402.”

“Deaths. No cardiac arrests and no sudden deaths were noted program-wide in any of the treatment groups throughout the entirety of the program. There were two deaths in the program: Subject 208-032-7002, a 58-year-old female who died of hemorrhagic cystitis 10 days after study drug administration, had received SKY0402 600 mg; and Subject 208-005-3030, a 71-year-old female who died of massive pulmonary embolus 3 days after study drug administration, had received bupivacaine 150 mg.”

Reviewer’s comments: No syncope, seizure or sudden cardiac deaths were reported. One case of ventricular tachycardia was reported in the >300-750- mg dose group. The most common TEAEs in the Cardiac Disorders SOC were tachycardia and bradycardia. Some of these events were confounded by co-morbidities associated with changes in heart rate (i.e., blood loss, fever, etc.).

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of bupivacaine’s clinical pharmacology.

4 SPONSOR’S SUBMISSION

4.1 OVERVIEW

QT-IRT did not previously review the protocols for the two QT studies. The sponsor submitted the reports for Study SKY0402-C-105 and Study SKY0402-C-107, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

SKY0402-C-105

Evaluation Of The Effects Of Therapeutic And Supra-therapeutic Single Doses Of SKY0402 Given As Subcutaneous Injection On The QT/QTc Interval In Young Healthy Volunteers. A Prospective, Randomized, Placebo- And Positive-controlled, Double Blind, Single-centre, Crossover Phase I Study

SKY0402C-107

Evaluation Of The Effects Of Single Doses Of SKY0402 600 mg and SKY0402 750 mg Given As Subcutaneous Injections On The QT/QTc Interval In Young Healthy Volunteers. A Prospective, Sequential Dose, Open Label, Single-Centre, Phase I Study

4.2.2 Protocol Number

SKY0402-C-105

SKY0402-C-107

4.2.3 Study Dates

SKY0402-C-105

Start Clinical Phase: 23rd May 2007

End Clinical Phase: 10 August 2007

SKY0402-C-107

Start Clinical Phase: 19 January 2008

End Clinical Phase: 08 May 2008

4.2.4 Objectives

SKY0402-C-105

The primary objective of the trial was to compare the effect of a suprathreshold single dose of SKY0402 (450 mg subcutaneous) to placebo, on the largest time-matched mean QTc variation, from baseline to under treatment values, using the best heart rate correction method chosen under blinded conditions (from Individual, Population, Fridericia, and Bazett correction formulae).

Secondary objectives:

- To compare the effects of both dose levels of SKY0402 (300 mg subcutaneous and 450 mg subcutaneous) to placebo at each assessment time point, on uncorrected QT and on QTc using the best heart rate correction method chosen under blinded conditions.
- To describe categorical QT/QTc interval data and qualitative and quantitative ECG variations from baseline.
- To describe and compare the number and the rates of adverse events under each treatment.
- To compare moxifloxacin 400 mg (single dose) to placebo on the largest time-matched mean QTc variation, from baseline to under treatment values, using the best heart rate correction method chosen under blinded conditions, in order to assess the ability of the study to detect differences of clinical significance.

- To describe the pharmacokinetic profiles of SKY0402 and moxifloxacin in the study population.

SKY0402-C-107

The primary objective of the trial was to compare the effect of single doses of SKY0402 600 mg subcutaneous and 750 mg subcutaneous to placebo (the placebo effect on the QTc will be depicted from the original SKY0402-C-105 thorough QTc study) on the largest time-matched mean QTc variation, from baseline to under treatment values, using the best heart rate correction method chosen under blinded conditions (from Individual, Population, Fridericia's and Bazett's correction formulae).

Secondary objectives:

- To compare the effects of both dose levels of SKY0402 (600 mg subcutaneous and 750 mg subcutaneous) on uncorrected QT.
- To describe categorical QT/QTc interval data, and qualitative and quantitative ECG variations from baseline.
- To describe and compare the number and the rates of adverse events under each treatment.
- To describe the pharmacokinetic profiles of SKY0402 in the study population following the single doses of 600 mg subcutaneous and 750 mg subcutaneous.

4.2.5 Study Description

4.2.5.1 Design

SKY0402-C-105

This was a single centre, randomized, double blind, placebo- and positive-controlled, five-way, cross-over study.

SKY0402-C-107

This was Phase I, a single centre, sequential dose, open-label study.

4.2.5.2 Controls

SKY0402-C-105

The sponsor used both placebo (to moxifloxacin) and positive (moxifloxacin) controls in this study.

4.2.5.3 Blinding

SKY0402-C-105

All treatment arms were administered blinded.

SKY0402-C-10

All treatment arms were administered open-label.

4.2.5.4 Treatment Regimen

4.2.5.5 Treatment Arms

SKY0402-C-105

- A single dose of moxifloxacin 400 mg dose on Day 1, in Period 1 or 2.

- A single dose of placebo for moxifloxacin on Day 1, in Period 1 or 2; and single doses on Day -1 in both Period 1 and 2.
- A single subcutaneous injection of SKY0402 300 mg on Day 1 in either Period 3, 4, or 5
- A single subcutaneous injection of SKY0402 450 mg on Day 1 in either Period 3, 4, or 5.
- A single subcutaneous injection of Placebo for SKY0402 on Day 1 in either Period 3, 4, or 5; and single subcutaneous injections on Day -1 of Periods 3, 4, and 5.

SKY0402-C-107

- A single dose of 600 mg given subcutaneously on Day 1 in Period 1.
- A single dose of 750 mg given subcutaneously on Day 1 in Period 2.
- A single dose of placebo administered subcutaneously on Day -1 in either Period 1 or 2.

4.2.5.6 Sponsor's Justification for Doses

SKY0402-C-105

“The results of the preclinical and clinical studies thus far indicated that the therapeutic and suprathreshold doses of SKY0402 selected for this trial (300 mg and 450 mg, respectively) were safe to administer to healthy volunteers with no significant systemic or local toxicities expected.

“The dose of bupivacaine given in clinical circumstances is driven by the surgical procedure and the individual patient. The 300 mg dose selected for this study was expected to be close to the anticipated maximum therapeutic dose of SKY0402.”

SKY0402-C-107

“The recently finished thorough QTc study (protocol SKY0402-C-105) has shown that single 300 mg and 450 mg doses of SKY0402 do not prolong QTc. The doses for that trial were chosen considering the maximum dose bupivacaine is licensed for, clinical practice, and safety of volunteers. However, the plasma levels of bupivacaine achieved with these doses were significantly lower than those normally seen in previous patient studies when the drug had been administered by wound infiltration. The 600 mg and 750 mg doses of SKY0402 administered in this trial were selected in order to achieve the plasma levels normally seen in postoperative patients thus allowing an assessment of the effect of these plasma levels on QTc.”

Reviewer's Comment: The 600-mg dose tested in Study SKY0402-C-107 represents the maximum (b) (4) dose and therefore is acceptable. Using 750 mg as suprathreshold dose yields 40% increase in maximum exposure. In patients with moderate hepatic impairment, the C_{max} increases by 50-60%. The suprathreshold dose tested in the trial is slightly (10~ 20%) lower than the maximum exposure achieved in patients with moderate hepatic impairment. Because bupivacaine demonstrates concentration-dependent QTc interval shortening, the maximum exposure in patients with moderate hepatic impairment is unlikely to be associated with meaningful QTc interval prolongation.

Because bupivacaine is administered directly into the surgical wound, inadvertent intra-vascular drug administration is possible. However, intravascular administration of bupivacaine changes the intended route of administration. Exposure increase due to overdose or change in route of administration does not need to be covered / investigated by using suprathreshold exposure in a TQT study.

4.2.5.7 Instructions with Regard to Meals

For both Study SKY0402-C-105 and Study SKY0402-C-107, in the Run-in phase (Day -2), subjects were served a light standard lunch and a standard dinner at the corresponding times as on Day -1 and Day 1.

Reviewer's Comment: Acceptable. Bupivacaine is administered directly to the local wound. No food effect is anticipated.

4.2.5.8 ECG and PK Assessments

SKY0402-C-105

ECG

“The baseline ECG recordings, at the beginning of each treatment period, were treatment and period specific and baseline ECG values were scheduled to match the “on-treatment” and PK sampling time points. All recordings were in triplicate and were compliant with RPLs SOPs for the correct recording of ECGs in thorough QTc studies.

Pharmacokinetic:

“Blood for analysis of moxifloxacin levels was collected at the following times for each period (Periods 1 and 2 only): pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 hours post-dose. All PK samples were taken after the corresponding ECG recordings.

“Blood collections: blood for pharmacokinetic analysis of SKY0402 (bupivacaine) was collected at the following times for each period (Periods 3, 4, and 5 only): pre-dose, 0.5, 4, 8, 14, 24, 28, 32, 38, 48, 52, 56, 62, 72, 76, 80, 86, and 96 hours post-dose. This corresponded to samples being taken at approximately 9:00, 13:00, 17:00, and 23:00 of Days 1 to 4, and 9:00 on Day 5.”

SKY0402-C-107

ECG

“The baseline ECG recordings, at the beginning of each treatment period, were treatment and period specific and baseline ECG values were scheduled to match the “on-treatment” and PK sampling time points.”

Pharmacokinetic:

“Blood collections: blood for pharmacokinetic analysis of SKY0402 (bupivacaine) were collected at the following times for each period: pre-dose, 0.5, 4, 8, 14, 24, 28, 32, 38, 48, 52, 56, 62, 72, 76, 80, 86, 96, 110, 120, 134, 144, 158, 168, 216, 312, 480 and 600 hours post-dose.”

Reviewer's Comment: Acceptable based on the absorption characteristics of the liposomal formulation.

4.2.5.9 Baseline

The sponsor used time-matched QTc values collected on Day -1 as baseline values for both studies.

4.2.6 ECG Collection

The 12-lead ECGs were recorded using a MAC1200® recorder connected to the MUSE CV® information system. The ECGs were stored electronically on the MUSE CV® information system. ECG printouts were filed in the subject's CRF.

At each time point, the ECGs were recorded in triplicate, to reduce variance and improve the precision of measurement. The triplicates were performed at 1-minute intervals during 3 minutes. Each ECG recording lasted 10 seconds.

Before any ECG recording, the subjects maintained an undisturbed supine resting position for at least 10 minutes. The volunteers avoided postural changes during the ECG recordings. The use of a semi permanent skin marker ensured consistent placement of the leads.

Recordings were clearly identified (Subject ID, theoretical and actual times of ECG recordings), complete (without missing lead), and enabled reading and analyzing of at least 5 complexes per derivation.

All ECGs were reviewed by a Research Physician on an ongoing basis. If a subject showed an abnormal ECG at any stage, repeat recordings may have been made and the abnormality followed to resolution, if required. ECG over-readings were performed by a cardiologist. All ECGs of a given subject were over-read by one cardiologist.

4.2.7 Sponsor's Results

4.2.7.1 Study Subjects

Study SKY0402-C-105

This study planned to enroll 48 subjects who were randomized for at least 40 subjects to complete study periods 3, 4, and 5. Three subjects did not complete the study. Subject 12 and Subject 38 both withdrew their consent for personal reasons, and Subject 26 withdrew due to an unforeseen family emergency. The subject demographic characteristics were summarized in Table 4.

SKY0402-C-107

The aim of this study was to enroll as many subjects as possible who had previously completed SKY0402-C-105, up to a maximum of 46 subjects. In total, 16 subjects were included in this study and all 16 completed the study according to the protocol. The subject demographic characteristics were summarized in Table 5.

Table 4: Subject Demographic Characteristics

	Sequence						All (N = 49)
	I (N = 8)	II (N = 8)	III (N = 8)	IV (N = 8)	V (N = 8)	VI (N = 9)	
Age, years							
Mean	24.00	29.50	25.63	24.88	25.00	26.56	25.94
SD	3.817	6.024	4.470	4.454	5.345	4.275	4.858
Min – Max	20.0 – 29.0	20.0 – 39.0	21.0 – 32.0	20.0 – 33.0	19.0 – 34.0	22.0 – 34.0	19.0 – 39.0
Gender, n (%)							
Male	5 (62.5%)	6 (75.0%)	6 (75.0%)	6 (75.0%)	7 (87.5%)	4 (44.4%)	34 (69.4%)
Female	3 (37.5%)	2 (25.0%)	2 (25.0%)	2 (25.0%)	1 (12.5%)	5 (55.6%)	15 (30.6%)
Weight, kg							
Mean	68.74	72.36	75.93	74.95	68.33	68.01	71.32
SD	7.257	8.612	12.261	10.965	7.877	11.000	9.887
Min – Max	57.1 – 81.0	60.7 – 85.5	62.0 – 101.1	63.0 – 93.6	57.0 – 79.9	51.7 – 80.8	51.7 – 101.1
Height, cm							
Mean	169.99	170.35	176.40	173.69	175.23	169.12	172.39
SD	11.036	7.646	7.175	6.577	7.152	9.964	8.489
Min – Max	150.0 – 183.0	162.0 – 183.9	166.7 – 190.0	167.5 – 188.0	165.0 – 184.0	153.0 – 188.9	150.0 – 190.0
BMI, kg/m²							
Mean	23.83	24.98	24.33	24.74	22.21	23.36	23.89
SD	1.689	2.805	2.966	2.391	1.583	2.800	2.495
Min – Max	22.4 – 27.6	21.3 – 29.0	20.2 – 28.4	20.7 – 28.1	19.8 – 24.7	19.1 – 27.0	19.1 – 29.0
Ethnic Group, n (%)							
Caucasian	8 (100%)	7 (87.5%)	8 (100%)	8 (100%)	8 (100%)	9 (100%)	48 (98.0%)
Other	0 (0.0%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)

Source: Section 14.1, Table 14.1.1 and Appendix 16.2.4, Listing 16.2.2.2

SD = standard deviation; Min = minimum; Max = maximum.

