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RESEARCH**

APPLICATION NUMBER:

206940Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

NDA/BLA # NDA 206940/Eluxadoline (VIBERZI)
Product Name:

PREA PMR Description Conduct a dose ranging study to determine the safety and effectiveness of eluxadoline in pediatric patients 6 through 17 years with diarrhea-predominant irritable bowel syndrome (IBS-D). The pharmacokinetics of eluxadoline in these pediatric patients should also be characterized.

PMR Schedule Milestones: Final Protocol Submission: 06/01/2016
Study Completion: 10/15/2019
Final Report Submission: 01/15/2020

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

The adult studies are completed and ready for approval.

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

The goal of this phase 2 study is to assess the safety and effectiveness of eluxadoline in pediatric patients with IBS-D. (b) (4)

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 dose ranging study to determine the safety and effectiveness of eluxadoline in pediatric patients 6 through 17 years IBS-D.

Required

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

Continuation of Question 4

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

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

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

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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

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

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

NDA/BLA # NDA 206940/Eluxadoline (VIBERZI)
Product Name:

PREA PMR Description: Conduct a randomized, double-blind study to determine the safety and effectiveness of eluxadoline in pediatric patients 6 through 17 years with diarrhea-predominant irritable bowel syndrome (IBS-D)

PMR Schedule Milestones:	Final Protocol Submission:	<u>03/31/2020</u>
	Study Completion:	<u>03/15/2026</u>
	Final Report Submission:	<u>06/15/2026</u>

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

The adult studies are completed and ready for approval.

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

The goal of this phase 3 study is to confirm the safety and effectiveness of eluxadoline in pediatric patients (ages 6 to 17) with IBS-D. (b) (4)

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 randomized, double-blind, placebo-controlled clinical trial to determine the safety and effectiveness of eluxadoline in pediatric patients 6 through 17 years IBS-D.

Required

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

Continuation of Question 4

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

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

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

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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

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

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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.

An open-label extension study to evaluate the safety of eluxadoline administered for up to 52 weeks in pediatric patients 6 through 17 years with IBS-D who completed the confirmatory efficacy and safety study.

Required

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

Continuation of Question 4

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

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Clinical trial primarily designed to further define long-term safety.

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

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

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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

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

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

NDA/BLA # 206940
Product Name: Viberzi (eluxadoline)

PMR Description: A dedicated clinical pharmacology trial to evaluate the impact of renal impairment on eluxadoline pharmacokinetics and the risk for euphoria and other central nervous system (CNS) adverse effects.

PMR Schedule Milestones:	Final Protocol Submission:	<u>01/01/2016</u>
	Study/Trial Completion:	<u>12/31/2017</u>
	Final Report Submission:	<u>06/30/2018</u>

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

Eluxadoline appears to have low bioavailability and only 0.1% of the drug was recovered in urine in the mass balance study. Therefore, it was agreed at the pre-NDA stage that the renal impairment study can be conducted post-approval.

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

The goal of the study is to assess the effect of renal impairment on the pharmacokinetics of eluxadoline and assess the potential risks related to euphoria and other CNS adverse effects.

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.

The study will be conducted in healthy subjects and subjects with End Stage Renal Disease (ESRD) not yet on dialysis.

Required

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

Continuation of Question 4

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

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

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

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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

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

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

NDA/BLA # NDA 206940
Product Name: Viberzi (eluxadoline)

PMC Description: *An in vitro* study to determine the specific isozymes involved in the metabolism of eluxadoline.

PMC Schedule Milestones:	Final Protocol Submission:	<u>01/01/2016</u>
	Study/Trial Completion:	<u>12/31/2016</u>
	Final Report Submission:	<u>03/31/2017</u>

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

The sponsor did conduct *in-vitro* metabolism studies in the submission. However, the *in-vitro* test systems used to evaluate the potential metabolism (human hepatocytes, microsomes and S9) of eluxadoline were not adequately characterized in respect to various phase 1 and 2 enzymes prior to the studies. Therefore, metabolism of eluxadoline cannot be ruled out. Hence, an adequate *in-vitro* metabolism study is requested as a PMC.

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.”

The goal of this *in-vitro* study is to adequately characterize the metabolism of eluxadoline.

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.

This will be an *in-vitro* metabolism study.

Required

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

Continuation of Question 4

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

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

Agreed upon:

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

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

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMC Development Template

NDA/BLA # 206940
Product Name: Viberzi (eluxadoline)

PMC Description: An *in vitro* study to assess the time-dependent inhibition of CYP3A4 by eluxadoline.

PMC Schedule Milestones:	Final Protocol Submission:	<u>01/01/2016</u>
	Study/Trial Completion:	<u>12/31/2016</u>
	Final Report Submission:	<u>03/31/2017</u>

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

Preliminary *in-vitro* data suggest time-dependent inhibition of CYP3A4 by eluxadoline at a concentration (50 uM) that can be achieved in the gut (I_{gut} is estimated to be 400 µg/mL or 700 uM). Further *in-vitro* studies are necessary to allow an adequate assessment of *in-vivo* relevance of this interaction.

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.”

The goal of this *in-vitro* study is to assess the *in-vivo* relevance of time-dependent inhibition of CYP3A4 by eluxadoline.

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.

This will be an *in-vitro* study.

Required

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

Continuation of Question 4

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

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

In-vitro study

Other

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

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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

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

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMC Development Template

NDA/BLA # 206940
Product Name: Viberzi (eluxadoline)

PMC Description: *An in vitro* study to estimate the IC₅₀ (or K_i) value of eluxadoline with respect to P-gp and predict the *in vivo* relevance of this interaction.

PMC Schedule Milestones:	Final Protocol Submission:	<u>01/01/2016</u>
	Study/Trial Completion:	<u>12/31/2016</u>
	Final Report Submission:	<u>03/31/2017</u>

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

Inhibition potential of eluxadoline toward transporters was only evaluated at one concentration, 400 ng/mL (no inhibition was demonstrated), and thus, IC₅₀ (or K_i) values were not determined in this submission. Although the systemic concentration of eluxadoline (C_{max} is 2-4 ng/ml) is almost 100-fold lower than the tested concentration, the eluxadoline concentration in the gut (I_{gut} is estimated to be 400 µg/mL), which has expression of P-gp, can be about 1000-fold higher than the tested concentration. Therefore, further assessment is necessary for P-gp transporter.

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.”

The goal of this *in-vitro* study is to assess the potential of eluxadoline to inhibit P-gp transporter in-vivo, particularly in the gut.

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.

This will be an *in-vitro* study

Required

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

Continuation of Question 4

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

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

Agreed upon:

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

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

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMC Development Template

NDA/BLA # 206940
Product Name: Viberzi (eluxadoline)

PMC Description: Conduct *in-vitro* study to evaluate the potential of eluxadoline to inhibit CYP2C8 and induce CYP2B6.

PMC Schedule Milestones:	Final Protocol Submission:	<u>01/01/2016</u>
	Study/Trial Completion:	<u>12/31/2016</u>
	Final Report Submission:	<u>03/31/2017</u>

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

Potential of eluxadoline to inhibit CYP2C8 or induce CYP2B6 was not assessed in this submission.

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.”

The goal of this *in-vitro* study is to assess the potential of eluxadoline to inhibit CYP2C8 and induce CYP2B6.

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.

<i>In-vitro</i> study.

Required

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

Continuation of Question 4

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

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

In-vitro study

Other

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

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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

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

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMC Development Template

NDA/BLA # 206940
Product Name: Viberzi (eluxadoline)

PMC Description: **Conduct a study of the product dissolution and acceptance criterion to assess post-approval product quality using the following:**

- Re-evaluate the dissolution acceptance criterion based on the dissolution data collected from at least 10 batches of commercial drug products (5 batches of 75 mg and 5 batches of 100 mg), manufactured over a maximum period of 1 year post-launch.
 - Add a 15- minute time-point to the dissolution test at time of product release and in the stability protocol where profiles will be followed at 10, 15, 20, 30, 45, and 60 minutes.
 - Assess the dissolution criterion of $Q = \frac{(b)}{(4)}\%$ at 10, 15, or 20-minute time points and submit the newly proposed dissolution criterion with supportive dissolution profile data to the Agency for review.
-

PMC Schedule Milestones:	Completion of dissolution data assessment:	Launch + 12 months
	Submission of dissolution data assessment:	Launch + 14 months

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

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.”

To assure product quality

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.

Required

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

Continuation of Question 4

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

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

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

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

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- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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/s/

JENNIFER S SARCHET
05/27/2015

LAURIE B MULDOWNNEY
05/27/2015

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

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

Memorandum

Date: April 28, 2015

To: Anissa Davis, RN, BSN, MPH, CPHM, Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer,
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Pharm.D., Team Leader, OPDP

Subject: NDA# 206940 - (b) (4) (eluxadoline) tablets, for oral Use

Reference is made to DGIEP's consult request dated October 9, 2014, requesting review of the proposed Package Insert (PI), Carton/Container Labeling, and Medication guide (MG) for (b) (4) (eluxadoline) tablets, for oral use ((b) (4)).

OPDP has reviewed the proposed PI entitled, "CURRENT LABEL Eluxadoline PI with team edits 4 13 15.doc" that was available in SharePoint on April 15, 2015. OPDP's comments on the proposed PI are provided directly on the attached copy of the labeling (see below).

OPDP has also reviewed the proposed Carton/Container labeling entitled, "draft-carton-container-labels.pdf" that was sent from DGIEP to OPDP on April 23, 2015. OPDP has no comments at this time on the proposed Carton/Container labeling.

Please note that comments on the proposed MG were provided on April 27, 2015 under separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP).

Thank you for your consult. If you have any questions please contact me at (240) 402-5039 or adewale.adeleye@fda.hhs.gov

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/s/

ADEWALE A ADELEYE
04/28/2015

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

PATIENT LABELING REVIEW

Date: April 27, 2015

To: Donna Griebel, MD
Director
**Division of Gastroenterology and Inborn Errors
Products (DGIEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN, BSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Adewale Adeleye, Pharm.D., MBA
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): TRADENAME (eluxadoline)

Dosage Form and Route: tablets, for oral use, C-(Pending determination)

Application Type/Number: NDA 206940

Applicant: Furiex Pharmaceuticals, Inc.

1 INTRODUCTION

On June 26, 2014, Furiex Pharmaceuticals, Inc. submitted for the Agency's review New Drug Application (NDA) 206940 for TRADENAME (eluxadoline) tablets, with the proposed indication for the treatment of pain and diarrhea associated with diarrhea-predominant Irritable Bowel Syndrome (IBS-d).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to the requests by the Division of Gastroenterology and Inborn Errors Products (DGIEP) on September 11, 2014, and October 9, 2014, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TRADENAME (eluxadoline) tablets.

2 MATERIAL REVIEWED

- Draft TRADENAME (eluxadoline) tablets MG submitted on June 26, 2014 and received by DMPP and OPDP on April 14, 2015.
- Draft TRADENAME (eluxadoline) tablets Prescribing Information (PI) submitted on June 26, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 14, 2015.

3 REVIEW METHODS

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

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
04/27/2015

ADEWALE A ADELEYE
04/27/2015

SHAWNA L HUTCHINS
04/27/2015



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: April 21, 2015

To: Donna Greibel, M.D., Director
Division of Gastroenterology and Inborn Errors Products

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff (CSS)

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Eluxadoline (JNJ-27018966; Viberzi)
NDA 206940 (IND 79,214)
Indication: Diarrhea-predominant form of irritable bowel syndrome (IBS-d)
Sponsor: Furiex Pharmaceuticals, Inc.
PDUFA Goal Date: May 27, 2015

Materials reviewed: Abuse-related preclinical and clinical data in NDA (submission #000, 6/27/14); medical officer NDA review (Dr. Laurie Muldowney, DARRTS 2/25/15); pharmacology/toxicology NDA review (Dr. Tamal Chakraborti, DARRTS 1/23/15); statistical review of human abuse potential studies, Dr. Feng Zhou, DARRTS 2/27/15)

Table of Contents

1	BACKGROUND	2
2	CONCLUSIONS:	2
3	RECOMMENDATIONS:	6
4	DISCUSSION:	7

1. Background

This memorandum responds to a consult request to CSS by the Division of Gastroenterology and Inborn Errors Products (DGIEP) to evaluate abuse-related preclinical and clinical data submitted in NDA 206,940 for eluxadoline (Viberzi). The Sponsor is Furiex Pharmaceuticals, Inc.

Eluxadoline is new molecular entity that acts as a mixed mu and kappa opioid receptor agonist, as well as delta opioid receptor antagonist. It is being developed as an oral therapeutic for diarrhea-predominant and alternating diarrhea/constipation forms of irritable bowel syndrome (IBS-d). The Sponsor claims that eluxadoline has very low oral bioavailability, and normalizes altered GI motility by acting at peripheral opioid receptors in the GI tract. Thus, the mechanism of eluxadoline in treating IBS-d is purported to be from local activity within the gastrointestinal (GI) tract, where opioid receptors play a role in reducing GI motility, secretion, and visceral sensation. However, as shown below in the review of the animal and human data, eluxadoline is psychoactive following oral, intranasal and intravenous routes of administration in animals and/or humans.

The Sponsor is seeking approval to market 75 and 100 mg oral tablets of eluxadoline. The recommended therapeutic regimen is 100 mg twice daily (BID) dosing with food, although a 75 mg BID dose with food is recommended for patients with prior cholecystectomy or for those who cannot tolerate the 100 mg dose.

2. Conclusions

a) CSS has reviewed the nonclinical and clinical abuse-related data submitted in NDA 204,422 for eluxadoline and concludes that the drug has abuse potential. This conclusion is based on the data described below:

- Eluxadoline is not chemically similar to any opioid agonist that is currently scheduled under the Controlled Substances Act. The synthesis of eluxadoline requires an in depth knowledge and skills in organic chemistry that makes purification and crystallization of the substance difficult. However, eluxadoline substance is soluble in methanol at room temperature and in a mixture of isopropyl alcohol + water above 70°C. Whole tablets are easily crushed once they are cracked. Over 70% of eluxadoline is extractable from tablets in 10 ml of water using heat and stirring speed higher than 10 rpm. However, the Sponsor did not test methanol extraction with crushed tablets. These data suggest that eluxadoline could be extracted for abuse purposes.
- In receptor binding studies and functional assays, eluxadoline was shown to be a high affinity mu opioid agonist ($K_i = 0.6-153$ nM in rat tissue, 1.8 nM in human cells), kappa opioid agonist (KOR; $K_i = 55$ nM) and delta opioid antagonist (DOR; $K_i = 4.3-407$ nM in rat tissue and 674 nM in human cells).