Sequence I = Moxifloxacin 400mg/Placebo1/SKY0402 300mg/SKY0402 450mg/Placebo2

Sequence II = Moxifloxacin 400mg/Placebo1/SKY0402 450mg/Placebo2/SKY0402 300mg

Sequence III = Moxifloxacin 400mg/Placebo1/Placebo2/SKY0402 300mg/SKY0402 450mg

Sequence IV = Placebo1/Moxifloxacin 400mg/SKY0402 300mg/SKY0402 450mg/Placebo2

Sequence V = Placebo1/Moxifloxacin 400mg/SKY0402 450mg/Placebo2/SKY0402 300mg

Source: CSR, Table 6, Page 61

Table 5: Subject Demographic Characteristics

	Description/Summary Statistics
	(N=16)
Age, years	
Mean	27.19
SD	5.671
Min – Max	20.0 – 40.0
Height, cm	
Mean	173.43
SD	11.716
Min – Max	152.8 – 196.0
Weight, kg	
Mean	71.13
SD	12.395
Min – Max	50.5 – 102.9
BMI, kg/m²	
Mean	23.51
SD	1.991
Min – Max	20.3 – 27.1
Race, n (%)	
White	12 (75.0%)
Asian	4 (25.0%)
Ethnicity, n (5%)	
Hispanic	1 (6.5%)
Non-Hispanic	15 (93.8%)
Sex, n (%)	
Female	6 (37.5%)
Male	10 (62.5%)

Source: Section 14.1, Table 14.1.1 and Appendix 16.2.4, Listing 16.2.2.2.

SD = standard deviation; Min = minimum; Max = maximum. Race was captured differently in this study (SKY0402-C-107) compared to the SKY0402-C-105 study. All subjects who participated in this study (SKY0402-C-107) also participated in the SKY0402-C-105 study and were Caucasian.

Source: CSR, Table 7, page 59.

4.2.7.2 Statistical Analyses

4.2.7.2.1 Primary Analysis

SKY0402-C-105:

The primary endpoint was the largest time-matched mean difference between SKY0402 450 mg and placebo in QTcI. The sponsor used a general linear mixed model and the result presented in Table 6. The model included baseline as a covariate, treatment, gender, period and sequence as fixed effects, and subject as random effect. The largest time-matched mean difference between SKY0402 450 mg and placebo was -2.5 ms (occurred at 32 hours) with a 90% CI of -3.9 to -1.0 ms, indicating no QTc prolonging effect. The sponsor also presented the results for the mean difference between SKY0402 300 mg and placebo (see Table 7). The largest time-matched mean QTcI difference between moxifloxacin 400 mg and placebo was 11.9 ms with a 90% CI of 9.9 to 14.0 ms, demonstrating a significant effect of moxifloxacin on QTc interval (see Table 8).

Table 6: Sponsor's Results of $\Delta\Delta$ QTcI for SKY0402 450 mg (SKY0402-C-105)

Time (hours)	Estimate	Standard Error	90% CI	
			Lower	Upper
0.00	0.15	1.22	-1.89	2.19
0.50	0.08	1.21	-1.95	2.10
4.00	0.71	1.18	-1.26	2.68
8.00	-0.52	1.00	-2.18	1.14
14.00	-2.22	1.22	-4.26	-0.18
24.00	-1.40	1.17	-3.34	0.54
28.00	0.12	1.05	-1.64	1.87
32.00	-2.45	0.88	-3.92	-0.97
38.00	-0.54	1.09	-2.36	1.27
48.00	-0.64	1.28	-2.77	1.50
52.00	-0.77	0.95	-2.36	0.81
56.00	-1.35	1.04	-3.08	0.39
62.00	-0.05	1.08	-1.86	1.76
72.00	-0.12	1.04	-1.85	1.62
76.00	0.95	1.19	-1.03	2.92
80.00	-1.48	1.04	-3.22	0.26
86.00	-0.58	1.21	-2.61	1.44
96.00	0.09	1.37	-2.19	2.37

Source: Table 11, page 80/3459

Table 7: Sponsor's Results of $\Delta\Delta QTCI$ for SKY0402 300 mg (SKY0402-C-105)

Time (hours)	Estimate	Standard Error	90% CI	
			Lower	Upper
0.00	0.17	1.24	-1.90	2.23
0.50	0.78	1.21	-1.23	2.79
4.00	0.32	1.19	-1.66	2.30
8.00	-2.24	1.00	-3.91	-0.56
14.00	-0.82	1.22	-2.86	1.22
24.00	-0.20	1.18	-2.17	1.77
28.00	-1.59	1.06	-3.35	0.17
32.00	-1.54	0.89	-3.02	-0.05
38.00	0.26	1.09	-1.55	2.08
48.00	-0.69	1.30	-2.86	1.47
52.00	-1.71	0.95	-3.29	-0.12
56.00	-1.38	1.05	-3.13	0.36
62.00	0.67	1.09	-1.15	2.49
72.00	0.14	1.06	-1.62	1.90
76.00	-0.40	1.19	-2.38	1.58
80.00	-1.12	1.05	-2.87	0.63
86.00	-1.43	1.21	-3.46	0.59
96.00	0.81	1.39	-1.50	3.12

Table 8: Sponsor's Results of $\Delta\Delta QTCI$ for Moxifloxacin 400 mg (SKY0402-C-105)

Time (hours)	Estimate	Standard Error	90% CI	
			Lower	Upper
0.00	0.05	1.37	-2.25	2.35
0.50	7.87	1.77	4.89	10.85
1.00	11.91	1.21	9.87	13.96
1.50	11.86	1.36	9.57	14.16
2.00	11.11	1.35	8.84	13.38
2.50	10.30	1.28	8.16	12.45
3.00	11.89	1.16	9.93	13.84
4.00	10.33	0.96	8.71	11.94
5.00	8.11	0.97	6.47	9.74
6.00	8.04	1.09	6.20	9.87
8.00	7.39	1.06	5.61	9.18
10.00	7.57	0.93	6.02	9.13
12.00	7.74	0.91	6.21	9.27
24.00	4.92	0.94	3.33	6.51

Source: Table 13, page 82/3459

SKY0402-C-107

The primary endpoint was the largest time-matched mean difference between SKY0402 750 mg and placebo in QTcI. The treatment effect of SKY0402 as compared to placebo on the QTc change per time point was estimated using a general linear mixed model adapted to the cross-over design, with treatment, gender, period and sequence as fixed effects, baseline as a covariate,

and subject as random effect. The largest time-matched mean QTcI difference between SKY0402 750 mg and placebo was -7.7 ms with a 90% confidence interval of between -11.9 and -3.5 ms (see Table 9). The largest time-matched mean difference in QTcI between SKY0402 600 mg and placebo was -3.6 ms with a 90% confidence interval of between -7.3 and 0.1 ms (see Table 10). Therefore, the sponsor concluded that the SKY0402 600 mg and 750 mg did not prolong QTc interval.

Table 9: Sponsor’s Results of $\Delta\Delta$ QTcI for SKY0402 750 mg (SKY0402-C-107)

Time (hours)	Estimate	Standard Error	90% CI	
			Lower	Upper
0.00	-2.88	3.21	-8.35	2.59
0.50	-0.90	3.08	-6.13	4.34
4.00	-0.39	2.72	-5.01	4.22
8.00	-4.73	2.70	-9.32	-0.14
14.00	-6.76	3.07	-11.92	-1.60
24.00	-3.71	2.80	-8.49	1.08
28.00	-3.88	2.69	-8.45	0.68
32.00	-7.67	2.47	-11.87	-3.46
38.00	-3.21	2.38	-7.21	0.79
48.00	-3.20	3.11	-8.50	2.11
52.00	-4.19	2.38	-8.23	-0.14
56.00	-5.10	2.47	-9.31	-0.89
62.00	-5.86	2.94	-10.85	-0.86
72.00	-4.42	2.38	-8.48	-0.37
76.00	-7.06	2.15	-10.71	-3.40
80.00	-5.17	1.81	-8.24	-2.10
86.00	-6.07	3.39	-11.77	-0.36
96.00	-2.37	2.77	-7.08	2.34

Table 10: Sponsor’s Result of $\Delta\Delta$ QTcI for SKY0402 600 mg (SKY0402-C-107)

Time (hours)	Estimate	Standard Error	90% CI	
			Lower	Upper
0.00	2.03	3.36	-3.68	7.74
0.50	1.03	3.19	-4.39	6.44
4.00	-3.51	2.73	-8.13	1.12
8.00	0.63	2.78	-4.09	5.36
14.00	-0.36	3.08	-5.53	4.81
24.00	-0.94	2.93	-5.92	4.04
28.00	-3.20	2.69	-7.78	1.37
32.00	-1.82	2.55	-6.14	2.51
38.00	0.37	2.39	-3.65	4.38
48.00	0.75	3.24	-4.75	6.26
52.00	-2.79	2.39	-6.84	1.26
56.00	-2.92	2.50	-7.17	1.32
62.00	2.35	2.94	-2.66	7.36
72.00	-2.44	2.49	-6.66	1.79
76.00	-3.60	2.16	-7.27	0.07
80.00	-3.06	1.87	-6.23	0.11
86.00	-3.29	3.45	-9.10	2.51
96.00	0.51	2.92	-4.44	5.47

Reviewer's Comments:

(b) (4)

The positive control should have an effect on the mean QT/QTc interval of about 5 ms which is evidenced by the largest lower bound being greater than 5 ms. The multiple endpoint adjustment should also be considered.

Study SKY0402-C-107 consisted only two doses of the study drug arm given in a sequential order. There is no randomization and no positive and negative controls.

Our independent analysis results are presented in Section 5.2.

4.2.7.3 Safety Analysis

Study SKY0402-C-105

Subject 30 suffered a moderate adverse event (acute hepatitis) following SKY0402 450 mg treatment. A second subject (Subject 47) suffered a severe adverse event (syncope) prior to her first dose on Period 1 Day 1 (moxifloxacin placebo). She recovered from the event and continued on the study.

Following moxifloxacin 400 mg treatment, the most frequently reported adverse event was nausea (3 [6.3%] subjects). Abdominal pain, allergy to arthropod bite, dizziness, syncope, and dry throat were each reported by 1 (2.1%) subject.

Following SKY0402 450 mg treatment, the most frequently reported adverse events were headache and pharyngolaryngeal pain, each reported by 3 (6.4%) subjects. Abdominal pain and injection site irritation were each reported by 2 (4.3%) subjects, chapped lips, dyspepsia, dry lips, lip haemorrhage, hyperhidrosis, injection site pain, malaise, acute hepatitis, and back pain were each reported by 1 (2.1%) subject.

Following SKY0402 300 mg treatment, the most frequently reported adverse event was abdominal pain (2 [4.3%] subjects). Dyspepsia, injection site irritation, injection site pain, allergy to arthropod bite, influenza, myalgia, headache, dysmenorrhoea, generalized rash, and skin irritation were each reported by 1 (2.1%) subject.

Following SKY0402 placebo treatment, the most frequently reported adverse event was headache (4 [8.5%] subjects). Musculoskeletal pain, pharyngolaryngeal pain, and pruritus generalized were each reported by 1 (2.1%) subject.

SKY0402-C-107

All subjects received a single subcutaneous injection of SKY0402 600 mg on Day 1 of Period 1 and SKY0402 750 mg on Day 1 of Period 2.

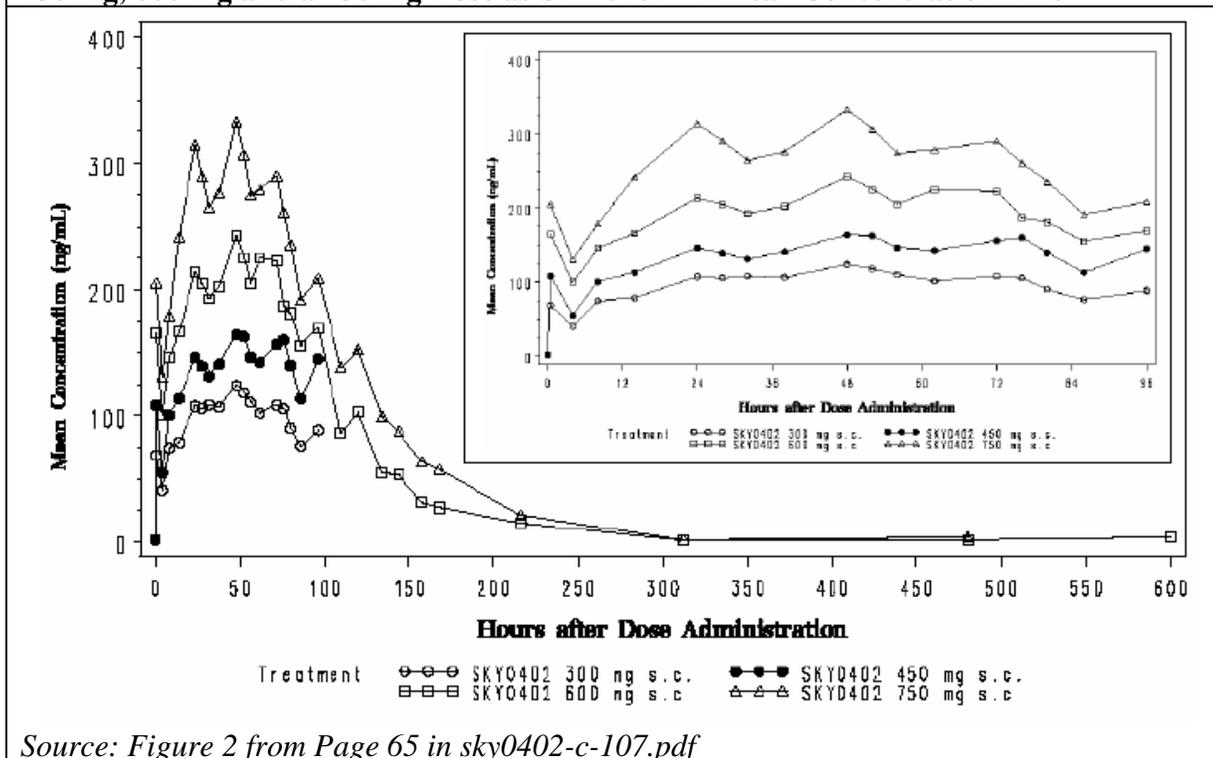
There were no serious adverse events reported during the study and no subject was withdrawn from the study due to a drug-related adverse event. In total, 43 adverse events were reported by 10 subjects of which 8 subjects had treatment related adverse events. The most frequently reported adverse events in both treatment groups were nervous system disorders, injury, poisoning and procedural complications, and gastrointestinal disorders.

4.2.7.4 Clinical Pharmacology

4.2.7.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 11 (SKY0402) and Table 12 (moxifloxacin). The C_{max} and AUC_{0-96} parameters for all four doses appeared to be dose proportional. C_{max} and AUC values in the thorough QT study were 1.4-fold higher following administration of 750 mg SKY0402, the suprathereapeutic dose, compared with 600 mg SKY0402, the intended clinical dose. Figure 1 shows the mean plasma SKY0402 concentrations versus time after single 300-mg, 450-mg, 600-mg and 750-mg dose.

Figure 1: Mean Plasma SKY0402 Concentrations Versus Time After a Single 300 mg, 450 mg, 600 mg and a 750 mg Dose as SKY0402 – Linear Concentration Axis



Source: Figure 2 from Page 65 in sky0402-c-107.pdf

Table 11: Summary of Pharmacokinetic Parameters for SKY0402 300 mg, 450 mg, 600 mg, and 750 mg

	SKY0402			
	300 mg (N = 16)	450 mg (N = 16)	600 mg (N = 16)	750 mg (N = 16)
C_{max} (ng/mL)				
Mean (±SD)	153.01 (52.90)	216.81 (74.18)	310.15 (114.00)	427.75 (142.32)
CV (%)	34.57	34.21	36.76	33.27
Min	95.05	117.83	153.53	178.19
Max	260.83	407.58	608.82	646.76
AUC₀₋₉₆ (ng.hr/L)				
Mean (±SD)	9258.65 (2275.02)	12933.75 (4311.62)	18396.52 (4859.97)	24612.71 (7560.05)
CV (%)	24.57	33.34	26.42	30.72
Min	5449.68	6636.78	10647.37	12775.90
Max	13127.54	22317.81	26840.48	39200.35
t_{max} (hours)				
Median	52.00	62.00	52.00	52.00
Min	24.00	0.50	0.50	0.50
Max	96.00	96.00	96.00	120.00

Source: Section 14, Table 14.2.5.1.2.1a, Table 14.2.5.1.2.4a, Table 14.2.5.1.2.5a.

SD = standard deviation; CV=coefficient of variation; Min = minimum; Max = maximum.

Source: Table 9 from Page 66 in sky0402-c-107.pdf

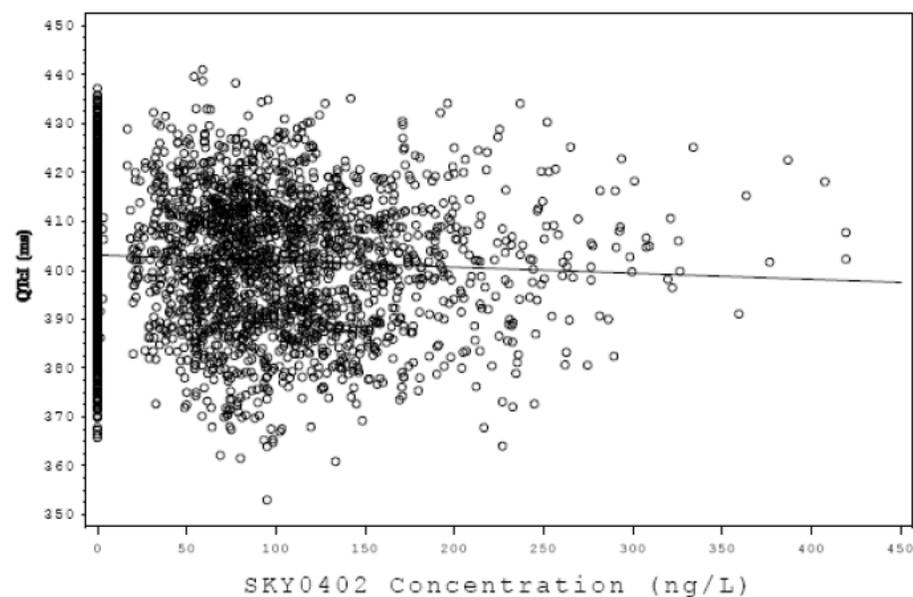
Table 12: Summary of Pharmacokinetic Parameters for Moxifloxacin 400 mg.

	Moxifloxacin
	400 mg (N = 48)
C_{max} (µg/mL)	
Mean (±SD)	2.51 (0.59)
CV (%)	23.36
Min	1.69
Max	4.20
AUC₀₋₂₄ (µg/mL.h)	
Mean (±SD)	24.89 (4.50)
CV (%)	18.08
Min	17.88
Max	38.19
t_{max} (hours)	
Median	1.25
Min	0.50
Max	4.00
t_{1/2} (hours)	
Mean (±SD)	10.46 (1.85)
CV (%)	17.66
Median	10.38
Min	6.31
Max	15.25

4.2.7.4.2 Exposure-Response Analysis

The relationship between QTcI and SKY0402 concentrations are shown in Figure 2.

Figure 2: Relationship Between QTcI and SKY0402 in Plasma in Sky0402-c-105.



Source: Figure 3 from Page 105 in sky0402-c-105.pdf

Reviewer’s Analysis: A plot of $\Delta\Delta QTcI$ vs. drug concentrations is presented in **Figure 8**

5 REVIEWERS’ ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

5.2 STATISTICAL ASSESSMENTS

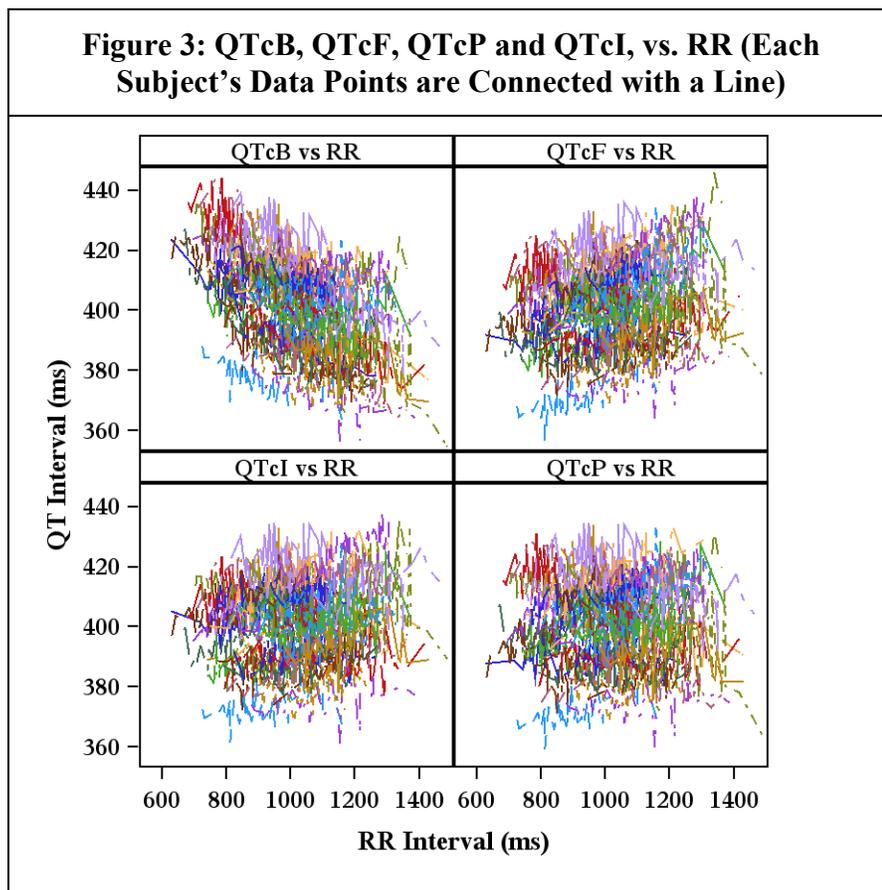
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 13 for SKY0402-C-105 study, it appears that QTcI is the best correction method. We also evaluated SKY0402-C-107 study; the MSSS results produced by QTcI, QTcF and QTcP were very similar. To be consistent with the sponsor’s proposed primary endpoint, this reviewer used QTcI as the primary correction method.

Table 13: Average of Sum of Squared Slopes for Different QT-RR Correction Methods (SKY0402-C-105)

Treatment Group	Correction Method							
	QTcB		QTcF		QTcI		QTcP	
	N	MSSS	N	MSSS	N	MSSS	N	MSSS
Moxifloxacin 400 mg	48	0.0021	48	0.0012	48	0.0007	48	0.0008
Placebo	49	0.0026	49	0.0014	49	0.0007	49	0.0010
SKY0402 300 mg	46	0.0020	46	0.0021	46	0.0014	46	0.0013
SKY0402 450 mg	47	0.0020	47	0.0018	47	0.0011	47	0.0011
All	49	0.0018	49	0.0011	49	0.0005	49	0.0007

The QT-RR interval relationship is presented in Figure 3 together with the Bazett’s

(QTcB), Fridericia (QTcF), Individual correction (QTcI), and Population-based correction (QTcP).



5.2.1 QTc Analysis

SKY0402-C-105

The statistical reviewer used mixed model to analyze the Δ QTcI effect. The model includes treatment, period and sequence as fixed effects, subject as random effect and baseline values as a covariate. The analysis results are listed in Table 14. The largest upper bounds of the two-sided 90% CI for the mean differences between SKY0402 300 mg and placebo, and between SKY0402 450 mg and placebo are 3.5 ms and 3.6 ms, respectively.