- In tests of general behavior, eluxadoline did not produce any behavioral changes after acute oral or subcutaneous administration in mice, or after 14 day or 9 month oral administration in monkeys. However, eluxadoline HCl produces classic mu opioid agonist behavioral responses, during 14 days of intravenous administration to rats, and 7 days of intravenous administration to monkeys. Similarly, oral administration of eluxadoline did not produce an antinociceptive response in mice, while subcutaneous administration did produce analgesia, as did intravenous administration of eluxadoline HCl. The ability of eluxadoline to induce analgesia similarly demonstrates mu opioid agonist activity.
- In a drug discrimination study in monkeys, intravenous administration of eluxadoline HCl produced full generalization to the morphine cue, demonstrating that it has mu opioid agonist properties.
- In a self-administration study in monkeys, eluxadoline HCl was self-administered to a degree that was less than that of heroin but greater than that of saline. This shows that eluxadoline has rewarding properties indicative of abuse potential.
- Opioid overdose responses were observed in two studies conducted in monkeys that had received eluxadoline HCl intravenously. In a dose-finding study, acute administration of the opioid antagonist, naloxone, did not revive one monkey that had received 40 mg/kg of eluxadoline HCl. However, repeated doses of naloxone to monkeys that received a 30 mg/kg dose of eluxadoline HCl did reverse the opioid overdose in all monkeys. In the self-administration study in monkeys, intravenous administration of eluxadoline HCl produced an opioid overdose in three monkeys, one of which died after self-administering ~42 mg/kg of the drug. The other two animals were given the opioid antagonist, naltrexone, which reversed the overdose in the monkey that received ~56 mg/kg of eluxadoline HCl. However, the monkey that self-administered ~61 mg/kg of eluxadoline HCl did not show immediate reversal of severe sedation with naltrexone, even though the animal survived. These data suggest that acute administration of an opioid antagonist may be inadequate to reverse an eluxadoline overdose.
- There were no signs of physical dependence (as evidenced by the presence of withdrawal behaviors) following discontinuation of eluxadoline after acute and chronic administration in animals.
- In an oral administration human abuse potential study, eluxadoline at supratherapeutic oral doses (300 and/or 1000 mg) produced small but significant increases compared to placebo in positive subjective responses such as Drug Liking, Take Drug Again, Subjective Drug Value, Good Effects, High, and Euphoria. The positive subjective responses to eluxadoline were typically statistically significantly lower than those produced by oxycodone. Oral eluxadoline also produced a small but significant increase in Drug Disliking, Bad Effects, Dysphoria. Oxycodone (30 and 60 mg) produced similar positive and negative subjective responses, but to a degree that was statistically greater than

that of eluxadoline and placebo. Eluxadoline produced the AE of euphoria (ranging from 14-28%) that was greater than that after placebo (5%) but less than that of oxycodone (ranging from 73-76%). Mild somnolence was also reported after eluxadoline (ranging from 19-42%), but the lowest rate was reported at the highest dose (1000 mg). This was similar to the rate reported with oxycodone (38-41%), and overlaps with the rate after placebo (19%). These data show that oral eluxadoline produces positive subjective responses that are indicative of abuse potential.

- In an intranasal administration human abuse potential study, eluxadoline HCl (100 and 200 mg) produced small but significant increases compared to placebo in positive subjective responses such as Overall Drug Liking, Subjective Drug Value, Good Effects, High, and Euphoria. The positive subjective responses to eluxadoline were most often statistically less than those produced by oxycodone. Oral eluxadoline also produced a small but significant increase in Drug Disliking, Bad Effects, Dysphoria. Oxycodone (15 and 30 mg) produced similar positive and negative subjective responses, but to a degree that was statistically greater than that of eluxadoline and placebo. Eluxadoline produced the AE of euphoria (ranging from 19-22%) that was greater than that after placebo (0%) but less than that of oxycodone (ranging from 44-67%). These data show that intranasal eluxadoline produces positive subjective responses that are indicative of abuse potential.
- The pooled dataset for Phase 2 and 3 studies showed a low level of abuse-related AEs. The AE of euphoric mood was reported by only 2 IBS-d patients in the pooled Phase 2 and 3 safety set (0.2% of population). Similarly, feeling drunk was reported by only 2 subjects (0.1% of subjects in the 75 mg group and 0.1% of subjects in the 100 mg group). The most commonly reported abuse-related AEs other than euphoria were anxiety (1.7%) and somnolence (0.7%). There were a few other central nervous system-associated AEs, all of which are often seen in clinical trials: headache (4.0-4.5%), dizziness (2.2-3.2%), and fatigue (1.9-2.6%). However, these AEs demonstrate that eluxadoline does enter the systemic bloodstream after oral administration and crosses the blood brain barrier to affect behavior.
- The human physical dependence study was inadequately designed to evaluate whether chronic administration of eluxadoline produces withdrawal responses indicative of physical dependence.

b) The Sponsor submitted revised text for Section 9.0 of the label on March 11, 2015 (see Appendix). In the text, the Sponsor proposes that eluxadoline should be placed into Schedule IV of the Controlled Substances Act (CSA). CSS has revised the proposed text to accurately describe the abuse-related preclinical and clinical data that were submitted in the NDA (see Recommendations, below). However, CSS concurs with the Sponsor that eluxadoline should be recommended for placement into Schedule IV of the Controlled Substances Act (see Recommendations, below).

3. Recommendations

CSS recommends the following label text for Section 9.0:

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Pending

9.2 Abuse

In a drug discrimination study in monkeys, intravenous administration of eluxadoline HCl produced full generalization to the morphine cue. In a self-administration study in monkeys, eluxadoline HCl was self-administered to a degree that was less than that of heroin but greater than that of saline.



9.3 Dependence



b) The following information should be considered by the Division regarding the label text for Section 10 Overdose:

Opioid overdose responses were observed in two studies conducted in monkeys that received eluxadoline HCl intravenously. In a dose-finding study, acute administration of the opioid antagonist, naloxone, did not revive one monkey that had received 40 mg/kg of eluxadoline HCl. However, repeated doses of naloxone to monkeys that received a 30 mg/kg dose of eluxadoline HCl did reverse the opioid overdose induced in all monkeys. In the self-administration study in monkeys, intravenous administration of eluxadoline HCl produced an opioid overdose in three monkeys, one of which died after self-

administering ~42 mg/kg of the drug. The other two animals were given the opioid antagonist, naltrexone, which reversed the overdose in the monkey that received ~56 mg/kg of eluxadoline HCl. However, the monkey that self-administered ~61 mg/kg of eluxadoline HCl did not show immediate reversal of severe sedation with naltrexone, even though the animal survived.

Although these studies utilized an intravenous route of administration, the inability of acute doses of opioid antagonists to reverse the effects of eluxadoline is important safety information, especially in cases of medical error or intravenous abuse of eluxadoline.

c) Eluxadoline should be recommended for Schedule IV under the Controlled Substances Act.

4. Discussion

A. Chemistry of Eluxadoline

Eluxadoline tablets will be available as 75 mg and 100 mg ^{(b) (4)} coated tablets. The tablets are ^{(b) (4)} not formulated to possess abuse deterrent properties, and all the excipients are well characterized and commonly used.

1. Drug Substance

a. Chemical Properties

Eluxadoline (USAN name) is a new molecular entity, also known as JNJ-27018966, R497138 and T3301, identify by CAS registry number: 864821-90-9 It is chemically known as 5-[[[(2S)-2-amino-3-[4-aminocarbonyl]-2,6-dimethylphenyl]-1-oxopropyl]][(1S)—1-(5-phenyl-1H-imidazol-2-yl)ethyl]amino]methyl]-2-methoxybenzoic acid, and its chemical structure is depicted in **Figure 1**. It has a molecular formula of C₃₂H₃₅N₅O₅ and a molecular weight of 569.65. ^{(b) (4)}

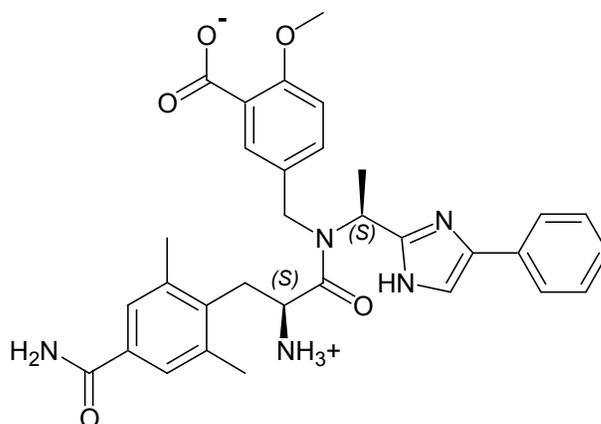


Figure 1. Eluxadoline Chemical Structure.

Eluxadoline has two asymmetric carbons (identified in **Figure 1** with an asterisk), and as such four different optical isomers can exist. However, when we refer to eluxadoline we refer to one optical isomer out of the possible four that is the (1*S*, 2*S*)-(+)-isomer. It is a white powder, slightly soluble in water and soluble in 0.1 N hydrochloric acid (0.1 N HCl). Due to the presence of a primary amine and a carboxylic acid drug exists as a zwitterion depending on pH; meaning that depending on the pH of the environment the primary amine will be protonated (positively charged) and the carboxylic acid will be deprotonated (negatively charged). The Sponsor reported the following ionization constants or pKa values: for the primary amine a pKa: 7.11, for the carboxylic acid a pKa: 3.77, and for the imidazole a pKa: 4.70. A Partition Coefficient for the zwitterionic form was reported as LogP=0.90. pKa is defined as negative logarithm of the equilibrium coefficient of the charged and neutral forms of a substance. Whereas knowledge of the pKa helps to determine the charge of a molecule at any given pH, the Log P measures how a substance partitions between a lipid (octanol) and water.

Conclusion: Eluxadoline is not structurally similar to any other opioid drug

b. Synthesis

The synthesis of eluxadoline is accomplished in  (b) (4)



 (b) (4)

 (b) (4)

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Conclusions:

- 1) Eluxadoline is not chemically similar to any opioid currently scheduled under the Controlled Substances Act.
- 2) The synthesis of eluxadoline requires an in depth knowledge and skills in organic chemistry.

3)

4)

(b) (4)

2. Drug Product

Eluxadoline tablets will be available as 75 mg and 100 mg film-coated tablets. Eluxadoline tablets are (b) (4) not formulated to have abuse deterrent properties, and all the excipients are very well characterized and commonly used. These excipients are silicified microcrystalline cellulose, (b) (4) colloidal silica (b) (4), mannitol (b) (4), croscopolvidone, (b) (4), magnesium stearate (b) (4). The pale yellow 75 mg tablets are coated with Opadry II (b) (4) and the pink-orange 100 mg tablets are coated with Opadry II (b) (4).

The overall size of the tablets is 618 mg for the 75 mg strength tablet and 824 mg for the 100 mg tablet.

a. Manipulation of Eluxadoline from Tablets

Although eluxadoline tablets are not formulated as abuse deterrent (and the Sponsor is not seeking an abuse deterrent claim), the Sponsor conducted extraction studies to demonstrate the feasibility of extracting eluxadoline for abuse purposes.

The Sponsor evaluated the ease of cutting and crushing the samples, and different solvents for extraction. The following sections describe and summarize the findings of these studies.

Physical Manipulations and Pretreatment

The ease of crushing whole tablets using a range of readily available household items was evaluated (Study #KCM-2012-0461-ANA). These tools included: spoons, pill crusher, hummer, pliers, razor blade, rolling pin and mortar and pestle.

The removal of the film coating was investigated by wiping the tablets with paper towels wet with water. Both strengths had a coating that was easily removed by this procedure.

In addition the Sponsor explored the effect of pretreating the tablets for 2 hours at -20°C and at 100°C.

Conclusions:

- 1) The whole tablets are fairly hard and have a tendency to shatter with initial force. However once cracked, the tablets were easily crushed. The best tools proved to be a tablet crusher and a mortar and pestle.
- 2) Removal of the film coating as well as pretreatment of the tablets did not alter the ease required to reduce the tablets to a powder that could be snorted or used for extractions.

Solubility/Extractability

The Sponsor conducted several extractability studies, including preparation for a solution suitable for intravenous injection and simulated smoking studies. The Sponsor conducted studies with a single and multiple tablets, and determined the percent of extracted eluxadoline in various aqueous and organic solvents. Extractions were conducted at 25°C and at 95°C, and while shaking the solutions on an orbital shaker at 100 rpm (Studies #KCM-2012-0559-ANA, and #KCM-2012-0461-ANA).

Single tablet: Experiments designed to simulate a solution of eluxadoline for injection were conducted by extracting a single intact or crusher 10 mg eluxadoline tablet and 10 mL of solvent, at 25°C with agitation. The Sponsor used the following solvents: water, 0.1 M HCl, ethanol, buffer pH 2, pH 4, pH 7 and pH 10, saline 10%, ethanol/water, isopropanol, hexane and acetone.

Percent recoveries were variable. The extraction of eluxadoline was highly efficient in acidic and basic solutions (0.1 M HCl, pH 2 and 10 buffers. For water saline, ethanol, pH 4 and pH 7 buffers and isopropanol was relatively effective, hexane and acetone were not good solvents for extraction.

The results for all solvents were comparable for both crushed and whole tablets, with some solvents such as isopropanol and 10% ethanol extracting relative a higher amount of eluxadoline from crushed tablets.

Filtration reduced the recovery from all solvents, indicating that a suspension may form when extracting.

The Sponsor reported a great degree of variability in the extraction results, however a high percent recovery of eluxadoline was observed in 0.1 M HCl, 10% and 40% ethanol, pH 2 and pH 10 buffers at elevated temperatures

Multiple tablet extraction: Extractions with 10 ml of solvent (water and 0.1 M HCl) were conducted using 2 and 4 crushed tablets, at 95°C and while shaking the solutions on

an orbital shaker at 100 rpm. Data presented by the Sponsor showed that the amount of eluxadoline extracted from 2 tablets is more effective than using 4 tablets.

Note: The Sponsor did not report using methanol, (b) (4)

Syringibility

All solutions were easily loaded into a disposable syringe using a 25 gauge needle.

Simulated smoking

Browning and charring was evident when tablets and ground product were heated at 225°C. No detectable eluxadoline was vaporized from ground or crushed tablets.

Extraction followed by evaporation

The Sponsor studied the feasibility of obtaining a sample of eluxadoline powder for the purpose of snorting after extraction and evaporation (KCM-2014-0015-ANA). These studies showed that a highly concentration solution of eluxadoline can be obtained in acidic solvent, and complete evaporation of the solution containing eluxadoline was possible by blowing an air current over a 10 mL solution. The resulting material from evaporation was glass-like and adhered to the evaporation dish. After scraping the dish, the material found to be sticky and flaky. And the HPLC analysis showed that the material contain approximately 44% of eluxadoline. Precipitation with IPA was also explored, though it produced a low yield of drug.

Effect of shaking speed

The influence of shaking speed during extraction was studied by the Sponsor. Extractions were performed on an orbital shaker at 150 rpm and 200 rpm. These studies showed that extraction of eluxadoline increased with increasing shaking speed, and high temperatures. A higher percentage of eluxadoline was recovered at 10 minutes from intact (76% vs 40%) and ground tablets (74% vs 39%) in water at and at 95°C by increasing the agitation from 100 rpm to 150 rpm.

Note: Magnetic stirrers can easily reach speeds that range up to 1500 rpm. Hotplate stirrers and magnets can be easily purchased over the Internet.

Conclusions:

- 1) In the hands of the Sponsor, once the tablets were cracked, they were easily crushed using a tablet crusher or a mortar and pestle.

- 2) When attempting extraction of eluxadoline, the recovery of eluxadoline was variable under most of the conditions used by the Sponsor, and presented some level of difficulty.
- 3) The Sponsor did not report using methanol, [REDACTED] (b) (4).
- 4) Over 70% of eluxadoline was extracted in 10 mL of water, at 10 minutes, increasing the speed of stirring from 100 to 150 rpm and at 95°C. Hotplate stirrers can reach higher speed than 150 rpm, and can be easily purchased over the Internet.
- 5) The predictive value of the *in vitro* manipulation data is limited to the experimental conditions tested, and it can't be precluded that abusers may find a way to manipulate the formulation and efficiently extract eluxadoline for purposes of abuse.

B. Pharmacology of Eluxadoline

1. Receptor Binding and Functional Studies

a. Receptor Binding Studies with Eluxadoline (Study #DD07380, DD07362, DD07371, DD07373, DD07435, DD07364, DD07352, 100006176)

Eluxadoline was tested in receptor binding studies and found to have very high affinity at the mu opioid receptor (MOR; $K_i = 0.6\text{-}153$ nM in rat tissue, 1.8 nM in human cells) and delta opioid receptor (DOR; $K_i = 4.3\text{-}407$ nM in rat tissue and 674 nM in human cells). It also has high affinity for kappa opioid receptors (KOR; $K_i = 55$ nM).

There was no significant affinity of eluxadoline for other binding sites, including sites associated with abuse potential (GABA/ benzodiazepine, dopamine (D1 and D2), serotonin (1A, 1B, 2A, 3, 5A, 6, and 7), cannabinoid (CB1, CB2), NMDA/glutamate, channels (calcium, potassium, sodium, chloride), transporters (dopamine, norepinephrine)) and sites that are not associated with abuse potential (acetylcholine (muscarinic and nicotinic), adenosine, norepinephrine (alpha and beta), histamine, and neurokinin).

b. Functional Assays with Eluxadoline (Study #DD07373)

Functional assays were conducted to determine if eluxadoline acts as an agonist or antagonist at MOR, DOR and KOR. In cells transfected with MOR, eluxadoline stimulated [35 S]GTP γ S binding with an EC₅₀ of 0.96-2.7 nM. Eluxadoline was also tested for its ability to inhibit contraction in isolated guinea pig proximal colon, a test of KOR agonism. Both eluxadoline and the KOR agonist, ICI 204,448, inhibited activity in the colon, with respective EC₅₀ values of 1.6 μ M and 7.7 nM. In contrast, eluxadoline did not stimulate [35 S]GTP γ S binding in cells transfected with DOR at concentrations up to 10 μ M. However, eluxadoline did block the [35 S]GTP γ S binding stimulated by the DOR agonist, SNC 80 (1 μ M).

Thus, in these studies, eluxadoline has potent agonist activity at MOR and KOR, but antagonist activity at DOR.

2. Preclinical Behavioral Studies

Animal studies were conducted with two forms of eluxadoline, depending on the route of administration to be used. For studies that used oral or subcutaneous administration, the (b) (4) form of eluxadoline (similar to that used in the proposed therapeutic formulation) was administered. (b) (4) studies that used intravenous administration utilized the bis-hydrochloride salt form of eluxadoline (represented below as “eluxadoline HCl”).

a. General Behavioral Observations

Irwin Test (Acute Subcutaneous and Oral Administration) (Study #1808-014, DD07345)

Mice received subcutaneous doses of eluxadoline at 500, 1000, or 2000 mg/kg in the Irwin test, but there were no observable behaviors produced by any of these doses. Similarly, rats received 30 or 300 mg/kg eluxadoline by oral gavage and observed for motor activity, reflexes, excitation, body tone, righting reflex, and rotorod tests. There were no changes observed in any behavior or in body temperature after either dose.

9-Month Oral Administration Toxicity Study in Cynomolgus Monkeys with 4-week Recovery (Study #1808-004)

Cynomolgus monkeys (n = 4-7/sex/group) were given eluxadoline (50, 100, and 200 mg/kg/day) or vehicle via oral gavage for 9 months, followed by a 4 week recovery period (for the vehicle and 200 mg/kg groups). Animals showed no changes in behavior during the 39-week treatment period at any dose.

14-day Intravenous Administration Toxicity Study in Rats with 2-week recovery (Study #1808-014)

Rats were given 14 consecutive days of intravenous administration of eluxadoline HCl at 5, 10, and 20 mg/kg/day, followed by a 14 day recovery period. Classic opioid-related behaviors were observed following drug administration at the 10 and 20 mg/kg/day dose levels, including changes in general arousal, handling reactivity, stereotypy, tail pinch response, touch response, posture, gait, mobility, righting reflex, stereotypy, respiration and hindlimb splay.

Notably, the protocol states that in the case of apparent opioid overdose signs, 0.1 mg/kg of the opioid antagonist, naloxone, would be administered intravenously or subcutaneously (to more or less severely affected animals, respectively). However, a search of the study report did not reveal any reports of naloxone use during the study.

Dose-Range Finding Intravenous Administration Toxicity Study in Cynomolgus Monkeys (Study #1808-015)

Cynomolgus monkeys (n = 3/sex/group) were given eluxadoline HCl (5, 10, 20, 40/30 mg/kg/day) or vehicle intravenously for 7 consecutive days. Animals showed few changes in behavior during the treatment period at 5 and 10 mg/kg doses, while opioid-associated behaviors such as decreased respiration and periods of unconsciousness began to emerge at 20 mg/kg and were severely pronounced at the 40 mg/kg dose.

All animals in the highest dose group (40 mg/kg, reduced to 30 mg/kg on the second day of dosing after one animal died) experienced opioid overdose symptoms, including decreased activity, unresponsiveness, and decreased body temperature and/or respiration rates. Animals were all treated with 0.1 mg/kg of the opioid antagonist, naloxone, either intravenously or subcutaneously (to more or less severely affected animals, respectively). After the first monkey died from insufficient dosing with naloxone, all monkeys at the 30 mg/kg dose that experienced opioid overdose symptoms received repeated dosing with naloxone. No other animals died upon repeated naloxone administration.

14-day Oral Administration Toxicity Study in Cynomolgus Monkeys with 2-week recovery (Study #1808-012)

Cynomolgus monkeys (n = 4-7/sex/group) were given eluxadoline HCl (5, 10 and 20 mg/kg/day) or vehicle via oral gavage for 14 consecutive days, followed by a 2 week recovery period (for the vehicle and 20 mg/kg groups). Animals showed few changes in behavior during the 14 day treatment period at any dose. Tremor were observed in 3 monkeys at 20 mg/kg/day on Day 1, but at no other time or in any other animals throughout the study. Although soft feces were observed during drug administration at the 10 and 20 mg/kg doses, this effect is the opposite of that expected from opioid administration. Soft feces persisted during the drug discontinuation period.

Notably, the protocol states that in the case of apparent opioid overdose signs, 0.1 mg/kg of the opioid antagonist, naloxone, would be administered intravenously or subcutaneously (to more or less severely affected animals, respectively). However, the study report states that naloxone intervention was not required.

b. Antinociceptive Effects in Mice (Study DD07369, DD07378)

A hot-plate test of antinociception was used to evaluate the effects of eluxadoline in mice (n = 5-10). When eluxadoline was given orally up to doses of 1000 mg/kg, there was no significant analgesic responses. However, when eluxadoline was administered subcutaneously, both 10 and 60 mg/kg produced significant increases in hot plate latencies (suggesting analgesia), as well as concurrent opioid-associated behaviors such as Straub tail and increased limb tone (tiptoeing). Similarly, a 1 mg/kg intravenous dose of eluxadoline HCl produced antinociceptive effects rapidly. These results demonstrate

that oral administration of eluxadoline does not produce centrally-mediated analgesia, while subcutaneous and intravenous administration do.

In contrast, when the pain model was a localized hyperalgesic response to colorectal balloon distension during an acute, zymosan-induced colitis, eluxadoline reduced the hyperalgesic response following either oral or intraperitoneal administration. This shows that eluxadoline is able to act locally in the gut as an opioid analgesic.

c. Abuse-Related Preclinical Studies (Drug Discrimination and Self-Administration)

Dose Finding Study for Intravenous Administration in Monkeys

Given that oral and intraperitoneal doses of eluxadoline did not produce significant opioid behavioral effects, it was determined that the monkey drug discrimination study and the monkey self-administration study should be conducted using intravenous administration of eluxadoline HCl. Thus, it was necessary to conduct dose range-finding studies using intravenous administration using eluxadoline HCl.

Before describing the process the Sponsor used to estimate intravenous doses that would approximate human intravenous doses, it is important to note how the dose of eluxadoline was prepared for these monkey studies.

As noted in the NDA review of Dr. Laurie Muldowney, the Medical Officer in DGIEP:

In order to test whether an intravenous form of eluxadoline had abuse potential, the animal abuse-related studies were conducted with the bis-hydrochloride salt (eluxadoline HCl). (b) (4)

The eluxadoline HCl substance used in the animal studies was a (b) (4) (b) (4) was yet known at the time of the studies.

(b) (4)

It should be noted that **for the early drug discrimination and self-administration studies**, (b) (4) as the investigator was not aware of the chemical structure of the test material.

This means that for both monkey studies, animals were intravenously injected (repeatedly, in the case of self-administration) with an extremely acidic solution that likely induced pain. However, since eluxadoline is a mu and kappa opioid agonist, this pain may have been obviated by the pharmacological effects of the drug, despite the lasting caustic insult to the veins and injection site.

For the dose-finding study, testing was initiated at 0.032 mg/kg and advanced at 0.25 log dose increments in successive test sessions until a behavioral signal was observed. Observation of a behavioral signal at a particular dose was to be confirmed by administration of eluxadoline at that dose to a second monkey, and this process was repeated up to a dose exerting behavioral effects in N = 2 monkeys. Each monkey could respond under a multiple schedule of food presentation in one component and shock stimulus termination (SST) in a second component.

There were no changes in response rate on either food reward or SST schedules following intravenous doses of eluxadoline HCl less than 56.0 mg/kg. In the two monkeys that received the 56.0 mg/kg dose there was an increase in the response rates for both food reward and SST paradigms in one monkey, while the other monkey rapidly became unresponsive. Reduced rates of response in both food reward and SST behaviors were observed in one monkey following administration of 100 mg/kg, the highest dose administered in the dose range finding study.

Typically, drug discrimination studies are conducted with animal doses that produce plasma levels that are equivalent to and 2-3 times greater than the plasma levels produced by the highest proposed human therapeutic dose. However, these calculations are based on the presumption that oral administration of the drug therapeutically is likely to produce a centrally-mediated interoceptive cue. Since eluxadoline does not produce behavioral effects after oral administration, the drug discrimination study was planned using an intravenous route of administration. Given that there are no human pharmacokinetic data generated from studies using intravenous administration, it was necessary for the Sponsor to estimate what doses in animals would parallel those in humans after intravenous administration.

In order to calculate an appropriate intravenous dose for drug discrimination studies, the Sponsor used allometric scaling. This method is generally reserved for estimating a safe first-in-human dose, based on pharmacokinetic data generated in animals during toxicology studies. But in the absence of plasma data derived from human studies with intravenous administration of eluxadoline, allometric was the only viable method of estimating doses between species. For this calculation, the Sponsor used toxicokinetic data from the 14 day intravenous studies in monkeys using eluxadoline HCl, as shown below:

Estimated Human Oral, IN, or IV dose that Produce the Same C_{max} as IV Doses of 0.32, 1.0, 3.2, 10.0, and 17.8 mg/kg in Rhesus Monkey Abuse Liability Studies

Rhesus Monkey IV Dose (mg/kg)	Human Oral Dose	Human Intranasal Dose	Human Intravenous Dose
0.32	102 grams	3 grams	30 mg
1	319 grams	10 grams	100 mg
3.2	1023 grams	31 grams	320 mg
10	3197 grams	96 grams	1000 mg
17.8	5690 grams	171 grams	1770 mg

Human oral dose = $[100 \text{ mg} * (\text{monkey IV } C_{\text{max}} / \text{human } 100 \text{ mg oral } C_{\text{max}})] / 1000$

Human IN dose = $1/2 * \{ [100 \text{ mg} * (\text{monkey IV } C_{\text{max}} / \text{human } 100 \text{ mg IN } C_{\text{max}})] / 1000 + [200 \text{ mg} * (\text{monkey IV } C_{\text{max}} / \text{human } 200 \text{ mg IN } C_{\text{max}})] / 1000 \}$

Human IV dose = $[100 \text{ mg} * (\text{monkey IV } C_{\text{max}} / \text{estimated human } 100 \text{ mg IV } C_{\text{max}})] / 1000$

Source: Study DD07334 Addendum Table 6.8

Drug Discrimination Study (Study #DD7374)

Rhesus monkeys (N = 3) were trained to discriminate between morphine and vehicle in test sessions using a shock stimulus termination (SST) procedure. Each session was comprised of 15 minutes (10 minute “time out” period followed by a 5 minute response period). At the start of the session, monkeys would receive an 1.0 mg/kg subcutaneous administration of either morphine or vehicle immediately prior to the beginning of the first of eight 15-minute test cycles (i.e., a 2-hour test session). During the response period, a stimulus light signaled that a mild foot shock was scheduled to occur every 15 seconds. Monkeys could end each possible shock by bar pressing either 5 or 10 consecutive times (fixed ratio 5 or 10; FR5 or FR10) on the correct drug-associated lever, depending on experimental condition (morphine or saline). [Note that there is conflicting information in different study reports regarding the schedule of reinforcement.] Correct bar pressing would reset the next scheduled shock to 30 seconds from the time of bar pressing. During the time out period, stimulus lights were not illuminated, and responding had no scheduled consequences. Successful training was determined by 80% correct bar pressing in 5 consecutive sessions out of 8 sessions, or 6 of 7 sessions.

The SST-drug discrimination training procedure is inadequately described in the study report (comprised of little more than the summarized information above). However, in a published paper by the same investigator (Dr. Charles France at the University of Texas), a more elaborated SST-drug discrimination procedure was described (*France and Gerak. Discriminative Stimulus Effects of Flumazenil in Rhesus Monkeys Treated Chronically With Chlordiazepoxide. Pharmacology Biochemistry and Behavior 56(3):447-455, 1997*) that may parallel the procedures in the present drug discrimination study:

“Prior to drug discrimination training, monkeys were trained to respond under a fixed-ratio (FR) schedule of stimulus-shock termination, followed by training sessions during which monkeys responded in different components under either the stimulus-shock

termination schedule or a FR schedule of food presentation. The food component was discontinued and drug discrimination training commenced with vehicle and 0.056 mg/kg of the test drug. Monkeys responded only under a schedule of stimulus-shock termination during drug discrimination training; injections of vehicle and the test drug alternated under both single- and double-alternation schedules.

“Once drug stimulus control was established, the FR food component was re-introduced and training continued (with the multiple FR food, FR stimulus-shock termination [drug discrimination] schedule) until drug stimulus control was re-established. A single session was conducted each day using the following terminal experimental conditions: a 10-min timeout (TO) period, during which the experimental chamber was dark and lever presses had no programmed consequence; a 4-min response period, during which a green light was illuminated over the center lever and a FR 10 schedule of food presentation was in effect only on the center lever; a 2-min TO; and a 4-min response period during which a red light was illuminated over each left and right lever and a FR 10 schedule of stimulus-shock termination was in effect on the left and right levers (i.e., drug discrimination).