Table 14: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for SKY0402 300 mg and SKY0402 450 mg (SKY0402-C-105)

		Treatment Group					
		SKY0402 300 mg			SKY0402 450 mg		
	Placebo	Δ QTc	$\Delta\Delta$ QTc		Δ QTc	$\Delta\Delta$ QTc	
Time (h)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
0	-3.3	-2.2	1.1	(-1.1, 3.4)	-2.0	1.4	(-0.9, 3.6)
0.5	-3.0	-2.8	0.2	(-2.7, 3.0)	-4.0	-1.0	(-3.9, 1.9)
4	-1.6	-1.8	-0.2	(-2.0, 1.6)	-0.7	0.9	(-0.9, 2.7)
8	-2.3	-5.4	-3.1	(-5.3, -0.9)	-3.2	-0.9	(-3.1, 1.3)
14	0.2	0.3	0.0	(-2.2, 2.2)	-1.5	-1.8	(-4.0, 0.4)
24	-0.3	-2.2	-1.9	(-4.4, 0.5)	-3.1	-2.8	(-5.2, -0.3)
28	-2.8	-4.9	-2.1	(-4.0, -0.2)	-2.5	0.3	(-1.6, 2.2)
32	-1.4	-3.5	-2.2	(-4.6, 0.3)	-3.8	-2.4	(-4.8, -0.0)
38	-3.5	-3.1	0.4	(-1.9, 2.6)	-4.2	-0.7	(-3.0, 1.5)
48	-2.1	-3.9	-1.8	(-4.2, 0.6)	-4.5	-2.3	(-4.8, 0.1)
52	-4.3	-6.1	-1.8	(-3.9, 0.3)	-3.9	0.3	(-1.8, 2.4)
56	-2.3	-4.4	-2.0	(-4.5, 0.4)	-3.4	-1.1	(-3.5, 1.3)
62	-0.2	0.8	1.0	(-1.4, 3.3)	-0.6	-0.4	(-2.7, 1.9)
72	-0.7	-1.8	-1.1	(-3.9, 1.8)	-2.0	-1.3	(-4.1, 1.5)
76	-3.2	-3.8	-0.5	(-2.7, 1.7)	-2.5	0.8	(-1.4, 2.9)
80	-3.3	-5.2	-1.9	(-4.4, 0.6)	-4.4	-1.1	(-3.5, 1.4)
86	-0.2	0.1	0.4	(-2.1, 2.8)	-0.5	-0.2	(-2.6, 2.2)
96	-2.8	-1.7	1.1	(-1.3, 3.5)	-3.6	-0.8	(-3.2, 1.6)

SKY0402-C-107

This is a sequential study which consisted of only the study drug arm with two doses. The sponsor stated the placebo effect on the QTc depicted from the original SKY0402-C-105 thorough QTc study. This statistical reviewer used the same model to analyze the Δ QTcI effect. The analysis results are listed in Table 15. The largest upper bounds of the two-sided 90% CI for the mean differences between SKY0402 600 mg and placebo, and between SKY0402 750 mg and placebo are 8.1 ms and 3.9 ms, respectively. Since placebo administered in the previous study SKY0402-C-105 was at least a month earlier, we believe a single delta analysis might provide a more accurate estimate. Based on our analyses, both the largest upper 90% confidence bounds of Δ QTcI and $\Delta\Delta$ QTcI are less than 10 ms.

Table 15: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for SKY0402 600 mg and SKY0402 750 mg (SKY0402-C-107)

		Treatment Group					
		SKY0402 600 mg			SKY0402 750 mg		
	Placebo	Δ QTc	$\Delta\Delta$ QTc		Δ QTc	$\Delta\Delta$ QTc	
Time (h)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
0	-3.2	0.3	3.6	(-0.9, 8.1)	-5.3	-2.1	(-6.5, 2.3)
0.5	-1.6	0.2	1.8	(-3.5, 7.0)	-2.8	-1.2	(-6.4, 3.9)
4	-0.9	-4.1	-3.2	(-8.3, 1.8)	-2.2	-1.3	(-6.4, 3.7)
8	-0.8	-2.4	-1.6	(-7.1, 3.9)	-6.2	-5.4	(-10.9, 0.1)
14	1.9	2.9	0.9	(-3.9, 5.8)	-2.9	-4.9	(-9.7, -0.1)
24	1.1	-3.6	-4.7	(-8.4, -1.0)	-1.1	-2.3	(-6.0, 1.5)
28	-2.0	-4.5	-2.6	(-7.8, 2.7)	-4.7	-2.7	(-7.9, 2.5)
32	0.8	-1.1	-1.8	(-7.0, 3.4)	-6.7	-7.5	(-12.7, -2.3)
38	-2.4	-1.7	0.7	(-3.2, 4.7)	-6.4	-4.0	(-7.9, -0.1)
48	1.9	-4.2	-6.1	(-10.5, -1.7)	-3.0	-4.9	(-9.3, -0.5)
52	-2.6	-4.7	-2.1	(-7.1, 2.9)	-6.5	-3.9	(-8.8, 1.1)
56	-0.1	-2.9	-2.8	(-9.0, 3.4)	-3.9	-3.8	(-10.0, 2.3)
62	-0.1	2.4	2.5	(-2.6, 7.6)	-5.6	-5.4	(-10.5, -0.3)
72	1.8	-4.3	-6.0	(-9.5, -2.6)	-1.7	-3.5	(-6.9, -0.0)
76	-1.0	-4.0	-3.0	(-7.7, 1.8)	-6.6	-5.6	(-10.4, -0.9)
80	-1.2	-4.8	-3.6	(-7.2, 0.0)	-6.9	-5.7	(-9.3, -2.1)
86	0.8	-0.1	-1.0	(-6.6, 4.7)	-5.0	-5.8	(-11.4, -0.2)
96	-0.7	-4.5	-3.7	(-7.3, -0.2)	-3.3	-2.6	(-6.2, 1.0)

5.2.1.1 Assay Sensitivity Analysis

SKY0402-C-105

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 16. The largest unadjusted 90% lower confidence interval is 9.0 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 8.3 ms, which indicates that an at least 5-ms QTcI effect due to moxifloxacin can be detected from the study.

Table 16: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for Moxifloxacin 400 mg (SKY0402-C-105)

Time (h)	Treatment Group				
	Moxifloxacin 400 mg				
	Placebo	Δ QTc	$\Delta\Delta$ QTc		
	LS Mean	LS Mean	LS Mean	90% CI	*Adj. 90% CI
0	-0.3	-1.1	-0.7	(-2.6, 1.1)	(-3.3, 1.8)
0.5	-1.3	7.0	8.3	(5.7, 10.9)	(4.7, 11.9)
1	-1.0	9.7	10.7	(8.6, 12.8)	(7.8, 13.6)
1.5	-1.1	8.4	9.5	(7.1, 11.8)	(6.3, 12.7)
2	-2.3	8.0	10.3	(7.8, 12.7)	(6.9, 13.7)
2.5	-1.2	9.4	10.5	(8.5, 12.5)	(7.7, 13.3)
3	-1.2	9.8	11.0	(9.0, 12.9)	(8.3, 13.7)
4	-2.5	8.4	10.9	(8.9, 13.0)	(8.1, 13.8)
5	-1.8	5.2	7.0	(5.6, 8.4)	(5.1, 8.9)
6	-2.3	6.4	8.7	(6.9, 10.5)	(6.2, 11.2)
8	-2.5	4.8	7.3	(5.4, 9.2)	(4.7, 9.9)
10	-4.7	1.8	6.5	(4.9, 8.1)	(4.3, 8.6)
12	-0.9	5.7	6.7	(5.2, 8.2)	(4.6, 8.7)
24	0.2	5.4	5.1	(3.7, 6.6)	(3.1, 7.2)

*Bonferroni method was applied for moxifloxacin and placebo comparison based on 4 time points.

SKY0402-C-107

This reviewer did not perform assay sensitivity analysis for SKY0402-C-107 because the study did not have a positive control arm.

5.2.1.2 Graph of $\Delta\Delta$ QTcI Over Time

Figure 4 displays the time profiles of $\Delta\Delta$ QTcI for SKY0402 (300 mg and 450 mg) treatment groups and moxifloxacin 400 mg in Study SKY0402-C-105. Figure 5 displays the time profiles of $\Delta\Delta$ QTcI for SKY0402 (600 mg and 750 mg) in Study SKY0402-C-107.

Figure 4: Mean and 90% CI $\Delta\Delta QTCI$ Time Course for SKY0402 Treatment Group and Moxifloxacin 400 mg (SKY0402-C-105)

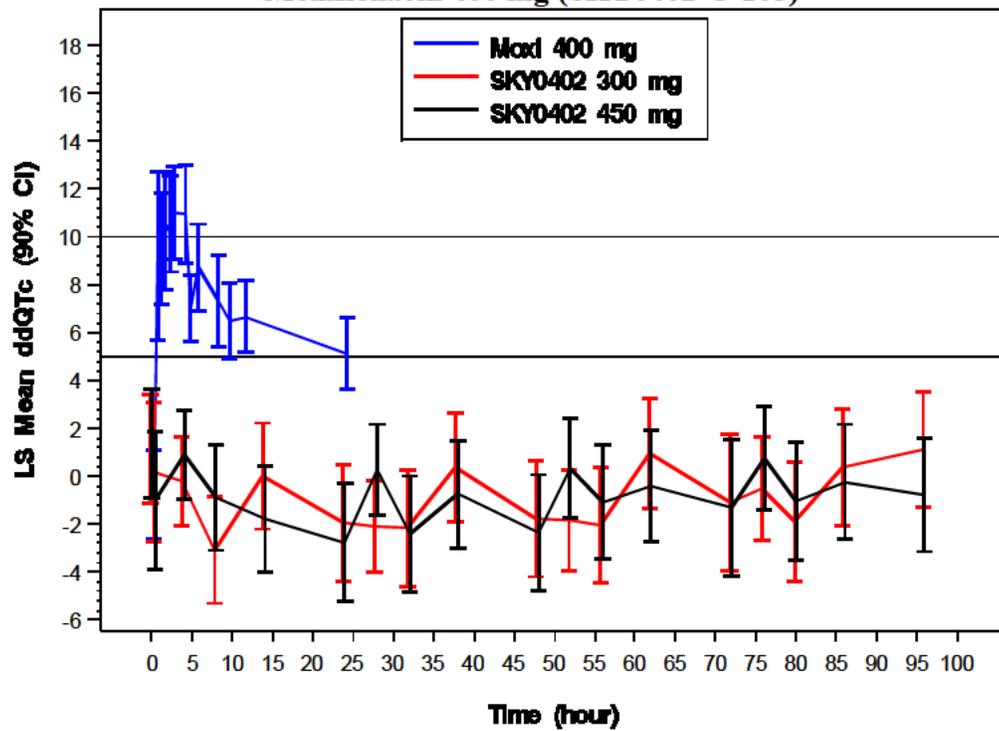
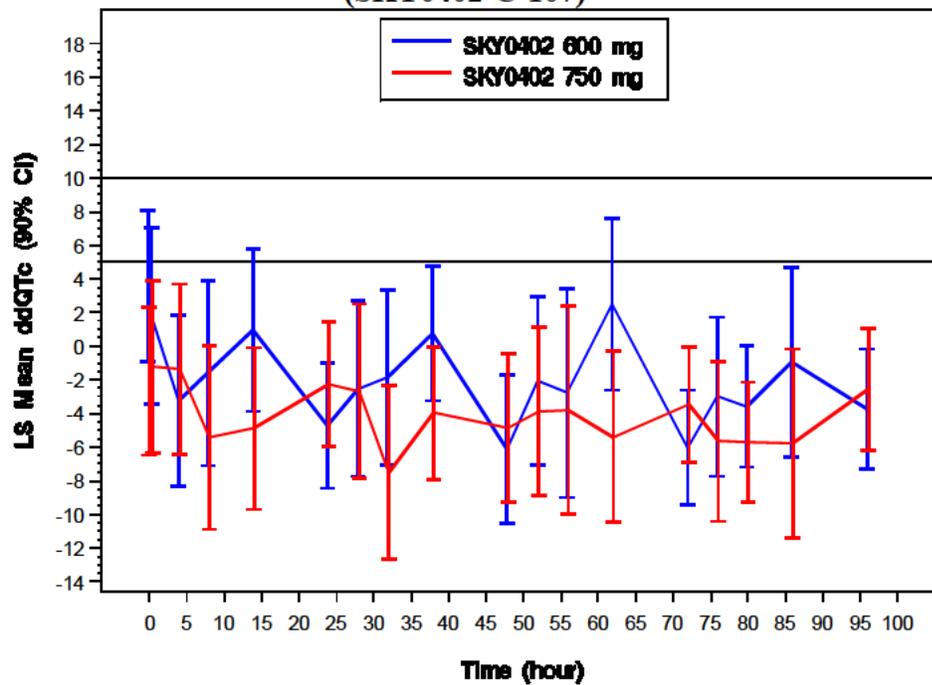


Figure 5: Mean and 90% CI $\Delta\Delta QTCI$ Time Course for SKY0402 Treatment Group (SKY0402-C-107)



5.2.1.3 Categorical Analysis

SKY0402-C-105

Table 17 lists the number of subjects as well as the number of observations whose QTcI values are ≤ 450 ms, and between 450 ms and 480 ms. No subject's QTcI is above 480 ms.