“During the first 4-min response period, stimulus lights were extinguished after 4 min or 50 food presentations, whichever occurred first. During the second 4-min response period, brief electric shock was scheduled to be delivered every 15 sec; monkeys could postpone shock and extinguish stimulus lights for 30 sec by responding 10 times on the lever designated correct according to an injection administered during the first min of the 10-min TO (left = test drug, right = vehicle for one monkey and left = vehicle, right = test drug for the other monkey). Drug discrimination response periods ended after 4 min or the delivery of 4 shocks, whichever occurred first.

“Test sessions began when the following criteria were satisfied for 5 consecutive sessions: >80% responding on the correct lever and <10 responses on the incorrect lever prior to the first reinforcer. Test sessions were identical to training sessions except that responding on either lever postponed shock and various doses of the test drug or other drugs were administered during the first minute of the TO. Test sessions typically were conducted after monkeys satisfied the testing criteria (see above) for at least two consecutive training sessions, with the exception that on several occasions (i.e., with the smallest doses of some test drugs) tests were conducted over consecutive days.”

When all 3 monkeys were challenged with a 1.78 mg/kg intravenous dose of morphine (which is higher than the 1.0 mg/kg subcutaneous dose monkeys received during training) there was full generalization (100%) to morphine. Saline produced no generalization (< 20%) in all 3 monkeys.

In the challenge sessions with eluxadoline, the drug was administered intravenously over a range of doses (1.0, 3.2, 10.0 and 17.8 mg/kg) as the bis-hydrochloride salt form. As noted above in the Dose Finding Study section, the eluxadoline HCl solution was extremely acidic (pH ^{(b) (4)}). Data for eluxadoline is the best behavioral response across up to 8 testing cycles.

Eluxadoline HCl produced full generalization (100%) to morphine at 17.8 mg/kg in the only monkey tested (n = 1). When this same monkey was tested at next lowest dose of 10 mg/kg, there was no generalization (14%). However, the 10 mg/kg dose in a different

monkey produced full generalization (100%). The lowest doses of eluxadoline at 1.0 (n = 1) and 3.2 mg/kg (n = 2) produced no generalization (< 20%) to morphine.

Discriminative Stimulus Effects of Morphine, Saline and Eluxadoline

Subject	Morphine (mg/kg)	Saline	Test Substance (mg/kg)			
			1.0	3.2	10.0	17.8
CI	100 (100±0)	0 (0)	n.s.	n.s.	14.3 (3.9±2.0)	100 (97.2±1.8)
CA	100 (100±0)	2.2 (0.3±0.3)	n.s.	12.5 (3.6±1.9)	n.s.	n.s.
AM	100 (100±0)	0 (0)	13.5 (3.2±2.1)	25.5 (15.5±3.1)	100 (80.0±6.8)	n.s.

Reviewer Comments:

The following issues are raised from the inadequate information provided in the drug discrimination study report:

- No justification was provided regarding why training with morphine was conducted after subcutaneous administration, when the challenge sessions were conducted using intravenous administration
- No information is provided to confirm that the challenge sessions were conducted at Tmax of the test compounds.
- No information is provided regarding the plasma levels produced by the selected eluxadoline HCl intravenous doses and how they relate to the plasma levels produced by the highest proposed oral therapeutic dose.
- Given that the challenge sessions were conducted in 1-2 monkeys, it is not clear if the results are statistically valid.
- The solution of eluxadoline HCl was extremely acidic (pH ^{(b) (4)}), which is inappropriate for an intravenous drug solution and may have interfered with the monkeys performance.

Conclusions

Despite the inadequate information provided (as listed above), intravenous administration of eluxadoline HCl produced full generalization to the morphine cue in a monkey drug discrimination study. This provides a strong signal that eluxadoline, a mu opioid agonist, produces an interoceptive cue similar to that of the mu opioid agonist, morphine.

Self-Administration Study (Study #DD7334)

Eluxadoline HCl was tested in a self-administration study with monkeys (n = 5). Two of the monkeys were trained to intravenously self-administer heroin at 0.032 mg/kg/infusion while three other monkeys in later sessions were trained to intravenously self-administer

heroin at 0.010 mg/kg/infusion. Each training session lasted 90 minutes, with a maximum of 30 heroin infusions, over a 5 day period. Monkeys had to bar press under a fixed ratio 30 (FR30) schedule of reinforcement prior to each drug infusion. After heroin training, animals were challenged with 3 days of saline to confirm that self-administration would extinguish.

Monkeys were then challenged with eluxadoline HCl (0.32, 1.0 and 3.2 mg/kg/infusion; 5 days at each dose), with each dose interspersed with 3 days of saline sessions. Notably, the eluxadoline HCl solution was extremely acidic (pH ^{(b) (4)}). As seen in the chart below, the 0.32 and 1.0 mg/kg/infusion doses of eluxadoline HCl did not produce self-administration in 1 monkey trained to self-administer the higher 0.032 mg/kg/infusion dose of heroin, or in 3 other monkeys trained to self-administer the lower 0.001 mg/kg/infusion dose of heroin.

When the highest dose of eluxadoline HCl was tested first in the two monkeys trained at the higher dose of heroin, both self-administered eluxadoline HCl at a rate inbetween that of heroin and saline (stated to be 13-19 times/session in the narrative, but the chart below does not list 19 times as an infusion number). Although the two animals appeared “normal” to investigators when returned to their home cages after the session, the monkey that had self-administered 13 times (for a total drug intake of 41.6 mg/kg) was later found dead in its cage. The animal was subsequently found to have substantial pathology of the liver, lungs and kidneys, as described in the toxicology report:

“The monkey showed amyloidosis in the liver, which caused pronounced distortion of the liver architecture and likely resulted in reduced hepatic function. Chronic pulmonary edema was observed with alveolar macrophages, early fibrosis, pleural thickening and interstitial inflammatory infiltrates. Extensive pathology of the kidney, suggestive of ongoing inflammatory processes, as well as amyloidosis of the renal pelvis were severe enough to likely have impaired renal function. Amyloidosis was also present in the duodenum, ileum and rectum. Histologically, apparent nucleated RBCs were noted in vessels in most organs and were numerous in the lungs, kidney, spleen, adrenal and liver, suggestive of anemia or other hematologic alterations. Other observations noted were diffuse neutrophilic infiltration of the heart, decreased vacuolization of the adrenal zona fascicularis and vasculitis and lymphoid depletion in the spleen. The liver, lungs and kidneys each had substantial pathology, such that any could have been the direct cause of death or contributory to death. The lesions were generally suggestive of a long-standing inflammatory process.”

The other monkey that had self-administered the 3.2 mg/kg/infusion dose 19 times (for a total dose of 60.8 mg/kg) was found sedated and slumped in its home cage. Although a 1 mg/kg dose of naltrexone did not immediately reverse the severe sedation, the monkey fully recovered over time. (The lack of rapid reversal was noted to be unexpected, given that this dose of naltrexone was able to reverse an eluxadoline HCl overdose at the slightly lower dose of 56 mg/kg in a parallel pharmacokinetic study in monkeys).

Following the death and/or distress of the two monkeys at the 3.2 mg/kg/infusion dose of eluxadoline HCl, a second set of monkeys (n = 3) was trained with heroin at 0.010 mg/kg/infusion. The rationale for dropping the dose of the training drug is not provided when 2 of the 3 monkeys were still challenged with the problematic 3.2 mg/kg/infusion dose of eluxadoline HCl. At this dose, one monkey did not self-administer any drug while the other monkey self-administered 10 times, which was equivalent to its self-administration of heroin. However, at the lower doses of 0.32 or 1.0 mg/kg/infusion, the self-administration was similar to that for saline.

Self-administration Study in Rhesus Monkeys

Subject	Heroin (mg/kg/infusion)		JNJ-27018966 (mg/kg/infusion)				
	0.032	Saline	0.32	Saline	1.0	Saline	3.2
MA	19.0	4.0	-	-	-	-	13.0**
JA	26.3	1.7	-	-	-	-	14.3
	18.7	4.7	2.0	2.0	0	0.3	10.0 [§]
SE	0.010	Saline	0.32	Saline	1.0	Saline	3.2
	27.0	2.3	1.7	3.3	5.0	-	-
NA	17.3	4.3	0	1.3	1.0	0.7	0
AN	9.7	1.3	3.7	3.7	2.3	3.3	10.0

** Data from the single session preceding the death of this monkey.

§ Data from a single session, maximum of 10 infusions possible.

Reviewer Comments:

- Use of an FR30 schedule of reinforcement is much higher than the more typical FR10. Thus, animals had to work harder than in other self-administration studies to obtain an intravenous dose of eluxadoline. Despite this high work requirement, monkeys still self-administered eluxadoline that was either equivalent to that of heroin or inbetween that of heroin and saline. This suggests that eluxadoline has strong rewarding properties.
- The solution of eluxadoline HCl was extremely acidic (pH ^{(b) (4)}) which is inappropriate for an intravenous drug solution and may have interfered with the monkeys performance. However, the fact that monkeys self-administered eluxadoline HCl at all suggests that the drug has powerful rewarding effects despite pain (which may have been masked by the mu and kappa opioid effects of the drug).
- Although the doses of eluxadoline were selected on the basis of allometric scaling to estimated human plasma levels, the animal doses are logarithmic, rather than directly paralleling human pharmacokinetics from therapeutic and supra-therapeutic doses. Thus, it is possible that eluxadoline doses inbetween 1.0 and 3.2 mg/kg/infusion may have also produced self-administration, especially if the schedule of reinforcement was lower than FR30.

- The 3.2 mg/kg/infusion dose of eluxadoline (which is cumulatively equivalent to ~40-60 mg/kg) produced rewarding properties (as evidenced by self-administration) that were concurrent with severe safety concerns (as evidenced by serious physical distress that culminated in death in one of two animals).
- It is not clear why the animal in severe physical distress (which self-administered the equivalent of ~61 mg/kg eluxadoline) did not respond immediately to administration of naloxone, especially since this dose of naloxone had previously been used to reverse an overdose induced by 56 mg/kg eluxadoline. However, this suggests that naloxone may not provide an adequate rescue response to an eluxadoline overdose at very high doses.

Conclusions:

Eluxadoline produces clear self-administration, indicating that the drug produces sufficiently rewarding effects to induce reinforcement. The doses that produce this rewarding response, however, are unsafe because they produce classic mu opioid overdose responses.

3. Physical Dependence Studies in Animals

a. Acute Eluxadoline Administration with Naloxone-Precipitated Withdrawal in Mice (Study #7370)

Mice (n = 8-10 mice/group) were acutely treated either subcutaneously with 50 mg/kg morphine or orally with 300 mg/kg eluxadoline. Approximately 45 minutes after morphine administration, mice exhibited classic mu opioid agonist effects (circling locomotion and Straub tail). However, 45 minutes after eluxadoline administration, there was no evidence of any mu opioid agonist behaviors. Three hours after drug administration, mice were treated intraperitoneally with 10 mg/kg naloxone and observed for 15 minutes. In morphine-treated mice, there were classic opioid withdrawal behaviors, such as jumping, paw tremors and ptosis. In contrast, naloxone did not precipitate any withdrawal-like behaviors in mice treated with eluxadoline.

b. 9-Month Oral Administration Toxicity Study in Cynomolgus Monkeys with 4-week Recovery (Study #1808-004)

Cynomolgus monkeys (n = 4-7/sex/group) were given eluxadoline (50, 100, and 200 mg/kg/day) or vehicle via oral gavage for 9 months, followed by a 4 week recovery period (for the vehicle and 200 mg/kg groups). Animals showed no changes in behavior during the 39-week treatment period at any dose. There were no behaviors indicative of withdrawal during the 4 week recovery period.

c. 14-day Intravenous Toxicity Study in Rats with 2-week recovery (Study #1808-014)

Rats were given 14 consecutive days of intravenous administration of eluxadoline HCl at 5, 10, and 20 mg/kg/day, followed by a 14 day recovery period. Although classic opioid-related behaviors were observed following drug administration at the 10 and 20 mg/kg/day dose levels (general arousal, handling reactivity, stereotypy, tail pinch response, touch response, posture, gait, mobility, righting reflex, stereotypy, respiration and hindlimb splay), there were no behaviors observed during the 2-week drug discontinuation period, or were there any changes in food intake, body weight. Thus, eluxadoline did not produce withdrawal signs following chronic administration.

d. 14-day Intravenous Administration Toxicity Study in Cynomolgus Monkeys with 2-week recovery (Study #1808-012)

Cynomolgus monkeys (n = 4-7/sex/group) were given eluxadoline HCl (5, 10 and 20 mg/kg/day) or vehicle via oral gavage for 14 consecutive days, followed by a 2 week recovery period (for the vehicle and 20 mg/kg groups). Animals showed few changes in behavior during the 14 day treatment period at any dose. There were no behaviors observed during the 2-week drug discontinuation period. Thus, eluxadoline did not produce withdrawal signs following chronic administration.

Reviewer Comments:

- An acute dosing regimen is inappropriate to assess the development of physical dependence. Additionally, a justification is not provided for the dose of eluxadoline tested. Thus, the acute administration study does not contribute to the evaluation of the ability of eluxadoline to produce physical dependence.
- The other three studies are well-designed to evaluate whether eluxadoline produces physical dependence.

Conclusions:

Overall, the studies in which eluxadoline was administered chronically, following by an extended drug discontinuation and observation period, were designed and conducted properly. The results from these studies do not show that the drug produces any changes in behavior during the drug discontinuation period. This lack of withdrawal signs suggests that eluxadoline does not produce physical dependence.

Pharmacokinetics

1. Absorption

After a single oral dose of 100 mg eluxadoline, T_{max} was approximately 2 hours and the mean t_{1/2} ranged from 4-6 hours. The C_{max} ranged from 2-4 ng/ml, with an AUC of 12-22 ng.h/ml. The variability of eluxadoline PK parameters ranges from 51% to 98%.

In humans, eluxadoline has low bioavailability (~1.3%) when administered orally (its therapeutic route of administration), due to limited intestinal absorption and moderate hepatic first pass effect. This accounts for the low C_{max} of 3 ng/ml after administration of twice-daily oral therapeutic doses of 100 mg. Notably, increasing the oral dose 20 times to 2000 mg only increases the C_{max} to 29 ng/ml, showing that there is effectively no drug accumulation upon repeated twice-daily dosing.

In contrast, intranasal administration of 100 mg produced a C_{max} of 119 ng/ml, which is 40 times greater than the C_{max} produced by oral administration. When the intranasal dose was doubled to 200 mg, the C_{max} increased nearly double to 191 ng/ml. Thus, oral administration was not dose-proportional, while intranasal administration approximated dose proportionality.

2. Metabolism and Elimination

In humans, there are no major or active metabolites. This is similar to the pharmacokinetic profile of eluxadoline in rats, mice and primates. Following a single oral dose of 300 mg [¹⁴C] eluxadoline in healthy male subjects, 82.2% of the total radioactivity was recovered in feces within 336 hours and less than 1% was recovered in urine within 192 hours.

D. Clinical Safety, Efficacy and Physical Dependence Studies

1. Oral Administration Human Abuse Potential Study with Eluxadoline (Study #CPS-1006)

This was a randomized, double-blind, double-dummy, placebo- and active-controlled, 6-period, crossover study that evaluated the oral abuse potential, safety, tolerability, and PK of eluxadoline versus placebo and oxycodone immediate release (IR) in healthy nondependent recreational opioid users. The study consists of a Screening Phase, the Main Study (Qualification Phase and Treatment Phase) and a Follow-Up Visit. In the Treatment Phase, subjects were confined to the unit the day prior to the first study drug administration (at check-in) and for ~48 hours following last study drug administration.

Subjects

Number of Subjects

During the Main Study, 40 subjects (32 men, 8 women) were randomized from the Qualification Phase into the Treatment Phase. There were 33 completers.

Inclusion Criteria for participation in either study are standard but include the following criteria that are relevant for a human abuse potential study:

- Subject had used opioids for non-therapeutic purposes (i.e., for psychoactive effects) on at least 10 occasions within the past year and at least once in the 8 weeks prior to the Screening visit.
- Subject was a non-dependent recreational opioid user who was NOT physically dependent on opioids based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria.

Exclusion Criteria are standard but include the following criteria that are relevant for a human abuse potential study:

- Subject presented symptoms of withdrawal following administration of the NC test (i.e., Clinical Opiate Withdrawal Scale [COWS] score ≥ 5).
- Subject had a positive urine drug screen (UDS). If benzodiazepines (BZDs) or tetrahydrocannabinol (THC) were positive, inclusion was at the discretion of the investigator or designee, as long as the drug levels were stable or decreasing (due to long half-lives of these compounds).
- Subject had a positive breath alcohol test.
- Subject had a history or current diagnosis of substance dependence (excluding caffeine and nicotine), as assessed by the investigator using the DSM-IV-TR criteria.
- Subject had participated in, was currently participating in, or planned to seek treatment for substance-related disorders (excluding nicotine and caffeine).
- Subject had any condition in which an opioid is contraindicated, for example, significant respiratory depression, acute or severe bronchial asthma or hypercarbia, bronchitis, or had/was suspected of having paralytic ileus.

Naloxone Challenge Test

All subjects pass the Naloxone Challenge Test at least 12 hours prior to the administration of study drug in the Qualification Phase and the Treatment Phase (if subjects

leave the facility after the Qualification Phase), using the Objective Opiate Withdrawal Scale (OOWS).

A total of up to 0.8 mg naloxone HCl was administered. An initial dose of 0.2 mg naloxone HCl was administered as an intravenous (IV) bolus, followed by another IV bolus dose of 0.6 mg naloxone HCl for subjects who displayed no signs of withdrawal after the initial IV bolus dose.

Main Study:

Subjects must pass the following criteria in the Qualification Phase to be eligible to enter the Treatment Phase:

1. Ability to distinguish crushed oxycodone from placebo on Drug Liking visual analog scale (VAS), ≥ 15 point peak increase for Drug Liking relative to placebo within the first 2 hours following drug administration
2. Acceptable placebo response on Drug Liking VAS between 45 to 55, inclusive
3. Ability to tolerate study treatments (i.e., no episodes of vomiting within the first 2 hours postdose; no sneezing episodes within 30 minutes following dosing)
4. General behavior suggestive that they could successfully complete the study, as judged by the clinic staff.

On the bipolar Drug Liking VAS Emax, placebo responses were appropriate (mean = 50.5; range = 50-51), as were responses to oxycodone (mean = 96.4; range = 78-100) for those subjects who were allowed to participate in the Treatment Phase.

Oral Drug Doses

Subjects were required to abstain from food for at least 8 hours prior to dosing during the Qualification and Treatment Periods and for at least 4 hours post-dose.

Main Study

Qualification Phase (single blinded)

The following treatments were administered orally:

- Oxycodone HCl IR 40 mg (two 20 mg tablets)
- Placebo

The 40 mg dose of oxycodone was selected for use during the Qualification based on its being an intermediate dose to the 30 and 60 mg doses of oxycodone IR that were selected for use in the Treatment Phase.

Treatment Phase (double-blind)

The following treatments were administered orally:

- Eluxadoline 100 mg (one 100 mg eluxadoline tablet + nine eluxadoline placebo Tablet + three oxycodone placebo tablet, overencapsulated)
- Eluxadoline 300 mg (three 100 mg eluxadoline tablets + seven eluxadoline placebo tablets + three oxycodone placebo tablet, overencapsulated)
- Eluxadoline 1000 mg (ten 100 mg eluxadoline tablets + three oxycodone placebo tablets, overencapsulated)
- Oxycodone HCl IR 30 mg (ten eluxadoline placebo tablets + one 10 mg oxycodone tablet + two 20 mg oxycodone tablets + one oxycodone placebo tablet, overencapsulated)
- Oxycodone HCl IR 60 mg (ten eluxadoline placebo tablets + three 20 mg oxycodone tablets, overencapsulated)
- Placebo (ten eluxadoline placebo tablet + three oxycodone placebo tablets, encapsulated)

There was a washout period of at least 7 days inbetween treatments.

The doses of eluxadoline used in this study represent one, three and ten times the proposed therapeutic dose. In a previous Phase 1 study, the maximum single dose tested in males was 2000 mg and in females was 1000 mg. Since both sexes were used in the present study, the highest doses selected was 1000 mg.

The 30 mg and 60 mg oxycodone doses were selected on the basis of previous in-house studies in which these doses produced significantly higher ratings on Drug Liking compared to placebo. These studies also demonstrated that oxycodone IR 30 mg and 60 mg administered orally were safe when administered to recreational opioid users.

Pharmacodynamic Variables

All subjective endpoints were assessed at baseline, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hours after drug administration, except for VAS for Overall Drug Liking and Take Drug Again, which will only be assessed at 8, 12 and 24 hours.

Primary Measure:

Drug Liking VAS (Emax)

Secondary Measures:

Balance of effects:

- Drug Liking VAS (Emax, Emin and TA_AUE)
- Overall Drug Liking VAS (Emax, Emin; end-of-day and next day scores)
- Take Drug Again VAS (Emax; end-of-day and next day scores)
- SDV (end-of-day and next day scores)

Positive effects:

- High VAS (Emax and TA_AUE)
- Good Effects VAS (Emax and TA_AUE)
- ARCI MBG scale (Emax and TA_AUE)

Negative effects:

- Bad Effects VAS (Emax and TA_AUE)
- ARCI LSD scale (Emax and TA_AUE)

Other drug effects:

- Any Effects VAS (Emax and TA_AUE)
- Alertness/Drowsiness VAS (Emax and TA_AUE)
- ARCI PCAG scale
- Drug Similarity VAS (score at 12 hours)

Objective Measures:

- Pupillometry

Safety Variables

- Adverse events
- Clinical laboratory parameters
- Vital signs measurements
- 12-lead ECG

Results

Subjective Responses

The table below depicts the effects of study treatments on subjective measures used in this study.

Out of the 36 subjects who received eluxadoline, 18 subjects (50%) had a positive subjective response (i.e., >60 on Drug Liking VAS Emax, outside the acceptable placebo range of 40-60) to at least one of the eluxadoline doses (100 mg, 300 mg, or 1000 mg).

Effects of Oral Placebo, Oxycodone (30 and 60 mg) and Eluxadoline (100, 300 and 1000 mg) on Subjective Measures (VAS and ARCI) – Emax Scores

Measure	Placebo N = 37	Oxy 30 N = 37	Oxy 60 N = 37	Elux 100 N = 35	Elux 300 N = 36	Elux 1000 N = 36
Drug Liking VAS bipolar	54 ± 10	86 ± 14	91 ± 12	57 ± 14	59 ± 13	60 ± 15
Overall Drug Liking VAS bipolar	51 ± 13	78 ± 18	78 ± 19	51 ± 20	57 ± 25	51 ± 21
Take Drug Again VAS	15 ± 31	79 ± 26	74 ± 30	18 ± 34	24 ± 34	29 ± 35
SDV VAS (\$0.25-50.00)	\$3 ± 10	\$25 ± 16	\$25 ± 16	\$7 ± 16	\$9 ± 15	\$9 ± 15
Good Drug Effects VAS	17 ± 29	82 ± 24	89 ± 13	20 ± 31	35 ± 32	33 ± 33
High VAS	18 ± 27	80 ± 23	90 ± 14	23 ± 32	36 ± 32	36 ± 34
ARCI-MGB Euphoria (0-16)	3.4 ± 4.4	8.1 ± 4.8	8.9 ± 5.0	4.0 ± 4.6	4.4 ± 4.7	4.5 ± 4.6
Bad Drug Effects VAS	9 ± 22	23 ± 30	41 ± 38	13 ± 29	27 ± 28	23 ± 31
ARCI LSD Dysphoria	4.2 ± 1.8	5.8 ± 2.3	6.7 ± 2.4	4.6 ± 1.9	5.0 ± 2.2	5.3 ± 2.3
Any Drug Effect VAS	25 ± 32	83 ± 25	96 ± 9	26 ± 36	47 ± 33	48 ± 38
Drowsy/Alert VAS bipolar	37 ± 16	26 ± 20	16 ± 22	37 ± 22	33 ± 24	30 ± 23
ARCI PCAG Sedation	5.8 ± 3.1	8.4 ± 3.6	9.5 ± 3.3	6.1 ± 3.2	6.4 ± 3.3	7.0 ± 3.1
Drug ID: Codeine	8 ± 20	73 ± 33	71 ± 31	17 ± 28	25 ± 32	27 ± 32
Drug ID: Heroin	1 ± 1	64 ± 44	88 ± 9	8 ± 22	31 ± 34	24 ± 36
Drug ID: BZD	16 ± 32	45 ± 35	58 ± 31	22 ± 37	29 ± 36	20 ± 32
Drug ID: Placebo	63 ± 47	7 ± 24	2 ± 8	60 ± 47	35 ± 47	27 ± 43

Across all of the study treatments, there were wide variations in responses and the Sponsor acknowledges that the data were not normally distributed. This led to very large standard error values that were often larger than the mean values themselves. This also meant that there were great overlaps in mean/standard error values between all treatment groups on each subjective measure.

Thus, even though statistical tests showed significant differences between treatment groups (see below), the mean values between eluxadoline and placebo were typically small.

Statistical Analysis of Subjective Measures

The primary measure of Drug Liking was evaluated for statistically significant differences between eluxadoline, placebo and oxycodone by both the FDA Office of Biostatistics as well as by the Sponsor. However, a similar evaluation of the secondary measures was only conducted by the Sponsor.

Drug Liking VAS (bipolar), Emax score (liking):

- Oxycodone 30 mg and 60 mg produced significantly higher Emax scores on Drug Liking compared to placebo ($P < 0.0001$ for both). These data show that oxycodone was liked by subjects, which validates the study.
- Eluxadoline at the two suprathreshold doses (300 mg and 1000 mg) produced small but significantly higher Emax scores on Drug Liking compared to placebo ($P < 0.05$ for both). Eluxadoline at the therapeutic dose (100 mg) did not differentiate from placebo on Drug Liking.
- However, all three doses of eluxadoline (100, 300 and 1000 mg) produced significantly lower Emax scores on Drug Liking compared to either dose of oxycodone ($P < 0.0001$ for all).

Drug Liking VAS (bipolar), Emin score (disliking):

- Eluxadoline at the highest suprathreshold dose (1000 mg) produced a small but significantly lower Emin score on Drug Liking compared to placebo ($P < 0.05$). These data show that eluxadoline produced drug disliking compared to placebo. Notably, the Tmax of these negative effects preceded the Tmax of the positive effects (Emax scores).
- Oxycodone did not produce significantly different Emin (disliking) scores compared to placebo ($P < 0.0001$ for both).
- There were no differences between Emin scores (disliking) between oxycodone 60 mg and any dose of eluxadoline. In contrast, each dose of eluxadoline produced a greater Emin score (disliking) compared to oxycodone 30 mg ($P < 0.05$).

Overall Drug Liking VAS:

- Oxycodone (all doses) produced significantly increased overall drug liking compared to placebo ($P < 0.0001$), while eluxadoline (all doses) did not. Each dose of oxycodone produced more overall drug liking compared to each dose of eluxadoline ($P < 0.0001$).

Take Drug Again VAS:

- Oxycodone (all doses) produced significantly increased reports of wanting to take the drug again compared to placebo ($P < 0.0001$), as did the 300 mg dose of eluxadoline ($P < 0.02$), while the 100 and 1000 mg doses of eluxadoline did not. Each dose of oxycodone produced more wanting to take drug again compared to each dose of eluxadoline ($P < 0.0001$).

Subjective Drug Value (SDV):

- Each dose of oxycodone was deemed to be worth more money than placebo ($P < 0.0001$). Each dose of eluxadoline was deemed to be worth more money than placebo ($P < 0.05$), but less money compared to each dose of oxycodone ($P < 0.0001$).

Good Effects VAS:

- Each dose of oxycodone produced good drug effects that were greater than placebo ($P < 0.0001$). The two suprathreshold doses of eluxadoline (300 and 1000 mg) produced good drug effects that were greater than placebo ($P < 0.05$), but less than that produced by each dose of oxycodone ($P < 0.0001$).

High VAS:

- Each dose of oxycodone produced a high that was greater than placebo ($P < 0.0001$). The two suprathreshold doses of eluxadoline (300 and 1000 mg) produced a high that was greater than placebo ($P < 0.05$), but less than that produced by each dose of oxycodone ($P < 0.0001$).

ARCI – MBG (Euphoria):

- Each dose of oxycodone produced euphoria on the MBG scale that was greater than placebo ($P < 0.0001$). The 300 mg dose of eluxadoline produced euphoria that was greater than placebo ($P < 0.05$), but each dose of eluxadoline produced less euphoria than that produced by each dose of oxycodone ($P < 0.0001$).

Bad Effects VAS:

- Each dose of oxycodone produced greater bad drug effects compared to placebo ($P < 0.0001$). The two suprathreshold doses of eluxadoline (300 and 1000 mg) also produced greater bad drug effects compared to placebo ($P < 0.05$). There was no difference, however, between either dose of oxycodone and the 300 and 1000 mg doses of eluxadoline on bad drug effects.

ARCI – LSD (dysphoria):

- Each dose of oxycodone produced greater dysphoria compared to placebo ($P < 0.0001$). The two suprathreshold doses of eluxadoline (300 and 1000 mg) also produced greater dysphoria compared to placebo ($P < 0.05$). There was no difference, between the 30 mg dose of oxycodone and the 300 and 1000 mg doses of eluxadoline on dysphoria. However, the 60 mg dose of oxycodone produced more dysphoria than either suprathreshold dose of eluxadoline.

Any Drug Effects VAS:

- Each dose of oxycodone produced any drug effects that were greater than placebo ($P < 0.0001$). The two suprathreshold doses of eluxadoline (300 and 1000 mg) produced any drug effects that were greater than placebo ($P < 0.05$), but less than that produced by each dose of oxycodone ($P < 0.0001$).

Alertness/Drowsiness VAS:

- Each dose of oxycodone produced an increase in drowsiness that was greater than placebo ($P < 0.0001$). However, none of the 3 doses of eluxadoline produced an increase in drowsiness compared to placebo ($P < 0.05$). The degree of drowsiness produced by the two suprathreshold doses of eluxadoline (300 and 1000 mg) was similar to that produced by the 30 mg dose of oxycodone, but less than that produced by the 60 mg dose of oxycodone ($P < 0.0001$).