Table 17: Categorical Analysis for QTcI (SKY0402-C-105)

	Total N	Value \leq 450 ms	450 ms<Value \leq 480 ms
Moxifloxacin 400 mg	48	47 (97.9%)	1 (2.1%)
Placebo	49	48 (98.0%)	1 (2.0%)
SKY0402 300 mg	46	46 (100%)	0 (0.0%)
SKY0402 450 mg	47	47 (100%)	0 (0.0%)

Table 18 lists the categorical analysis for Δ QTcI. No subject's change from baseline is above 60 ms.

Table 18: Categorical Analysis of Δ QTcI (SKY0402-C-105)

Treatment Group	Total N	Value \leq 30 ms	30 ms<Value \leq 60 ms
Moxifloxacin 400 mg	48	48 (100%)	0 (0.0%)
Placebo	49	48 (98.0%)	1 (2.0%)
SKY0402 300 mg	46	46 (100%)	0 (0.0%)
SKY0402 450 mg	47	46 (97.9%)	1 (2.1%)

SKY0402-C-107

No subject's QTcI is above 450 ms.

Table 19 lists the categorical analysis for Δ QTcI. No subject's change from baseline is above 60 ms.

Table 19: Categorical Analysis of Δ QTcI (SKY0402-C-107)

Treatment Group	Total N	Value \leq 30 ms	30 ms<Value \leq 60 ms
Placebo	16	16 (100%)	0 (0.0%)
SKY0402 600 mg	16	15 (93.8%)	1 (6.3%)
SKY0402 750 mg	16	16 (100%)	0 (0.0%)

5.2.2 HR Analysis

SKY0402-C-105

The same statistical analysis was performed based on HR interval. The point estimates and the 90% confidence intervals are presented in Table 20. The largest upper bounds of the two-sided 90% CI for the HR mean differences between SKY402 300 mg and placebo, and between SKY402 450 mg and placebo are 3.8 bpm and 3.8 bpm, respectively.

Table 20: Analysis Results of Δ HR and $\Delta\Delta$ HR for SKY0402 300 mg and SKY0402 450 mg (SKY0402-C-105)

		Treatment Group						
		SKY0402 300 mg			SKY0402 450 mg			
		Placebo	Δ HR	$\Delta\Delta$ HR		Δ HR	$\Delta\Delta$ HR	
Time (h)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI	
0	-0.7	-0.3	0.3	(-1.2, 1.8)	0.9	1.6	(0.1, 3.1)	
0.5	-0.0	0.1	0.1	(-1.1, 1.3)	1.0	1.0	(-0.2, 2.2)	
4	-0.8	0.5	1.3	(-0.4, 3.0)	0.3	1.1	(-0.6, 2.7)	
8	2.2	2.2	-0.0	(-1.5, 1.5)	2.7	0.5	(-0.9, 2.0)	
14	0.3	0.5	0.2	(-1.3, 1.7)	0.7	0.5	(-1.0, 2.0)	
24	-0.4	0.7	1.1	(-0.7, 2.8)	-0.0	0.4	(-1.3, 2.1)	
28	0.7	2.5	1.8	(-0.2, 3.8)	0.8	0.1	(-1.8, 2.1)	
32	2.9	5.1	2.2	(0.6, 3.7)	4.1	1.2	(-0.3, 2.7)	
38	2.8	2.8	-0.0	(-1.5, 1.4)	3.9	1.1	(-0.4, 2.5)	
48	0.7	0.3	-0.4	(-1.8, 1.0)	0.5	-0.2	(-1.6, 1.2)	
52	1.4	1.8	0.3	(-1.8, 2.4)	2.1	0.6	(-1.4, 2.7)	
56	3.5	4.7	1.2	(-0.7, 3.1)	4.5	0.9	(-0.9, 2.8)	
62	1.8	2.0	0.3	(-1.3, 1.8)	2.7	0.9	(-0.6, 2.4)	
72	1.8	1.1	-0.6	(-2.6, 1.3)	0.5	-1.2	(-3.2, 0.7)	
76	0.0	1.6	1.6	(-0.6, 3.8)	1.6	1.6	(-0.6, 3.8)	
80	2.7	3.5	0.8	(-0.9, 2.5)	3.2	0.5	(-1.2, 2.3)	
86	0.7	1.7	1.0	(-0.6, 2.6)	2.0	1.3	(-0.2, 2.9)	
96	2.1	2.3	0.2	(-1.7, 2.1)	2.1	-0.1	(-2.0, 1.8)	

SKY0402-C-107

The same statistical analysis was performed based on HR interval. The point estimates and the 90% confidence intervals are presented in Table 21 . The largest upper bounds of the two-sided 90% CI for the HR mean differences between SKY402 600 mg and placebo, and between SKY402 750 mg and placebo are 6.7 bpm and 9.1 bpm, respectively. Table 22 presents the categorical analysis of HR. One subject who experienced HR interval greater than 100 bpm in SKY0402 treatment groups. Table 23 presents the list of individual subjects with HR \geq 100 bpm in treatment groups.

Table 21: Analysis Results of Δ HR and $\Delta\Delta$ HR for SKY0402 600 mg and SKY0402 750 mg (SKY0402-C-107)

		Treatment Group					
		SKY0402 600 mg			SKY0402 750 mg		
	Placebo	Δ HR	$\Delta\Delta$ HR		Δ HR	$\Delta\Delta$ HR	
Time (h)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
0	-2.0	-1.4	0.6	(-2.5, 3.7)	0.4	2.4	(-0.7, 5.5)
0.5	0.7	-0.1	-0.8	(-3.6, 1.9)	1.3	0.6	(-2.1, 3.4)
4	-1.3	0.7	2.0	(-2.8, 6.7)	3.0	4.3	(-0.5, 9.1)
8	1.4	1.9	0.4	(-3.1, 4.0)	2.6	1.2	(-2.4, 4.8)
14	-0.3	-0.8	-0.5	(-4.0, 3.0)	-0.3	-0.0	(-3.6, 3.5)
24	0.2	0.7	0.6	(-1.8, 2.9)	0.9	0.8	(-1.6, 3.1)
28	1.4	-3.9	-5.3	(-9.5, -1.1)	-3.2	-4.6	(-8.9, -0.4)
32	1.5	2.3	0.8	(-2.0, 3.5)	0.2	-1.3	(-4.1, 1.5)
38	2.1	-1.4	-3.5	(-5.5, -1.5)	-1.2	-3.3	(-5.3, -1.2)
48	1.6	0.9	-0.7	(-3.5, 2.2)	1.5	-0.1	(-3.0, 2.8)
52	3.5	-1.7	-5.1	(-10.2, 0.0)	-4.0	-7.4	(-12.6, -2.3)
56	2.7	3.1	0.4	(-3.0, 3.8)	2.4	-0.2	(-3.7, 3.2)
62	1.5	-1.0	-2.4	(-5.7, 0.9)	1.5	0.1	(-3.2, 3.4)
72	0.7	1.7	1.1	(-2.5, 4.6)	2.7	2.0	(-1.5, 5.5)
76	1.0	-3.1	-4.1	(-8.8, 0.7)	-0.6	-1.6	(-6.4, 3.1)
80	2.0	2.9	0.9	(-3.5, 5.4)	2.5	0.5	(-4.0, 5.0)
86	0.8	-2.2	-3.0	(-7.0, 1.0)	0.6	-0.2	(-4.2, 3.8)
96	2.7	1.2	-1.5	(-5.4, 2.3)	0.1	-2.6	(-6.5, 1.3)

Table 22: Categorical Analysis for HR (SKY0402-C-107)

Treatment Group	Total N	HR <100 bpm	HR \geq 100 bpm
Placebo	16	16 (100%)	0 (0.0%)
SKY0402 600 mg	16	16 (100%)	0 (0.0%)
SKY0402 750 mg	16	15 (93.8%)	1 (6.3%)

Table 23: List of Subjects with HR >100 bpm (SKY0402-C-107)

Subject ID	Treatment	Day	Time (h)	HR at Baseline	HR at Post-Dose	HR Change
105_107-001-0031	SKY0402 750 mg	1	4	78.5	107.5	29.0
	SKY0402 750 mg	1	8	83.2	113.5	30.3
	SKY0402 750 mg	1	14	75.7	100.0	24.3
	SKY0402 750 mg	1	48	92.8	102.0	9.3

5.2.3 PR Analysis**SKY0402-C-105**

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 24. The largest upper bounds of the two-sided 90% CI for the PR mean differences between SKY402 300 mg and placebo, and between SKY402 450 mg and placebo are 3.3 ms and 3.6 ms, respectively. Table 25 presents the categorical analysis of PR. Three subjects who experienced PR interval greater than 200 ms in SKY0402 treatment groups. Table 26 presents the list of individual subjects with PR \geq 200 ms in treatment groups.

Table 24: Analysis Results of Δ PR and $\Delta\Delta$ PR for SKY0402 300 mg and SKY0402 450 mg (SKY0402-C-105)

		Treatment Group					
		SKY0402 300 mg			SKY0402 450 mg		
		Placebo	Δ PR	$\Delta\Delta$ PR	Δ PR	$\Delta\Delta$ PR	
Time (h)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
0	1.7	-0.4	-2.1	(-4.2, 0.1)	0.3	-1.4	(-3.5, 0.8)
0.5	-0.2	-1.5	-1.3	(-3.3, 0.7)	0.6	0.8	(-1.1, 2.8)
4	-0.1	-1.7	-1.6	(-3.5, 0.3)	0.4	0.5	(-1.4, 2.4)
8	-2.0	-1.1	0.8	(-1.0, 2.6)	-1.0	1.0	(-0.8, 2.8)
14	0.8	0.7	-0.1	(-2.0, 1.9)	2.4	1.6	(-0.3, 3.5)
24	0.4	1.7	1.3	(-0.5, 3.0)	2.2	1.8	(0.1, 3.6)
28	0.7	-1.1	-1.8	(-3.6, -0.0)	-0.4	-1.1	(-2.9, 0.7)
32	-0.3	0.7	0.9	(-1.0, 2.8)	0.7	1.0	(-0.9, 2.9)
38	3.0	2.7	-0.4	(-2.5, 1.8)	1.8	-1.2	(-3.4, 0.9)
48	2.1	1.8	-0.3	(-2.5, 1.9)	1.9	-0.2	(-2.4, 1.9)

52	1.6	-1.2	-2.8	(-4.9, -0.7)	2.0	0.5	(-1.6, 2.5)
56	0.5	1.7	1.2	(-0.7, 3.1)	1.2	0.7	(-1.3, 2.6)
62	1.7	1.5	-0.2	(-2.1, 1.7)	2.0	0.2	(-1.7, 2.1)
72	2.3	1.5	-0.9	(-3.1, 1.4)	2.2	-0.2	(-2.4, 2.1)
76	1.2	0.6	-0.6	(-2.7, 1.4)	1.8	0.6	(-1.5, 2.6)
80	0.3	1.0	0.7	(-1.2, 2.6)	1.2	0.9	(-1.0, 2.8)
86	2.0	2.1	0.1	(-2.1, 2.2)	2.9	0.9	(-1.2, 3.0)
96	0.7	1.6	0.9	(-1.4, 3.3)	1.5	0.9	(-1.5, 3.3)

Table 25: Categorical Analysis for PR (SKY0402-C-105)

Treatment Group	Total N	PR <200 ms	PR ≥200 ms
Moxifloxacin 400 mg	48	45 (93.8%)	3 (6.3%)
Placebo	49	45 (91.8%)	4 (8.2%)
SKY0402 300 mg	46	44 (95.7%)	2 (4.3%)
SKY0402 450 mg	47	44 (93.6%)	3 (6.4%)

SKY0402-C-107

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 26. The largest upper bounds of the two-sided 90% CI for the PR mean differences between SKY402 600 mg and placebo, and between SKY402 750 mg and placebo are 6.9 ms and 9.1 ms, respectively. Table 27 presents the categorical analysis of PR. Two subjects who experienced PR interval greater than 200 ms in SKY0402 treatment groups.