ARCI – PCAG (Sedation):

- Each dose of oxycodone produced sedation that was greater than placebo ($P < 0.0001$) and each dose of eluxadoline ($P < 0.0001$). No dose of eluxadoline produced sedation greater than that produced by placebo.

Drug Identification:

- Oxycodone was identified most frequently as codeine (71-73), heroin (64-88) or benzodiazepine (45-58).
- Eluxadoline was not identified as being similar to any drug class. The therapeutic dose of eluxadoline was identified as placebo. Suprathreshold doses of eluxadoline were most frequently identified at a low level (< 50) as codeine (17-27), heroin (24-31) and benzodiazepine (20-29).
- Placebo was most frequently identified as placebo (63).

Conclusions about Subjective Measures

Following evaluation of the protocol and data from the oral abuse potential study, CSS has the following conclusions regarding the subjective measures:

- The study was validated by the significant increase in Drug Liking VAS in response to both oral doses of oxycodone (30 and 60 mg) compared to placebo. Oxycodone similarly significantly increased scores on other positive subjective responses such as Overall Drug Liking, Take Drug Again, Subjective Drug Value, Good Effects, High, Euphoria,
- Eluxadoline at suprathreshold oral doses (300 and/or 1000 mg) produced small but significant increases compared to placebo in positive subjective responses such as Drug Liking, Take Drug Again, Subjective Drug Value, Good Effects, High, and Euphoria. The positive subjective responses to eluxadoline were most often statistically less than those produced by oxycodone.
- Oral eluxadoline produced a small but significant increase in Drug Disliking, but this occurred 1-2 hours prior to the peak drug liking response. Additionally, there was no significant difference in drug disliking between eluxadoline and oxycodone 60 mg. Eluxadoline also produced a significant increase in Bad Effects, Dysphoria, but did not produce a significant increase in Overall Drug Liking, Drowsiness and Sedation. Oxycodone produced an increase in each of

these negative subjective measures, to a degree that was significantly greater than placebo and eluxadoline.

- Oral oxycodone was identified as an opioid (codeine or heroin) or less frequently as a benzodiazepine. In contrast, oral eluxadoline at supratherapeutic doses was most frequently observed as an opioid, but at a degree much less than that of oxycodone.
- Therefore, oral eluxadoline produced both positive and negative subjective responses (and a drug identification) that were similar to, but of lower magnitude, than those produced by oral administration of the Schedule II opioid, oxycodone.

Abuse-Related Adverse Events

Oral administration of eluxadoline produced an increase in numerous adverse events that are classically associated with mu agonist opioids. There was a dose-dependent increase in euphoria after eluxadoline (ranging from 14-28%) that was greater than that after placebo (5%) but less than that of oxycodone (ranging from 73-76%). All reports of euphoria were mild except for 2 subjects who reported moderate euphoria after oxycodone. Somnolence was also reported after eluxadoline (ranging from 19-42%), but the lowest rate was reported at the highest dose (1000 mg). This was similar to the rate reported with oxycodone (38-41%), and overlaps with the rate after placebo (19%). All reports of drug-induced somnolence were mild. Thus, although oral eluxadoline is alleged by the Sponsor to have effects that are localized to the gastrointestinal system, it is clear that eluxadoline is inducing centrally-mediated responses. Peripheral opioid-associated adverse events were also reported, including dry mouth (with a range of 11-19% for eluxadoline and 11-13% for oxycodone) and pruritis (with a range of 8-11% for eluxadoline and 54-70% for oxycodone). Thus, eluxadoline produces well-known opioid effects, although they are not as frequently reported as that of oxycodone.

Opioid-Related Adverse Events Following Oral Placebo, Oxycodone (30 and 60 mg) and Eluxadoline (100, 300 and 1000 mg)

AE	Placebo	Oxy 30	Oxy 60	Elux 100	Elux 300	Elux 1000
Euphoria	2 (5%)	28 (76%)	27 (73%)	5 (14%)	7 (19%)	10 (28%)
Somnolence	7 (19%)	14 (38%)	15 (41%)	11 (31%)	15 (42%)	7 (19%)
Dry Mouth	1 (3%)	5 (13%)	4 (11%)	4 (11%)	6 (17%)	7 (19%)
Pruritis	0 (0%)	20 (54%)	26 (70%)	4 (11%)	3 (8%)	4 (11%)
	N = 37	N = 37	N = 37	N = 35	N = 36	N = 36

Pupillometry

Mean pupillary constriction did not significantly differ for any dose of eluxadoline (100 mg (0.71 mm), 300 mg (0.86 mm), and 1000 mg (0.93 mm)) compared to placebo (0.82 mm). Thus, even though there were clear opioid subjective responses following eluxadoline administration, no dose of this drug produced a classic opioid response

physiologically as measured by pupil size. In contrast, there was a significant mean pupillary constriction following oxycodone 30 mg (2.19 mm) and 60 mg (2.57 mm), which occurred at the Cmax of oxycodone (~1.5 hours).

Pharmacokinetics

Tmax occurred ~1-2 hours after oral administration of eluxadoline (100 mg, 300 mg, and 1000 mg). This is similar to the Tmax of oxycodone (30 and 60 mg). Cmax was higher after oral administration of 1000 mg eluxadoline compared to 100 and 300 mg eluxadoline. However, the Sponsor states there was no relationship between eluxadoline Cmax and Drug Liking VAS Emax.

2. Intranasal Administration Human Abuse Potential Study with Eluxadoline (Study #CPS-1010)

This is a randomized, double-blind, placebo- and active-controlled, single-dose, crossover study to evaluate the abuse potential and safety of intranasally-administered crushed eluxadoline relative to intranasally-administered crushed oxycodone HCl IR and placebo in non-dependent healthy adult recreational opioid users with a history of intranasal abuse. The study consists of a Screening Phase, the Main Study (Qualification Phase and Treatment Phase) and a Follow-Up Visit. In the Treatment Phase, subjects were confined to the unit the day prior to the first study drug administration (at check-in) and for ~72 hours following last study drug administration.

Subjects

Number of Subjects

During the Main Study, 36 subjects (10 female, 26 male) were randomized from the Qualification Phase into the Treatment Phase. There were 31 completers.

Inclusion Criteria for participation in either study are standard but include the following criteria that are relevant for a human abuse potential study:

- Must be a non-dependent opioid abuser and (1) have used opioids for non-therapeutic purposes (i.e., for psychoactive effects) on at least 10 occasions in the past year and (2) have used opioids at least once in the 8 weeks prior to Screening.
- Must have experienced at least 3 occasions of intranasal opioid drug use for the purpose of recreational abuse/misuse in the last 12 months, and once in the past 3 months.

Exclusion Criteria are standard but include the following criteria that are relevant for a human abuse potential study:

- Subject presented symptoms of withdrawal following administration of the naloxone challenge test (clinical opiate withdrawal scale [COWS] score ≥ 5).
- Subject had a positive urine drug screen. If benzodiazepines or tetrahydrocannabinol were positive, inclusion was at the discretion of the investigator or designee, as long as drug levels were stable or decreasing
- Subject had a positive breath alcohol test. If a subject presented with a positive breath alcohol test, the subject could be rescheduled
- Subject had a history or current diagnosis of substance dependence (excluding caffeine and nicotine), as assessed by DSM-IV-TR criteria.
- Subject had participated in, was currently participating in, or planned to seek treatment for substance-related disorders (excluding nicotine and caffeine).
- Subject had any condition in which an opioid is contraindicated; e.g., significant respiratory depression, acute or severe bronchial asthma or hypercarbia, bronchitis, or had/was suspected of having paralytic ileus.
- Subject had clinically important changes in the intranasal cavity (including presence of a deviated septum, rhinorrhea or excessive sneezing) or any medical condition that in the opinion of the investigator would interfere with the study procedures or data integrity or compromise the safety of the subject.
- Subject had hypersensitivity or intolerance to eluxadoline or its excipients, or any opioid, including naloxone.

Naloxone Challenge Test

All subjects pass the Naloxone Challenge Test at least 12 hours prior to the administration of study drug in the Qualification Phase and the Treatment Phase (if subjects leave the facility after the Qualification Phase), using the Objective Opiate Withdrawal Scale (OOWS).

A total of up to 0.8 mg naloxone HCl was administered. An initial dose of 0.2 mg naloxone HCl was administered as an intravenous (IV) bolus, followed by another IV bolus dose of 0.6 mg naloxone HCl for subjects who displayed no signs of withdrawal after the initial IV bolus dose.

Main Study:

Subjects must pass the following criteria in the Qualification Phase to be eligible to enter the Treatment Phase:

- Ability to distinguish crushed oxycodone from placebo on Drug Liking visual analog scale (VAS), ≥ 15 point peak increase for Drug Liking relative to placebo within the first 2 hours following drug administration
- Acceptable placebo response on Drug Liking VAS between 45 to 55, inclusive
- Ability to tolerate study treatments (i.e., no episodes of vomiting within the first 2 hours postdose; no sneezing episodes within 30 minutes following dosing)
- General behavior suggestive that they could successfully complete the study, as judged by the clinic staff.

On the bipolar Drug Liking VAS Emax, placebo responses were appropriate (mean = 50.4; range = 50-52), as were responses to oxycodone (mean = 95.2; range = 70-100) for those subjects who were allowed to participate in the Treatment Phase.

Intranasal Drug Doses

Subjects were required to abstain from food for at least 8 hours prior to dosing during the Qualification and Treatment Periods and for at least 4 hours post-dose.

Main Study

Qualification Phase (single blinded)

The following treatments were administered intranasally:

- Oxycodone HCl IR 20 mg (two 10 mg tablets, crushed)
- Placebo (lactose tablets, crushed), weight matched to oxycodone HCl IR

Treatment Phase (double-blind)

The following treatments were administered intranasally via insufflation:

- Eluxadoline 100 mg (one 100 mg tablet, crushed)
- Eluxadoline 200 mg (two 100 mg tablets, crushed)
- Oxycodone HCl IR 15 mg (three 5 mg tablets, crushed)
- Oxycodone HCl IR 30 mg (three 10 mg tablets, crushed)
- Placebo (lactose tablets, crushed), weight matched to oxycodone HCl IR
- Placebo to match eluxadoline 200 mg (two placebo tablets, crushed)

The protocol states that the doses of eluxadoline (100 mg and 200 mg) were selected on the basis of estimating the maximum amount of powder that can be insufflated, which the Sponsor assumed would be 900-1000 mg (as shown in previous in-house studies). Since each 100 mg tablet of eluxadoline weighs 824 mg, two tablets (equivalent to 1648 mg) was determined to be the maximum possible intranasal dose. Clinical studies with oral eluxadoline previously administered up to 2000 mg in men and up to 1000 mg in women have been administered, with the maximum tolerated oral dose being 1500 mg in men and 1000 mg in women. Thus, the top intranasal dose of 200 mg was considered to be safe and likely to be tolerated.

The intranasal doses of oxycodone for the Treatment Phase are based on previous in-house clinical studies in which intranasal administration of 15 and 30 mg oxycodone produced scores on Drug Liking VAS that were significantly greater than that from placebo. The 20 mg intranasal dose of oxycodone in the Qualification Phase was an intermediate dose that was appropriate for qualifying subjects for the Treatment Phase.

Two doses of placebo that matched the weights of oxycodone HCl IR and eluxadoline (200 mg dose) were administered to maintain blinding.

Insufflation Procedures

All doses of study drugs in the Qualification Phase and the Treatment Phase were crushed individually for each subject and apportioned into sealed amber individual dosing containers. Subjects self-administered each dose intranasally via insufflation. Lighting conditions in the dosing room were adjusted to blue light to maintain the blind between oxycodone (blue), eluxadoline (white), and placebo (white) powder. Crushed doses of study drug were self-administered by subjects intranasally as quickly as possible but within a maximum of 5 minutes.

After administration, study staff inspected the vial, nose, and hands to ensure that the study drug has been inhaled adequately. If a sufficient residual amount of powder remained in the vial, study staff tapped the vial and instructed the subject to inhale the remaining study drug. All subjects were instructed to complete inhalation over a stainless steel dosing tray. The dosing tray was used to collect any drug product that was not fully inhaled by the subject, was inadvertently dropped from the inhalation straw onto the tray, or fell from the subject's nose immediately after inhalation. Subjects had an opportunity to inhale any remaining drug product from the dosing tray prior to collection and weighing. Following the 5-minute dosing period, any visible drug product was collected from the dosing tray and returned to the dosing vial by the clinic staff for recording of post-dose weight.

Pharmacodynamic Variables

All subjective endpoints were assessed at baseline, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hours after drug administration, except for VAS for Overall Drug Liking and Take Drug Again, which will only be assessed at 8, 12 and 24 hours.

Primary Measure:

Drug Liking VAS (Emax)

Secondary Measures:

Balance of effects:

- Drug Liking VAS (Emax, Emin and TA_AUE)
- Overall Drug Liking VAS (Emax, Emin; end-of-day and next day scores)
- Take Drug Again VAS (Emax; end-of-day and next day scores)
- SDV (end-of-day and next day scores)

Positive effects:

- High VAS (Emax and TA_AUE)
- Good Effects VAS (Emax and TA_AUE)
- ARCI MBG scale (Emax and TA_AUE)

Negative effects:

- Bad Effects VAS (Emax and TA_AUE)
- ARCI LSD scale (Emax and TA_AUE)

Other drug effects:

- Any Effects VAS (Emax and TA_AUE)
- Alertness/Drowsiness VAS (Emax and TA_AUE)
- ARCI PCAG scale
- Drug Similarity VAS (score at 12 hours)
- Subject-rated scale for nasal effects

Objective Measures:

- Pupillometry
- Observer-rated assessment of intranasal irritation
- Percentage of dose insufflated (mg %)

Safety Variables

- Adverse events
- Clinical laboratory parameters
- Vital signs measurements
- 12-lead ECG

Results

Subjective Responses

The table below depicts the effects of study treatments on subjective measures used in this study.