Table 26: Analysis Results of Δ PR and $\Delta\Delta$ PR for SKY0402 600 mg and SKY0402 750 mg (SKY0402-C-107)

	Treatment Group						
	Placebo	SKY0402 600 mg			SKY0402 750 mg		
		Δ PR	$\Delta\Delta$ PR		Δ PR	$\Delta\Delta$ PR	
Time (h)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
0	0.7	3.9	3.2	(-0.0, 6.4)	-1.3	-2.0	(-5.2, 1.2)
0.5	0.5	0.5	-0.0	(-4.0, 3.9)	-1.3	-1.8	(-5.8, 2.1)
4	1.2	-0.5	-1.7	(-4.2, 0.8)	-0.1	-1.3	(-3.8, 1.2)
8	-2.7	0.5	3.2	(0.1, 6.3)	-2.6	0.1	(-3.0, 3.2)
14	1.0	2.8	1.8	(-2.3, 5.9)	-0.6	-1.6	(-5.7, 2.5)

		Treatment Group					
		SKY0402 600 mg			SKY0402 750 mg		
	Placebo	Δ PR	$\Delta\Delta$ PR		Δ PR	$\Delta\Delta$ PR	
Time (h)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
24	2.6	-1.4	-4.0	(-6.7, -1.3)	2.8	0.2	(-2.5, 2.8)
28	2.7	1.3	-1.4	(-5.4, 2.6)	3.7	1.0	(-3.0, 5.0)
32	0.5	2.1	1.6	(-1.3, 4.5)	-1.3	-1.8	(-4.6, 1.1)
38	1.7	3.0	1.3	(-2.9, 5.6)	1.1	-0.6	(-4.8, 3.7)
48	4.3	-0.9	-5.2	(-9.2, -1.2)	-0.2	-4.5	(-8.5, -0.5)
52	2.9	1.1	-1.8	(-5.9, 2.2)	3.5	0.6	(-3.5, 4.6)
56	-0.2	2.6	2.9	(-1.2, 6.9)	0.4	0.6	(-3.5, 4.7)
62	1.2	1.9	0.7	(-4.4, 5.8)	0.3	-0.9	(-6.0, 4.2)
72	3.9	-1.2	-5.1	(-8.4, -1.8)	1.2	-2.7	(-6.0, 0.6)
76	0.7	1.4	0.8	(-3.4, 4.9)	5.6	5.0	(0.8, 9.1)
80	0.3	1.5	1.2	(-2.6, 4.9)	-0.0	-0.3	(-4.0, 3.4)
86	3.4	3.4	0.0	(-4.9, 5.0)	2.4	-1.0	(-5.9, 4.0)
96	1.6	-0.8	-2.4	(-5.8, 1.1)	1.9	0.3	(-3.2, 3.7)

Table 27: Categorical Analysis for PR (SKY0402-C-107)

Treatment Group	Total N	PR <200 ms	PR \geq 200 ms
Placebo	16	14 (87.5%)	2 (12.5%)
SKY0402 600 mg	16	15 (93.8%)	1 (6.3%)
SKY0402 750 mg	16	15 (93.8%)	1 (6.3%)

5.2.4 QRS Analysis

SKY0402-C-105

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 28. The largest upper bounds of the two-sided 90% CI for the QRS mean differences between SKY0402 300 mg and placebo, and between SKY0402 450 mg and placebo are 1.5 ms and 2.1 ms, respectively. Table 29 presents the categorical analysis of QRS. Five subjects who experienced QRS interval greater than 110 ms in SKY0402 treatment groups.

Table 28: Analysis Results of Δ QRS and $\Delta\Delta$ QRS SKY0402 300 mg and SKY0402 450 mg (SKY0402-C-105)

		Treatment Group					
		SKY0402 300 mg			SKY0402 450 mg		
	Placebo	Δ QRS	$\Delta\Delta$ QRS		Δ QRS	$\Delta\Delta$ QRS	
Time (h)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
0	-0.1	-0.4	-0.3	(-1.1, 0.6)	-0.5	-0.4	(-1.2, 0.5)
0.5	0.6	-0.6	-1.2	(-2.1, -0.3)	0.3	-0.4	(-1.3, 0.6)
4	0.4	0.6	0.2	(-0.7, 1.1)	0.0	-0.4	(-1.3, 0.5)
8	-0.2	-0.2	0.0	(-0.8, 0.8)	0.1	0.3	(-0.5, 1.1)
14	-1.1	-0.9	0.2	(-0.8, 1.1)	-1.3	-0.2	(-1.2, 0.8)
24	-0.0	-0.1	-0.0	(-1.1, 1.0)	0.1	0.2	(-0.9, 1.2)
28	0.3	0.3	0.1	(-0.9, 1.0)	1.0	0.7	(-0.2, 1.6)
32	0.3	-0.6	-0.9	(-1.8, -0.1)	0.2	-0.1	(-0.9, 0.7)
38	-0.7	-0.9	-0.1	(-1.2, 0.9)	-0.3	0.4	(-0.6, 1.4)
48	-0.2	-0.1	0.1	(-0.8, 1.0)	-0.1	0.1	(-0.9, 1.0)
52	0.4	0.7	0.4	(-0.6, 1.3)	0.6	0.3	(-0.7, 1.2)
56	0.7	-0.1	-0.8	(-1.8, 0.2)	0.8	0.2	(-0.8, 1.1)
62	-1.0	-1.0	0.0	(-1.0, 1.0)	-0.5	0.5	(-0.5, 1.6)
72	0.2	0.1	-0.0	(-1.1, 1.0)	1.2	1.0	(-0.0, 2.1)
76	0.8	1.3	0.5	(-0.4, 1.5)	1.4	0.6	(-0.3, 1.6)
80	0.6	-0.2	-0.8	(-1.7, 0.0)	1.0	0.4	(-0.5, 1.2)
86	0.8	0.4	-0.4	(-1.5, 0.7)	1.2	0.4	(-0.7, 1.4)
96	0.8	0.8	-0.0	(-1.1, 1.0)	0.7	-0.1	(-1.1, 0.9)

Table 29: Categorical Analysis for QRS (SKY0402-C-105)

Treatment Group	Total N	QRS <110 ms	QRS \geq 110 ms
Moxifloxacin 400 mg	48	44 (91.7%)	4 (8.3%)
Placebo	49	42 (85.7%)	7 (14.3%)
SKY0402 300 mg	46	44 (95.7%)	2 (4.3%)
SKY0402 450 mg	47	42 (89.4%)	5 (10.6%)

SKY0402-C-107

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 30. The largest upper bounds of the two-sided 90% CI for the QRS mean differences between SKY0402 600 mg and placebo, and between

SKY0402 750 mg and placebo are 2.8 ms and 2.6 ms, respectively. Table 31 presents the categorical analysis of QRS. One subjects who experienced QRS interval greater than 110 ms in SKY0402 treatment groups.

Table 30: Analysis Results of Δ QRS and $\Delta\Delta$ QRS SKY0402 600 mg and SKY0402 750 mg (SKY0402-C-107)

		Treatment Group					
		SKY0402 600 mg			SKY0402 750 mg		
	Placebo	Δ QRS	$\Delta\Delta$ QRS		Δ QRS	$\Delta\Delta$ QRS	
Time (h)	LS Mean	LS Mean	LS Mean	90% CI	LS Mean	LS Mean	90% CI
0	-0.2	-0.2	0.1	(-1.3, 1.4)	-0.4	-0.2	(-1.5, 1.1)
0.5	0.3	1.4	1.2	(-0.3, 2.6)	-0.7	-1.0	(-2.5, 0.4)
4	0.3	0.1	-0.2	(-1.3, 1.0)	0.7	0.4	(-0.8, 1.6)
8	-0.4	-1.3	-0.9	(-2.4, 0.7)	-0.4	-0.0	(-1.6, 1.5)
14	-0.6	-0.4	0.2	(-1.5, 2.0)	-0.5	0.2	(-1.6, 1.9)
24	0.0	0.5	0.5	(-0.8, 1.8)	0.1	0.1	(-1.2, 1.4)
28	0.4	-0.3	-0.8	(-2.3, 0.8)	0.7	0.3	(-1.2, 1.8)
32	0.4	-1.3	-1.7	(-3.2, -0.2)	-0.0	-0.4	(-2.0, 1.1)
38	-0.2	-0.3	-0.2	(-2.2, 1.9)	0.4	0.5	(-1.5, 2.6)
48	0.5	1.0	0.5	(-0.8, 1.9)	0.8	0.2	(-1.1, 1.6)
52	0.3	0.7	0.4	(-1.3, 2.2)	0.9	0.7	(-1.1, 2.4)
56	0.7	0.4	-0.3	(-2.3, 1.7)	-0.5	-1.2	(-3.2, 0.8)
62	-0.4	0.4	0.8	(-1.2, 2.8)	-0.7	-0.4	(-2.4, 1.7)
72	0.6	0.5	-0.1	(-1.7, 1.4)	0.8	0.1	(-1.4, 1.7)
76	0.6	0.8	0.2	(-1.4, 1.8)	2.1	1.5	(-0.1, 3.1)
80	0.7	0.3	-0.3	(-2.0, 1.4)	0.6	-0.1	(-1.8, 1.6)
86	1.1	0.2	-0.9	(-3.1, 1.3)	0.2	-0.8	(-3.0, 1.4)
96	0.7	0.6	-0.1	(-1.7, 1.4)	0.2	-0.5	(-2.1, 1.0)

Table 31: Categorical Analysis for QRS (SKY0402-C-107)

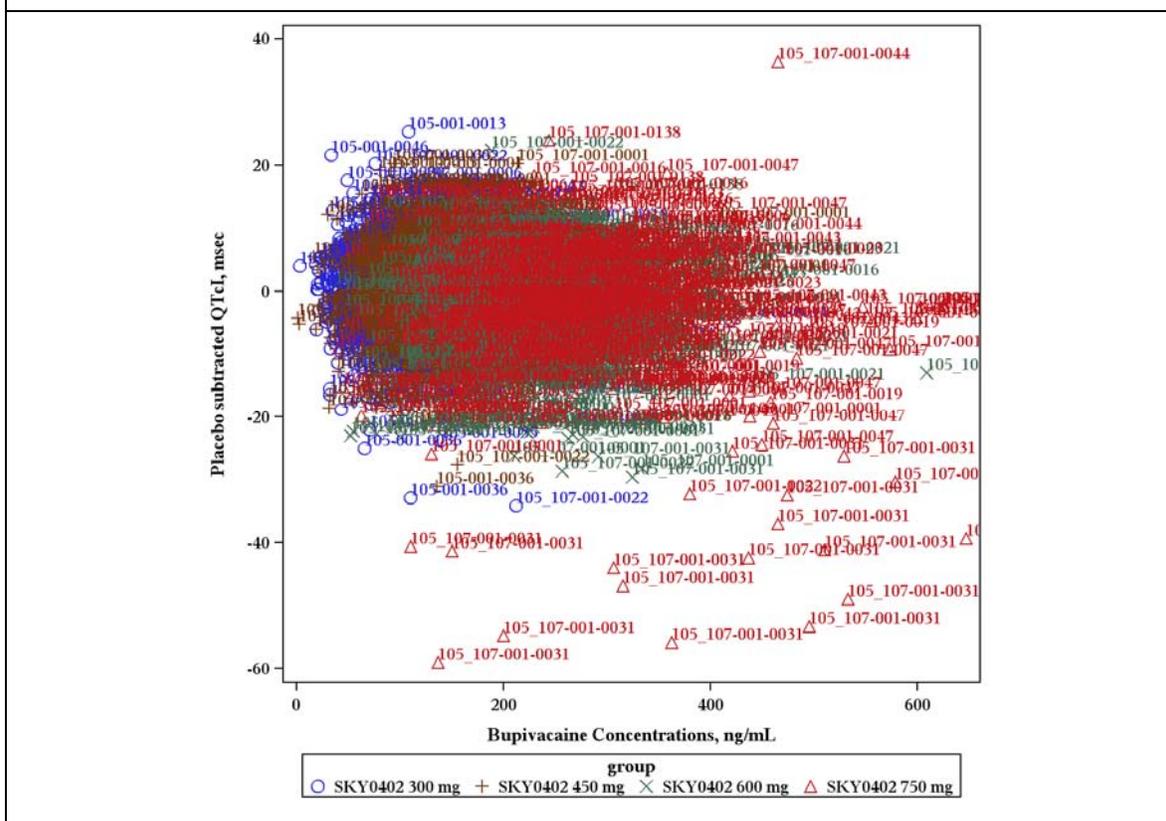
Treatment Group	Total N	QRS <110 ms	QRS \geq 110 ms
Placebo	16	14 (87.5%)	2 (12.5%)
SKY0402 600 mg	16	16 (100%)	0 (0.0%)
SKY0402 750 mg	16	15 (93.8%)	1 (6.3%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug concentration-time profile is illustrated in **Figure 1**.

The reviewer analyzed the relationship between baseline-corrected, placebo-subtracted QTcI ($\Delta\Delta$ QTcI) and SKY0402 concentrations after removal of data from a subject (Subject 105_107-001-0031) treated with 750 mg. As shown in Figure 6, Subject 105-107-001-0031 showed a different concentration-QT relationship with much lower QT values and therefore was considered as an outlier.

Figure 6: Relationship Between Baseline-Adjusted, Placebo Subtracted QTcI ($\Delta\Delta$ QTcI) and SKY0402 (Bupivacaine) Concentrations. The Data From Each Subject are Identified by Unique Subject ID in Each Dose Group.



The relationship between $\Delta\Delta$ QTcI and SKY0402 concentrations along with population predicted line, after removal of (Subject 105_107-001-0031), is visualized in Figure 7. Figure 8 shows the relationship between observed, population predicted $\Delta\Delta$ QTcI and midpoints of SKY0402 concentration quartiles from both studies. Figure 8 indicates that a linear model reasonably describes the data. Table 32 shows the slope estimates of the concentration-QT relationships by Study SKY0402-C-105 and Study SKY0402-C-107 separately or by pooling data from the two studies. The consistent concentration-QT relationships with similar slope estimates can be obtained from either Study SKY0402-C-105, Study SKY0402-C-107, or by pooling the data together. The findings suggest that

SKY0402 is associated with concentration-dependent QT interval shortening – QTc interval is shorter at higher concentrations.

Figure 7: Scatter Plot Showing the Relationship Between $\Delta\Delta QTcI$ (ms) and Bupivacaine Concentrations (ng/mL) in Studies SKY0402-C-105 and SKY0402-C-107 (Shown also are the Population Predicted Line Based on Linear Model for Both Studies)

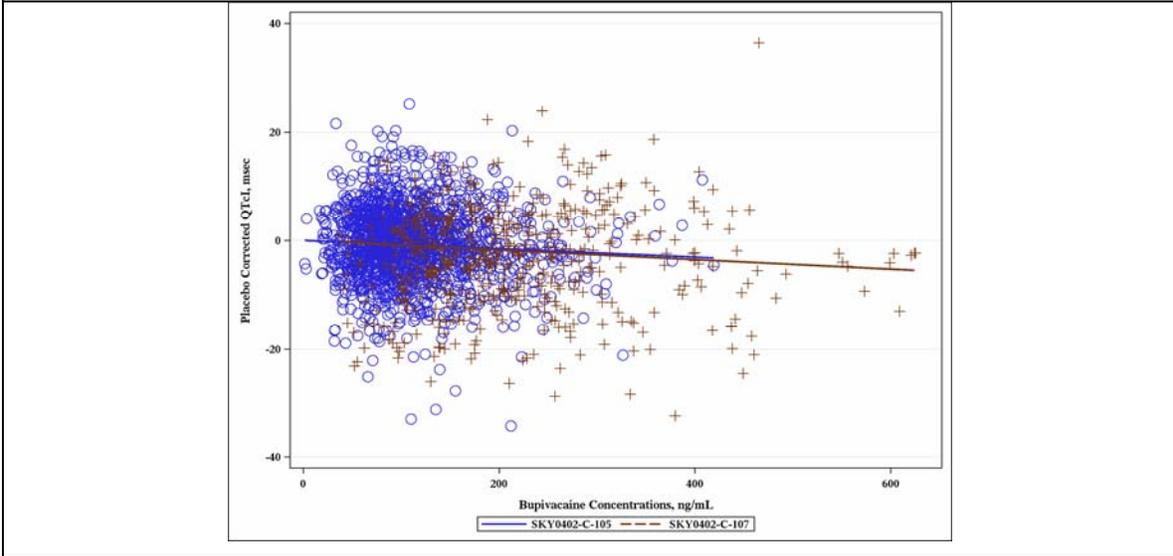


Figure 8: Relationship $\Delta\Delta QTcI$ (ms) and Bupivacaine Concentrations (ng/mL) by Midpoints of Concentration Quartiles (Shown also are the Population Predicted Line Based on Linear Model for Both Studies)

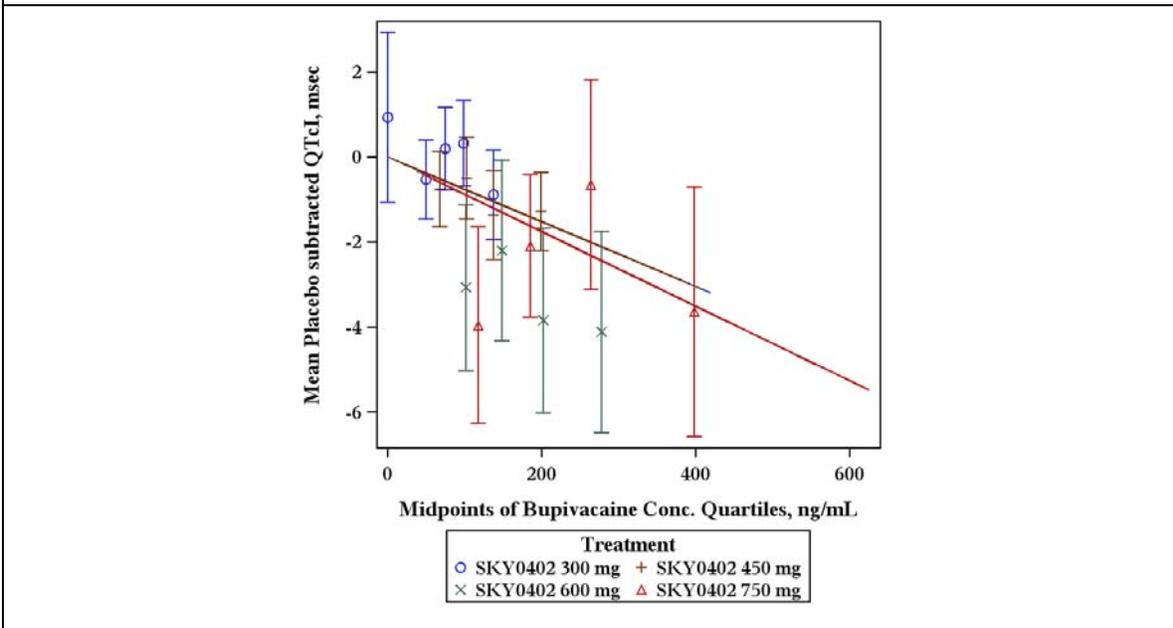


Table 32: Slope Estimates of $\Delta\Delta QTcI$ vs. SKY0402 (Bupivacaine) Concentrations Based on Linear Mixed Effects Analysis		
	Slope of $\Delta\Delta QTcI$ vs SKY0402 concentrations	p-value
Study SKY0402-C-105	-0.00759	0.0159
Study SKY0402-C-107	-0.00876	0.1783
Both studies combined	-0.00945	0.0046

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.

A slight QTc shortening was observed at the two doses tested in study SKY0402-C-107, mean effect was between -5.5 ms and lower bound was around -11 ms. These effects are not considered to be clinically relevant.

5.4.2 ECG assessments

SKY0402-C-105

Waveforms from the ECG warehouse were reviewed. ECG measurements were performed on the 'global' presentation of superimposed representative (median) PQRST complexes from all leads. Less than 1.75% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

SKY0402-C-107

Waveforms from the ECG warehouse were reviewed. ECG measurements were performed on the 'global' presentation of superimposed representative (median) PQRST complexes from all leads. Less than 3% 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

As indicated in the statistical assessments, SKY0402 does not affect PR and QRS intervals. Overall five subjects had a PR interval >200 ms with SKY0402, none of the subjects PR duration exceeded 215 ms. Six subject had an absolute QRS interval ≥ 110 ms but values were not clinically relevant, none of them had a QRS >113 ms.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	<p>Include maximum proposed clinical dosing regimen: The maximum dose of EXPAREL for single dose local administration should not exceed [REDACTED] (b)(4)</p>	
Maximum tolerated dose	<p>Include if studied or NOAEL dose: The highest dose evaluated was 750 mg given subcutaneously. Even at the highest dose evaluated, a maximum tolerated dose (MTD) has not been achieved. Because bupivacaine is known to produce acute CNS/CV changes at a known toxic threshold, a MTD for SKY0402 was not pursued. Since SKY0402 is liposomal, it is not feasible to give the drug intravenously to healthy volunteers, so the 750 mg dose delivered subcutaneously was the maximum dose that could be delivered in the TQT study.</p>	
Principal adverse events	<p>Include most common adverse events; dose limiting adverse events: In the 10 randomized, double-blind, wound infiltration studies, the most common adverse reactions (incidence $\geq 10\%$) following EXPAREL administration were nausea, constipation, and vomiting. No dose limiting adverse events were observed even at the highest wound infiltration dose (750 mg).</p>	
Maximum dose tested	Single Dose	750 mg (subcutaneous administration in healthy adults in the Thorough QT Trial)
	Multiple Dose	Not tested in humans
Exposures Achieved at Maximum Tested Dose	Single Dose	<p>Mean (%CV) C_{max} and AUC: <u>750 mg</u> C_{max} (ng/mL): 427.8 (33.3) AUC₍₀₋₉₆₎ (h·ng/mL): 24,612.71 (30.7) (Source: Module 5.3.3.1, SKY0402-C-107)</p>
	Multiple Dose	Not applicable
Range of linear PK	<p>Specify dosing regimen: Not applicable, multiple doses not tested or indicated.</p>	
Accumulation at steady state	<p>Mean (%CV); specify dosing regimen: Not applicable, multiple doses not tested or indicated. SKY0402 is intended for single-dose administration; therefore, accumulation of bupivacaine or its metabolites is not expected even in patients with impaired hepatic or renal function.</p>	

Metabolites	<p>Include listing of all metabolites and activity:</p> <p>Study SKY0402-C-110 evaluated the major metabolite of bupivacaine, Pipecolylxylidine (PPX). Bupivacaine is metabolized primarily in the liver via conjugation with glucuronic acid with approximately 5% converted to PPX.</p> <p>Bupivacaine and PPX pharmacokinetic results after SKY0402 300 mg administration are discussed in Module 5.3.3.3, SKY0402-C-110, CSR Body, Section 11.4.</p>	
Absorption	Absolute/Relative Bioavailability	<p>Mean (%CV):</p> <p>Not tested, as the pharmacology of bupivacaine has been extensively characterized, it was deemed not necessary to investigate it in further depth for SKY0402.</p>
	Tmax	<ul style="list-style-type: none"> • Median (range) for parent: Bupivacaine component of SKY0402: 52.0 hrs; 750 mg administered subcutaneously to healthy adults in the TQT Trial (source: Module 5.3.3.1, SKY0402-C-107) • Median (range) for metabolites: PPX: 72.0 hrs; 300 mg administered via subcutaneous infiltration to healthy adults (source: Module 5.3.3.3, SKY0402-C-110)
Distribution	Vd/F or Vd	<p>Mean (%CV):</p> <p>Not tested, after bupivacaine has been released from SKY0402 and is absorbed systemically, bupivacaine distribution is expected to be the same as for other bupivacaine formulations.</p>
	% bound	<p>Mean (%CV):</p> <p>Not tested, after bupivacaine has been released from SKY0402 and is absorbed systemically, bupivacaine distribution is expected to be the same as for other bupivacaine formulations.</p>
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes <p>Not tested, after bupivacaine HCl has been released from SKY0402 and is absorbed systemically, bupivacaine excretion is expected to be the same as for other bupivacaine formulations.</p>
	Terminal t½	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites <p>Not tested, after bupivacaine HCl has been released</p>

		from SKY0402 and is absorbed systemically, bupivacaine excretion is expected to be the same as for other bupivacaine formulations.
	CL/F or CL	Mean (%CV) Not tested, after bupivacaine HCl has been released from SKY0402 and is absorbed systemically, bupivacaine excretion is expected to be the same as for other bupivacaine formulations.
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC There were increases in Cmax/D, AUC(0-t)/D, and AUC(inf)/D as age increased over that range but these were not thought to be clinically significant. This increase in exposure is suggestive of a decrease in clearance (CL/F) with increasing age. However, there was no trend toward an increase in t½ with age and the regression was not significant. Source: Module 5.3.5.3, Integrated PK
	Sex	Specify mean changes in Cmax and AUC Values for Cmax/D, AUC(0-t)/D, and AUC(inf)/D were greater in females than in males and the differences were not thought to be clinically significant. There were no apparent differences in t½ between males and females. Source: Module 5.3.5.3, Integrated PK
	Race	Specify mean changes in Cmax and AUC No clinical studies were conducted for this NDA to evaluate PK differences between ethnic groups. No data identified in the MARCAINE label to support any ethnicity differences.
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC Consistent with the hepatic clearance of bupivacaine, mean plasma concentrations were higher in subjects with moderate hepatic impairment than in healthy controls with approximate 1.5- and 1.6-fold increases in the mean values for Cmax and area under the plasma concentration extrapolated to infinity [AUC(inf)] time curve. There was a corresponding increase in apparent terminal elimination half life (t½) of about 20%, from 37.6 (9.80) hours in healthy controls to 46.5 (26.3) hours in subjects with moderate hepatic impairment. This was studied in Study SKY0402-C-110