Effects of Intranasal Placebo, Oxycodone (15 and 30 mg) and Eluxadoline (100 and 200 mg) on Subjective Measures (VAS and ARCI)

Measure	P-Lact N = 32	P-Elux N = 34	Oxy 15 mg N = 32	Oxy 30 mg N = 32	Elux 100 mg N = 32	Elux 200 mg N = 32
Percent Dose Insufflated	86 ± 28	65 ± 33	91 ± 21 13.7 mg	96 ± 13 28.8 mg	55 ± 37 51 mg	51 ± 40 110 mg
Drug Liking VAS bipolar	49 ± 9	52 ± 9	80 ± 22	89 ± 15	53 ± 22	55 ± 21
Overall Drug Liking VAS bipolar	44 ± 17	38 ± 23	76 ± 25	81 ± 23	21 ± 30	17 ± 27
Take Drug Again VAS	7 ± 18	7 ± 19	78 ± 31	81 ± 23	15 ± 27	10 ± 24
SDV VAS (\$0.25-50.00)	1 ± 1	2 ± 8	19 ± 13	21 ± 14	5 ± 11	4 ± 10
Good Drug Effects VAS	4 ± 14	11 ± 23	69 ± 33	87 ± 18	27 ± 32	30 ± 36
High VAS	10 ± 20	14 ± 25	69 ± 30	88 ± 16	43 ± 33	50 ± 35
ARCI-MGB Euphoria (0-16)	1.3 ± 1.0	1.6 ± 1.5	8.1 ± 4.9	8.3 ± 4.5	2.8 ± 3.5	3.2 ± 4.0
Bad Drug Effects VAS	2 ± 9	17 ± 25	23 ± 28	35 ± 35	63 ± 39	74 ± 32
ARCI LSD Dysphoria (0-14)	4.2 ± 0.7	4.1 ± 0.8	5.9 ± 2.0	6.4 ± 2.2	6.7 ± 2.3	7.0 ± 2.5
Any Drug Effect VAS	8 ± 18	19 ± 29	74 ± 28	90 ± 17	72 ± 30	81 ± 25
Drowsy/Alert VAS bipolar	48 ± 17	42 ± 18	24 ± 16	18 ± 18	28 ± 16	30 ± 21
ARCI PCAG Sedation	3.9 ± 1.5	4.6 ± 2.6	8.4 ± 3.4	9.5 ± 3.5	8.9 ± 3.6	8.8 ± 3.8
Drug ID: Codeine	2 ± 12	6 ± 21	68 ± 33	78 ± 26	32 ± 35	34 ± 40
Drug ID: Heroin	0	0	52 ± 38	72 ± 37	2 ± 5	29 ± 40
Drug ID: BZD	0	3 ± 16	35 ± 37	41 ± 39	17 ± 25	14 ± 24
Drug ID: Placebo	82 ± 37	77 ± 42	3 ± 18	0	7 ± 25	10 ± 28
Nasal Congestion (0-5)	1.0 ± 1.0	1.6 ± 1.6	1.0 ± 1.0	1.0 ± 1.0	2.4 ± 1.6	2.7 ± 1.4

Out of the 32 subjects who received eluxadoline, only 2 (< 0.1%) had a positive subjective response (i.e., >60 on Drug Liking VAS Emax, outside the acceptable placebo range of 40-60) to at least one of the eluxadoline doses (100 mg or 200 mg).

This may be related to the fact that only 14 of 32 subjects (44%) were able to insufflate greater than 70% of the presented 200 mg intranasal eluxadoline dose. Of the remaining 18 subjects, 14 of 32 (44%) were not able to insufflate greater than 25% of the presented 200 mg intranasal eluxadoline dose, with 4 of 32 (12%) insufflating between 26-69% of the presented eluxadoline dose. Additionally the reported AEs show that 50% of subjects who received the 200 mg dose of eluxadoline had nasal congestion. Overall, this suggests that there were low plasma concentrations of eluxadoline in the majority of subjects, either due to inability to insufflate, or because nasal congestion prevented absorption.

In contrast, 91-96% of the presented intranasal oxycodone doses was able to be insufflated by subjects (with 25-28% nasal congestion) and a slightly lower amount of placebo dose was insufflated (65-86%, with 41% nasal congestion).

These data highlight why CSS requested that the Sponsor test eluxadoline API in the intranasal human abuse potential study, to determine whether the drug itself, unfettered by excipients, would produce a rewarding response.

Statistical Analysis of Subjective Measures

The primary measure of Drug Liking was evaluated for statistically significant differences between eluxadoline, placebo and oxycodone by both the FDA Office of Biostatistics as well as by the Sponsor. However, a similar evaluation of the secondary measures was only conducted by the Sponsor.

Drug Liking VAS (bipolar), Emax score (liking):

- Oxycodone 15 mg and 30 mg produced significantly higher Emax scores on Drug Liking compared to placebo ($P < 0.0001$ for both). These data show that oxycodone was liked by subjects, which validates the study.
- Eluxadoline (100 mg and 200 mg) did not produce small Emax scores on Drug Liking that were significantly different than placebo ($P < 0.05$ for both). Both doses of eluxadoline (100 and 200 mg) produced significantly lower Emax scores on Drug Liking compared to either dose of oxycodone ($P < 0.0001$ for all).

Drug Liking VAS (bipolar), Emin score (disliking):

- Eluxadoline (100 and 200 mg) produced a small but significantly lower Emin score on Drug Liking compared to placebo ($P < 0.0001$). These data show that eluxadoline produced drug disliking compared to placebo. Notably, the Tmax of these negative effects preceded the Tmax of the positive effects (Emax scores).
- Oxycodone (15 and 30 mg) did not produce significantly different Emin (disliking) scores compared to placebo ($P < 0.0001$ for both).
- Eluxadoline at both doses produced significantly more disliking than either dose of oxycodone ($P < 0.0001$).

Overall Drug Liking VAS:

- Oxycodone (15 and 30 mg) produced significantly increased overall drug liking compared to placebo ($P < 0.0001$), as did eluxadoline (100 and 200 mg) ($P < 0.0001$). Each dose of oxycodone produced more overall drug liking compared to each dose of eluxadoline ($P < 0.0001$).

Take Drug Again VAS:

- Oxycodone (15 and 30 mg) produced significantly increased reports of wanting to take the drug again compared to placebo ($P < 0.0001$), while eluxadoline (100 and 200 mg) did not. Each dose of oxycodone produced more wanting to take drug again compared to each dose of eluxadoline ($P < 0.0001$).

Subjective Drug Value (SDV):

- Each dose of oxycodone was deemed to be worth more money than placebo ($P < 0.0001$). Eluxadoline 100 mg (but not 200 mg) was deemed to be worth more money than placebo ($P < 0.02$), but less money compared to each dose of oxycodone ($P < 0.0001$).

Good Effects VAS:

- Each dose of oxycodone and each dose of eluxadoline produced good drug effects that were greater than placebo ($P < 0.0001$). However, the good drug effects of eluxadoline was less than that produced by oxycodone ($P < 0.0001$).

High VAS:

- Each dose of oxycodone and each dose of eluxadoline produced a high that was greater than placebo ($P < 0.0001$). However, the high produced by eluxadoline was less than that produced by oxycodone ($P < 0.0001$).

ARCI – MBG (Euphoria):

- Each dose of oxycodone produced euphoria on the MBG scale that was greater than placebo ($P < 0.0001$). Eluxadoline produced euphoria that was greater than placebo ($P < 0.05$), but each dose of eluxadoline produced less euphoria than that produced by each dose of oxycodone ($P < 0.0001$).

Bad Effects VAS:

- Each dose of oxycodone produced greater bad drug effects compared to placebo ($P < 0.002$). Eluxadoline (100 and 200 mg) also produced greater bad drug effects compared to placebo ($P < 0.0001$). However, eluxadoline produced significantly greater bad effects compared to oxycodone ($P < 0.0001$).

ARCI – LSD (dysphoria):

- Each dose of oxycodone produced greater dysphoria compared to placebo ($P < 0.0001$). Eluxadoline (100 and 200 mg) also produced greater dysphoria compared to placebo ($P < 0.0001$). There was no difference between the 30 mg dose of oxycodone and either dose of eluxadoline on dysphoria. However, the 15

mg dose of oxycodone produced more dysphoria than the 200 mg dose of eluxadoline.

Any Drug Effects VAS:

- Each dose of oxycodone produced any drug effects that were greater than placebo ($P < 0.0001$). Eluxadoline (100 and 200 mg) produce similar responses on any drug effects to oxycodone 15 mg. However, the 30 mg dose of oxycodone produced a greater degree of any drug effects compared to either dose of eluxadoline ($P < 0.05$). Eluxadoline at both doses produced a greater degree of any drug effects compared to placebo ($P < 0.0001$).

Alertness/Drowsiness VAS:

- Each dose of oxycodone produced drowsiness that was greater than placebo ($P < 0.0001$). Eluxadoline (100 and 200 mg) produce similar responses drowsiness to oxycodone 15 mg. However, the 30 mg dose of oxycodone produced a greater degree of drowsiness compared to either dose of eluxadoline ($P < 0.05$). Eluxadoline at both doses produced a greater degree of drowsiness compared to placebo ($P < 0.0001$).

ARCI – PCAG (Sedation):

- Each dose of oxycodone produced sedation that was greater than placebo ($P < 0.0001$). Eluxadoline (100 and 200 mg) produce similar sedation to oxycodone 15 and 30 mg. Eluxadoline at both doses produced a greater degree of sedation compared to placebo ($P < 0.0001$).

Nasal Congestion:

- On a scale of 0-5, neither placebo (1.0-1.6) or oxycodone (1.0) induced nasal congestion following insufflation. However, there was a moderate amount of nasal congestion following insufflation of eluxadoline (2.4-2.7). This may account for why the amount of eluxadoline that could be insufflated was so low.

Drug Identification:

- Oxycodone was identified most frequently as codeine (68-78), heroin (52-72). It was occasionally identified at a low level (< 50) as a benzodiazepine (35-41).
- Eluxadoline was not identified as being similar to any drug class, although it was occasionally identified at a low level (< 50) as codeine (32-34), heroin (2-29) and benzodiazepine (14-17).
- Placebo was most frequently identified as placebo (65-86).

Drug Liking VAS scores were inversely correlated with peak plasma concentrations of eluxadoline. In general, higher plasma concentrations within 1 hour of dosing were associated with lower Drug Liking VAS scores (disliking) and as plasma concentrations decreased, Drug Liking VAS scores increased slightly toward neutrality.

Conclusions about Subjective Measures

Following evaluation of the protocol and data from the intranasal abuse potential study, CSS has the following conclusions regarding the subjective measures:

- The doses of eluxadoline for the intranasal study were selected based on limitations in amount of crushed eluxadoline tablets that could theoretically be insufflated, rather than on the basis of an appropriate dose range. Thus, eluxadoline was only tested at the therapeutic dose (100 mg) and two times the therapeutic dose (200 mg), rather than testing the 300 mg dose of crushed eluxadoline.
- When CSS provided feedback to the Sponsor during the IND stage of drug development regarding the design of this intranasal study prior to its initiation, we suggested that the Sponsor test the eluxadoline API, in order to facilitate testing of a dose higher than 200 mg. The Sponsor chose not to include such an arm into the protocol design. This limits the ability to assess the full abuse potential of eluxadoline, especially when subjects in this study had difficulty insufflating crushed eluxadoline tablets (and its excipients).
- This may be related to the fact that the majority of subjects (18 of 32; 56%) were only able to insufflate less than 70% of the 200 mg intranasal dose of eluxadoline, suggesting that plasma levels of the drug were inadequate.

With these caveats in mind, the data from the intranasal study are summarized below.

On the primary subjective measure of Drug Liking visual analog scale (VAS), oxycodone at both doses produced significantly higher maximum (E_{max}) scores compared to placebo ($P < 0.0001$ for both), which validates the study. In contrast, eluxadoline (100 and 200 mg) did not produce E_{max} scores on Drug Liking that were different from that of placebo ($P < 0.05$ for both).

Results from the secondary subjective measures show that:

- Intranasal oxycodone (15 and 30 mg) significantly increased scores on other positive subjective responses such as the VAS for Overall Drug Liking, Take Drug Again, Subjective Drug Value, Good Drug Effects, High, and the Addiction Research Center Inventory-Morphine Benzodrine Group (ARCI-MBG, Euphoria).
- Intranasal eluxadoline (100 and 200 mg) produced small but significant increases compared to placebo in positive subjective responses such as VAS for Overall Drug Liking, Subjective Drug Value, Good Drug Effects, High, and ARCI-MBG (Euphoria). The positive subjective responses to eluxadoline were most often statistically less than those produced by either dose of oxycodone.

- Intranasal eluxadoline produced a small but significant increase in VAS for Drug Disliking (which temporally preceded the positive subjective responses) while oxycodone did not. Eluxadoline also produced a significant increase in VAS Bad Drug Effects, ARCI-Lysergic Acid Diethylamide (ARCI-LSD; Dysphoria), Drowsiness and Sedation. Oxycodone at both doses produced an increase in each of these negative subjective measures, to a degree that was significantly greater than placebo and eluxadoline at all doses.
- Both doses of oxycodone were identified as an opioid (codeine or heroin) or less frequently as a benzodiazepine. In contrast, eluxadoline was most frequently observed as an opioid, but at a degree that was much less than that of oxycodone.

Abuse-Related Adverse Events

Intranasal administration of eluxadoline produced an increase euphoria after the 100 mg dose (22%) and the 200 mg dose (19%). This rate of euphoria was less than that produced by oxycodone 15 mg (44%) and 30 mg (67%). All incidents of euphoria were mild in intensity. However, as noted above, this may be attributable to the fact that 51-55% of the eluxadoline dose could be insufflated, perhaps due to a high degree of nasal congestion (38-50%) and a low degree of nasal discomfort (6%). There was also a low level of reported dizziness after eluxadoline (3-9%) as well as nausea and vomiting (6%, both doses, similar to that of placebo). (b) (4)

it is clear that eluxadoline is inducing centrally-mediated responses. Oxycodone also produced somnolence (28-50%), dizziness (6-16%), nasal congestion (25-28%) and nasal discomfort (22-41%).

AE	P-Lact	P-Elux	Oxy 15	Oxy 30	Elux 100	Elux 200
Euphoria	0	0	14 (44%)	21 (67%)	7 (22%)	6 (19%)
Somnolence	4 (13%)	4 (12%)	9 (28%)	16 (50%)	4 (13%)	5 (16%)
Dizziness	0	0	2 (6%)	5 (16%)	1 (3%)	3 (9%)
Nasal Congestion	5 (16%)	14 (41%)	9 (28%)	8 (25%)	12 (38%)	16 (50%)
Nasal Discomfort	1 (3%)	6 (18%)	7 (22%)	13 (41%)	2 (6%)	2 (6%)

Pupillometry

Mean pupillary constriction was significantly different at 1.0 hour for both doses of eluxadoline (100 mg (1.09 mm) and 200 mg (1.14 mm)) compared to placebo (0.82 mm). Thus, the clear opioid subjective responses following eluxadoline administration was paralleled by a classic opioid response physiologically as measured by pupil size. There was also a significant mean pupillary constriction following oxycodone 15 mg (2.15 mm) and 30 mg (2.73 mm), which occurred at 0.5 hours.

Pharmacokinetics

C_{max} for eluxadoline occurred 15 minutes after intranasal insufflation, with higher plasma levels after 200 mg compared to 100 mg. However, there were large variations in plasma levels which is attributable to the variations in amount of drug insufflated, as detailed above.

3. Alternative Route of Administration for Abuse Purposes

Intravenous administration

At the recommendation of CSS, the Sponsor did not conduct any studies were to evaluate the pharmacokinetics or abuse potential of intravenous administration of eluxadoline. (b) (4)

[Redacted]

[Redacted] (b) (4)

CSS concludes that under the conditions studied by the Sponsor in the chemical studies (see above), the preparation of a solution for intravenous use seems difficult.

Buccal, sublingual and transmucosal administration

The Sponsor did not conduct any studies were to evaluate the pharmacokinetics or abuse potential of buccal, sublingual, or transmucosal administration of eluxadoline. (b) (4)

[Redacted]

[Redacted] (b) (4)

CSS agrees that the pKa data suggest that buccal, sublingual and transmucosal absorption of eluxadoline may be limited. We further agree that it is likely that this may limit the potential abuse of eluxadoline by these routes of administration. However, whether this proves to be true will depend on epidemiological data after eluxadoline is marketed.