		<p><u>Normals; mean (%CV):</u> Half life (hr): 37.6 (26.1) Cmax (ng/mL): 103 (36.6) AUC (ng·h/mL): 11,051 (40.7)</p> <p><u>Hepatic Impaired; mean (%CV):</u> Half life (hr): 46.5 (56.6) Cmax (ng/mL): 149 (28.6) AUC (ng·h/mL): 17,976 (13.6)</p> <p>Source: Module 5.3.3.3, SKY0402-C-110</p>
Extrinsic Factors	Drug interactions	<p>Include listing of studied DDI studies with mean changes in Cmax and AUC</p> <p>No clinical drug-drug interaction studies were conducted for this NDA. There were however, nonclinical (i.e. animal and in vitro) studies to evaluate the potential interaction between SKY0402 and lidocaine. Based on these studies, the proposed SKY0402 label recommends the following:</p> <p>SKY0402 should not be admixed with lidocaine or other non-bupivacaine based local anesthetics.</p> <p>SKY0402 may be locally administered after at least 20 minutes following local administration of lidocaine.</p> <p>Source: Module 2.5, Section 3.7, Drug-Drug Interaction Potential (Extrinsic Factors)</p> <p><u>MARCAINE label:</u> The administration of local anesthetic solutions containing epinephrine or norepinephrine to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe, prolonged hypertension. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential.</p> <p>Concurrent administration of vasopressor drugs and of ergot-type oxytocic drugs may cause severe, persistent hypertension or cerebrovascular accidents.</p>

		Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine.
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat) No clinical studies were conducted for this NDA to evaluate food effects. No data identified in the MARCAINE label to support any food effects. The drug is not administered by mouth
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose. Worst case scenario would be expected to be an inadvertent intra-vascular administration of the injection. This appears to have occurred in four instances over the program's 1307 exposures (as reported in the NDA): one instance in the epidural setting where the administering physician reported that he thought there was some vascular foray, and three instances where it was elucidated solely due to elevated pk values. Of note, the latter three instances all occurred in a study where ECG monitoring was being performed, and no discernable AE profile or ECG abnormality was noted among these three patients.	

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

/s/

HAO ZHU
04/28/2011

VENKATESH A BHATTARAM
04/29/2011

MOH JEE NG
04/29/2011

JOANNE ZHANG
04/29/2011

MONICA L FISZMAN
04/29/2011

NORMAN L STOCKBRIDGE
04/29/2011

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 # 022496 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Exparel Established/Proper Name: bupivacaine ER liposome injection Dosage Form: Injection Strengths: 150mg/10mL:300mg/mL		
Applicant: Pacira Pharmaceuticals Agent for Applicant (if applicable):		
Date of Application: Sept. 28, 2010 Date of Receipt: Sept. 28, 2010 Date clock started after UN:		
PDUFA Goal Date: July 28, 2011		Action Goal Date (if different):
Filing Date: Nov. 27, 2010		Date of Filing Meeting: Nov. 3, 2010
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): single-dose local administration as a single dose by local infiltration into the surgical wound prior to end of surgical procedure.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s):				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	√			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>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.</i>	√			
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)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	√			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		√		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	√			

<p><u>User Fee Status</u></p> <p><i>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.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>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.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>√</p>																		
<p>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)].</p>		<p>√</p>																		
<p>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)]?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>		<p>√</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="201 1430 1349 1570"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>√</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>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 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p> <p>Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</p>	<p>YES</p>	<p>NO</p> <p>√</p>	<p>NA</p>	<p>Comment</p>																

<p>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)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 3 years</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>				
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		√		
<p>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)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>		√		

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

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> 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				
<i>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.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	√			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
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)?	√			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	√			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	√			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(l) 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...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>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)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	√			

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			√	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>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 reviewed by PeRC prior to approval of the application/supplement.</i></p>	√			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		√		

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

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? <i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) <i>If no, request in 74-day letter</i>	√			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	√			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/DCRMS via the DCRMSRMP mailbox</i>		√		Submitted a Risk Management proposal only.
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	√			
Is the PI submitted in PLR format? ⁴	√			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	√			
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	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
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) <i>If yes, specify consult(s) and date(s) sent:</i>				To be submitted
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):		√		
<i>If yes, distribute minutes before filing meeting</i> Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): Feb. 16, 2010	√			

<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		√		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 3, 2010

BLA/NDA/Supp #: 22496

PROPRIETARY NAME: Exparel

ESTABLISHED/PROPER NAME: SKY002(bupivacaine extended-release liposome injection)

DOSAGE FORM/STRENGTH: 150mg/10mL and 300mg/20mL single use vial.

APPLICANT: Pacira Pharmaceuticals

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Single-dose local administration into the surgical wound to produce postsurgical analgesia.

BACKGROUND: This product is a 505(b)(2) and the RLD is Marcaine®. The Sponsor requested a Priority review, but following discussion at the filing meeting, the review team decided to grant a Standard review. The tradename, EXPAREL, was tentatively approved May 20, 2009. Therefore, the proposed name is currently under review by DMEPA. The Sponsor requested (b)(4) a pediatric deferral (2 years and older). The application was filed on November 27, 2010. The PDUFA date is July 28, 2011.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Tanya Clayton	Y
	CPMS/TL:	Sara Stadley, MS	N
Cross-Discipline Team Leader (CDTL)	Rigoberto Roca, MD		Y
Clinical	Reviewer:	Art Simone, MD, PhD	Y
	TL:	Rigoberto Roca, MD	
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		

Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Zhihong Li, PhD	Y
	TL:	Suresh Doddapaneni, PhD	Y
Biostatistics	Reviewer:	David Petullo, PhD	Y
	TL:	Dionne Price, PhD	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Gary Bond, PhD	Y
	TL:	Adam Wasserman, PhD	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Art Shaw, PhD; Ted Carver, PhD; Danae Christodoulou, PhD	Y
	TL:		
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Robert Mello, PhD	Y
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		

	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> 	<input type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>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</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • 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? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: request in 74 day letter</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Bob A. Rappaport, MD	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	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).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	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.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> 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)

<input type="checkbox"/>	<ul style="list-style-type: none"> notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	<p>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 (BLAs/BLA supplements only) [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]</p>
<input type="checkbox"/>	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/

TANYA D CLAYTON
12/10/2010

DSI CONSULT: Request for Clinical Inspections

Date: December 10, 2010

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Arthur Simone MD, PhD /Clinical Reviewer/DAAP/HFD-170
Rigoberto Roca, MD, Deputy Director/DAAP/HFD-170

From: Tanya Clayton, Senior Regulatory Health Project Manager/DAAP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-22496

Applicant/ Applicant contact information (to include phone/email): Pacira Pharmaceuticals, Inc.

Drug Proprietary Name: Exparel (Proposed)

NME or Original BLA (Yes/No): No

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): single-dose local administration into the surgical wound to produce postsurgical analgesia.

PDUFA: July 28, 2010

Action Goal Date: July 28, 2010

Inspection Summary Goal Date:

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
<p>Site #10, Republic of Georgia Tengiz Abuladze, MD, 5 Chachava, Tbilisi, Georgia (+995 32) 52 09 74 Tengiz_abuladze@yahoo.com</p> <p>Tengiz Bochoidze, MD, PhD 5 Chachava, Tbilisi, Georgia (+995 32) 52 20 19 Tengiz_Bochoidze@yahoo.com</p> <p>Beka Kevlishvili, MD 5 Chachava, Tbilisi, Georgia (+995 32) 36-44-85, 52 10 75 bekakevl@yahoo.com</p> <p>George Korakhashvili, MD 5 Chachava, Tbilisi, Georgia (+995 32) 52 20 79 giakorax@yahoo.com</p> <p>Baadur Mosidze, MD 5 Chachava, Tbilisi, Georgia (+995 32) 52 20 79 ncsurgery@yahoo.com</p> <p>Iuri Tavdidishvili, MD 5 Chachava, Tbilisi, Georgia (+995 32) 52 95 59 Iuri_tavdidishvili@yahoo.com</p>	SKY0402-C-316	40	Management of postoperative pain
<p>Site #11, Republic of Georgia Gulnazi Jinjikhadze, MD 29, Vazha-Pshavela Ave., 0160 Tbilisi, Georgia (+995 32) 39 55 38</p> <p>Gia Mukhashavria, MD 29, Vazha-Pshavela Ave., 0160 Tbilisi, Georgia (+995 32) 39 55 38</p>	SKY0402-C-316	2	Management of postoperative pain
<p>Site #12, Republic of Georgia Nino Archvadze, MD 6, Jikia Street, Tbilisi, 0186, Georgia</p>	SKY0402-C-316	14	Management of postoperative pain

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<p>(+995 32) 30 45 00</p> <p>Gocha Gorgodze, MD 6, Jikia Street, Tbilisi, 0186, Georgia (+995 32) 30 45 02</p> <p>Rema Gvamichava, MD 6, Jikia Street, Tbilisi, 0186, Georgia (+995 32) 30 45 02</p> <p>Givi Khorbaladze, MD 6, Jikia Street, Tbilisi, 0186, Georgia (+995 32) 30 45 02</p> <p>Spiridon Sanikidze, MD 6, Jikia Street, Tbilisi, 0186, Georgia (+995 32) 304 502</p>			
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<p>Site #13, Republic of Georgia David Jikia, MD 103 Uzmazde Street. Tbilisi, 0102, Georgia (+995 32) 94 33 02</p> <p>Teimuraz Kandelaki, MD 103 Uzmazde Street. Tbilisi, 0102, Georgia (+995 32) 95 26 24</p> <p>Mzia Petriashvili, nurse 103 Uzmazde Street. Tbilisi, 0102, Georgia (+995 32) 95 15 13</p> <p>Erckle Tchubabria, MD 103 Uzmazde Street. Tbilisi, 0102, Georgia (+995 32) 95 15 13</p>	<p>SKY0402-C-316</p>	<p>16</p>	<p>Management of postoperative pain</p>
<p>Site 100 – Austin TX Stephen Daniels, DO 3200 Red River, Suite 301 Austin TX 78705 512-320-1600 x 2102 Stephen.daniels@premier-research.com Fax: 512-320-0313</p>	<p>SKY-0402-C-317</p>	<p>59</p>	<p>Management of postoperative pain</p>
<p>Site 300 – Houston TX Alfredo C. Gueler, MD 5420 Dashwood Drive, Suite 302 Houston, TX 77081 832-426-7822 alguelermd@hotmail.com Fax: 832-778-6917</p>	<p>SKY-0402-C-317</p>	<p>58</p>	<p>Management of postoperative pain</p>

III. Site Selection/Rationale

Two placebo-controlled trials are critical to the approval of this product: C-316 and C-317. These were the only studies to successfully demonstrate efficacy: (b) (4)

Study C-316, which evaluated the 300 mg dose, the highest dose to be considered for approval, is the one that deserves the greatest scrutiny. The sites for this study were located in the countries of Georgia, Poland, and Serbia. Although there was a treatment effect in all countries, the treatment effect was largest at the 4 sites in the Republic of Georgia. Both the efficacy and the safety data from this study are critical to approval of the higher dose of this product.

Study C-317 evaluated the 120 mg dose. The safety findings from this study are not likely to be as critical as those from Study C-316 where a higher dose of drug product was administered in a more vascular region likely resulting in higher systemic exposures. Efficacy from C-317 was not driven by one group of sites or a single site; it was most favorably impacted by two sites: Austin and Houston, Texas, which enrolled the most subjects, 59 and 58, respectively, each accounting for approximately 25% of the subjects who participated in the trial.

Thus, we request that the four study sites in Georgia be investigated; all are located in Tbilisi. If resources permit only one of the 4 sites to be evaluated, that site should be #10, which had the highest number of subjects enrolled, 40 of the 72 (56%) from that country and 25% of all subjects enrolled in that study..

If a foreign investigation cannot be conducted, the study sites in Texas would be the alternative recommendations; although, the impact of these sites on the approvability of this product are minimal compared to those of the sites in the republic of Georgia.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- 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):

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) See discussion above.

IV. Tables of Specific Data to be Verified (if applicable)

Not applicable.

Should you require any additional information, please contact Tanya Clayton at 301-796-0871 or Arthur Simone at 301-796-1294.

Concurrence: (as needed)

Arthur Simone MD, PhD /Clinical Reviewer
Rigoberto Roca, MD, Deputy Director
Bob A. Rappaport, MD, Division Director (for foreign inspection requests or requests for 5 or more sites only)

******Things to consider in decision to submit request for DSI Audit***

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
 - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
 - *Expected commonly reported AEs are not reported in the NDA*

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- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

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/s/

TANYA D CLAYTON
12/10/2010

ARTHUR F SIMONE
12/10/2010

RIGOBERTO A ROCA on behalf of BOB A RAPPAPORT
12/10/2010