4. Abuse-Related Adverse Events in Clinical Studies

One Phase 2 clinical study (IBS-2001) and two Phase 3 clinical trials (IBS-3001 and IBS-3002) were conducted to support the efficacy claim for eluxadoline 100 mg BID and 75mg BID for the treatment of diarrhea and abdominal pain in male and female patients with diarrhea predominant irritable bowel syndrome (IBS-d). The daily response criteria was simultaneous improvement in both abdominal pain and stool consistency, for at least 50% of the days with diary entries during Weeks 1-12. A total of 807 patients were treated with 75 mg eluxadoline, 1032 patients were treated with 100 mg eluxadoline and 975 received placebo.

The pooled dataset for Phase 2 and 3 studies were examined for abuse-related AEs based on a list of MedDRA terms derived from the 2010 FDA *Draft Guidance for Industry: Assessment of Abuse Potential of Drugs*, a 2008 public presentation on AEs by the Controlled Substance Staff and the 210 terms proposed by FDA (Love et al., 2013). These AE terms included (but was not limited to): dizziness, fatigue, anxiety, depression, somnolence, hypoesthesia, paresthesia, asthenia, lethargy, nervousness, sedation, abnormal dreams, euphoric mood, feeling drunk, restlessness, affective disorder, agitation, depressed mood, disturbance in attention, emotional distress, energy increased, memory impairment, mood swings, and nightmare.

When these adverse events were evaluated, the AE of euphoric mood was reported by only 2 IBS-d patients in the pooled Phase 2 and 3 safety set (0.2% of population). Both of these patients received eluxadoline 100 mg BID. Similarly, feeling drunk was reported by only 2 subjects (0.1% of subjects in the 75 mg group and 0.1% of subjects in the 100 mg group). Thus, there was a very low incidence of euphoria-related AEs in these clinical studies. The most commonly reported abuse-related AEs other than euphoria were anxiety (1.7%) and somnolence (0.7%). There were a few other central nervous system-associated AEs, all of which are often seen in clinical trials: headache (4.0-4.5%), dizziness (2.2-3.2%), and fatigue (1.9-2.6%). However, these AEs demonstrate that eluxadoline does cross enter the systemic bloodstream after oral administration and cross the blood brain barrier to affect behavior.

5. Overdose

(b) (4)

However, CSS has concerns regarding the ability of opioid antagonists to reverse an eluxadoline overdose following intravenous administration (as may occur during an incident where an individual is abusing the drug). This concern is based on the following conditions reported in the monkey studies:

Opioid overdose responses were observed in two studies conducted in monkeys that received eluxadoline HCl intravenously. In a dose-finding study, acute administration of the opioid antagonist, naloxone, did not revive one monkey that had received 40 mg/kg of eluxadoline HCl. However, repeated doses of naloxone to monkeys that received a 30 mg/kg dose of eluxadoline HCl did reverse the opioid overdose induce in all monkeys. In the self-administration study in monkeys, intravenous administration of eluxadoline HCl produced an opioid overdose in three monkeys, one of which died after self-administering ~42 mg/kg of the drug. The other two animals were given the opioid antagonist, naltrexone, which reversed the overdose in the monkey that received ~56 mg/kg of eluxadoline HCl. However, the monkey that self-administered ~61 mg/kg of eluxadoline HCl did not show immediate reversal of severe sedation with naltrexone, even though the animal survived.

6. Human Physical Dependence Evaluation

Collection of Subjective Opiate Withdrawal Scale (SOWS) during Phase 3 Program (Study #27018966IBS3001 and #27018966IBS3002)

Two Phase 3 studies were conducted with eluxadoline in which the Sponsor asserted that physical dependence would be assessed during a discontinuation phase. However, as described below, neither of these studies were designed appropriately to assess whether eluxadoline produces withdrawal signs or symptoms upon discontinuation.

Study #3001 was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study that evaluated the efficacy and safety of orally administered eluxadoline in patients with IBS-d for 52 weeks, followed by a 2-week discontinuation period. Study #3002 was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study that evaluated the efficacy and safety of orally administered eluxadoline in patients with IBS-d for a 26-weeks, followed by a 4-week discontinuation period.

In each of these studies, the Subjective Opiate Withdrawal Scale (SOWS) was used to collect information from each patient regarding 16 withdrawal symptoms, each having a possible score of 0 to 4. The SOWS was completed at one time point only, at the conclusion of the active drug administration period (“at Week 52 (\pm 5 days)” or “at Week

26 (\pm 5 days)”, depending on the study, or upon early termination). No other instruments were used to collect information regarding possible withdrawal signs or symptoms associated with discontinuation of eluxadoline. Adverse events were monitored throughout the study period, however.

During the protocol planning stage of these studies, CSS informed the Sponsor that their proposed evaluation of physical dependence in these two Phase 3 studies was inadequate. CSS specifically requested the following changes to the design of the studies:

- Include the Clinical Opioid Withdrawal Scale (COWS; assessment by a clinical observer) in addition to the SOWS for collection of opioid withdrawal data.
- Assess opioid withdrawal using COWS and SOWS at multiple time points.
- Clarify the timing of the assessments (e.g., when the study questionnaires will be completed). Specifically, saying data will be collected “at week 52” (or “at Week 26”) does not provide any information on when the opioid withdrawal scales will be administered relative to the last dose of eluxadoline. Provide specific details on when the questionnaires will be administered (e.g., time after the last dose of eluxadoline). Provide a rationale for the time course of these assessments based on the half-life of the drug and expected time course of withdrawal symptoms.
- Administer the COWS and SOWS prior to the withdrawal phase of the study to obtain baseline data for comparison.

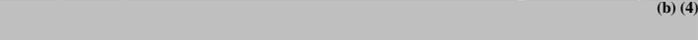
The Sponsor did not change either protocol to accommodate these recommendations.

Thus, the data resulting from these two studies represent single points, taken at a non-specified, non-standardized time (ranging from 5 days before drug discontinuation to 5 days after drug discontinuation), using only one subjective measure and monitoring of general (not withdrawal-specific) adverse events. This design is scientifically inadequate, as we informed the Sponsor when this study was being planned. Additionally, patients in Study #3002 who completed the study and withdrawal period were never presented with the SOWS at all.

Therefore, neither study is valid as a means of assessing whether eluxadoline produces physical dependence in humans and the minimal data submitted will not be presented or discussed.

However, data from the numerous preclinical studies do provide evidence that chronic administration of eluxadoline followed by drug discontinuation does not produce a withdrawal syndrome indicative of physical dependence (see studies above).

APPENDIX

The Sponsor submitted revised text for Section 9.0 of the label on March 11, 2015 (see below). In the text, the Sponsor proposes that eluxadoline should be placed into Schedule IV of the Controlled Substances Act (CSA). This text is a revision of the previously submitted text on June 27, 2014,  (b) (4)

 CSS has proposed a revision of this text, as shown in Section 3 (Recommendations).

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled substance

 (b) (4)

9.2 Abuse

 (b) (4)

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/s/

KATHERINE R BONSON
04/21/2015

SILVIA N CALDERON
04/21/2015

MICHAEL KLEIN
04/21/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, Office of Drug
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Division of Pediatric and Maternal Health Review

Date: February 26, 2015 **Consult Received:** August 7, 2014

From: Carol H. Kasten, MD, Medical Officer
Division of Pediatric and Maternal Health,
Office of Drug Evaluation IV (ODE IV)

Through: Tamara Johnson, MD, MS, Acting Team Leader
Division of Pediatric and Maternal Health, ODE IV

Lynne P. Yao, MD, Acting Director
Division of Pediatric and Maternal Health, ODE IV

To: Division of Gastroenterology and Inborn Errors Products (DGIEP)

NDA: 206940/000
Drug: Eluxadoline

Subject: NDA labeling review

Applicant: Furiex Pharmaceuticals

Proposed Indication: Indicated in adults for the treatment of irritable bowel syndrome with diarrhea (IBS-D)

Consult Request: Pregnancy and Lactation Labeling for this New Molecular Entity

Materials:

- Mid-Cycle Meeting Minutes, December 10, 2014.
- Sponsor's Table 12-7 "Eluxadoline Exposure in Pregnant Women During the Phase 3 Clinical Trials IBS-3001 and IBS-3002" Module 5.3.5. Integrated Summary of Safety Amendment, submitted October 23, 2014. pp.187-188.

INTRODUCTION

On June 27, 2014, Furiex Pharmaceuticals submitted a New Molecular Entity (NME) NDA for eluxadoline with a proposed indication in adults for the treatment of irritable bowel syndrome with diarrhea (IBS-D). The Division of Gastrointestinal and Inborn Errors Products (DGIEP) consulted the Division of Pediatric and Maternal Health - Maternal Health Team (DPMH-MHT) to review and provide labeling recommendations for Pregnancy (Section 8.1) and Lactation (Section 8.2).

BACKGROUND

Clinical Pharmacology

Eluxadoline belongs to a new class of drug, a mixed μ opioid receptor agonist and δ opioid receptor antagonist drug whose precise mechanism of action is unknown.¹ In mice, it has been demonstrated that inhibition of the δ receptor at the same time as the μ receptor is activated can provide analgesia with no opioid tolerance. Use of eluxadoline to treat humans with IBS-D is thought to be effective because the μ receptor stimulation slows intestinal motility and inhibition of the δ receptor is thought to prevent 'excessive' inhibition of motility.² Eluxadoline has limited oral bioavailability and its pharmacodynamic activity is thought to arise from its action on local gastrointestinal receptors.³ The drug is primarily excreted in the feces, has a half-life of [REDACTED] (b) (4) [REDACTED].⁴

Irritable Bowel Syndrome

IBS is a bowel disorder characterized by abdominal pain and altered bowel habits without detectable structural abnormalities.⁵ It affects 10 to 15% of the population^{6,7} with women being more frequently diagnosed with IBS. Some sources report that women are up to two or three times more likely to be diagnosed with IBS than men and may comprise up to 80% of the patients with severe IBS.^{8,9} There are three IBS subtypes described, IBS-D, IBS-C and IBS-M based on the patient's most dominant symptom; diarrhea, constipation or mixed diarrhea and constipation. The dominant IBS symptom often vacillates between diarrhea and constipation. Over a twelve month period three-quarters of IBS patients change subtypes with about a third of IBS patients switching between IBS-D and

¹ Ananthan S. Opioid ligands with mixed opioid receptor interactions: an emerging approach to novel analgesics. AAPS Journal 2006; 8;Article 14.

² See Ananthan.

³ [REDACTED] (b) (4)

⁴ Proposed eluxadoline labeling, NDA 206940.

⁵ Owyang C. Chapter 296. Irritable Bowel Syndrome. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson J, Loscalzo J. Longo D.L., Fauci A.S., Kasper D.L., Hauser S.L., Jameson J, Loscalzo J Eds. Dan L. Longo, et al.eds. Harrison's Principles of Internal Medicine, 18e. New York, NY: McGraw-Hill; 2012. <http://accessmedicine.mhmedical.com/content.aspx?bookid=331&Sectionid=40727090>. Accessed January 30, 2015.

⁶ Lovell R, Ford A. Effect of Gender on Prevalence of Irritable Bowel Syndrome in the Community: Systematic Review and Meta-Analysis. Am J Gastroenterol 2012; 107:991–1000.

⁷ Brenner D. Linaclotide for the treatment of irritable bowel syndrome with constipation: is it time to reshuffle the deck? Gastroenterology 2013;145:476-478.

⁸ See Owyang.

⁹ Mulak A, Taché Y, Larauche M. Sex hormones in the modulation of irritable bowel syndrome. World J Gastroenterol 2014 March 14; 20(10): 2433-2448 ISSN 1007-9327 (print) ISSN 2219-2840 (online)

IBS-C.¹⁰ This variability of patient symptoms and subtypes and the lack of a diagnostic biomarker pose challenges for the diagnosis and treatment of IBS-D.¹¹

The pathogenesis of IBS-D is poorly understood. Several different factors have been proposed: local gut phenomena such as abnormal motor or sensory neural activity, alterations in the gut mucosa or microbiome, and central nervous system dysregulation or psychological issues.¹² Patients with the IBS-D subtype usually have small volumes of loose stools which may be accompanied by large amounts of mucus. Therefore, treatments for IBS-D focus on gut-acting pharmacologic agents such as antispasmodics, fiber supplements and serotonin modulators.¹³ Antidiarrheal agents that are opiate-based, such as eluxadoline or loperamide (Imodium), are also used. For IBS-D patients with constant pain, antidepressants such as desipramine, paroxetine or citalopram may reduce symptoms.

The only approved drug for IBS-D is the serotonin receptor antagonist Lotronex (alosetron NDA 21107); however, prescription of Lotronex is under a restricted use Risk Management, Evaluation and Mitigation Strategy (REMS). Lotronex was approved on February 9, 2000, indicated for the treatment of IBS in women whose predominant bowel symptom is diarrhea. In November 2000, Lotronex was voluntarily withdrawn after the Agency had received reports of 54 cases of ischemic colitis and 23 cases of severe constipation in the Adverse Events Reporting System. The majority of the 77 patients required hospitalization, many required surgery, and three patients died. In April 2002, following an Advisory Committee Meeting, Lotronex was approved for restricted use in women with severe IBS-D with a REMS.

REVIEW

Data on Eluxadoline Use in Pregnancy from the Integrated Safety Summary¹⁴

There were seven pregnant women who were exposed to eluxadoline during the first trimester while participating in phase 3 clinical trials. All women were taken off the drug as soon as pregnancy was reported. The pregnant women were exposed to eluxadoline for varying durations (less than 3 to 10 weeks gestation) at twice daily doses of either 75 or 100 mg capsules. Two women had spontaneous abortions; one woman, treated with 100 mg capsules, had had two previous spontaneous abortions and the other woman, treated with 75 mg capsules, had a spontaneous abortion following physical trauma. A third woman had an elective termination. A fourth woman with hypertension during pregnancy was treated with a mixed alpha/beta adrenergic antagonist (labetalol) and delivered at 39 weeks a five pound, 9 ounce baby whose weight was below the 5th percentile for its gestational age. The remaining three women, one treated with 75 mg and two with 100 mg, delivered term neonates. All of the neonates had a weight appropriate for their gestational age.

¹⁰ See Owyang.

¹¹ See Owyang.

¹² See Owyang.

¹³ See Chey, *et al.*.

¹⁴ Sponsor's Table 12-7 "Eluxadoline Exposure in Pregnant Women during the Phase 3 Clinical Trials IBS-3001 and IBS-3002" Module 5.3.5. Integrated Summary of Safety Amendment, submitted October 23, 2014. pp.187-188.

Database and Literature Review

Eluxadoline is an NME and, therefore, the drug has not been reviewed in the Reprotox,¹⁵ TERIS¹⁶ or Shephard's Catalog¹⁷ databases. There is an applicant supported publication describing the results of the Phase 2 trial.¹⁸ It contains no information on the women who became pregnant while in the treatment arm of the study. There are no other publications on the use of eluxadoline in pregnant women.

There are no reviews in LACTMED®¹⁹ or Hale's Medications and Mother's Milk.²⁰ Nor are there publications regarding the presence of eluxadoline in human breast milk.

DISCUSSION

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"²¹ also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products for pregnancy and lactation, and creates a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and replaced with a narrative Risk Summary as part of a new format to include information about the risks and benefits of using these products during pregnancy and lactation.

The PLLR will take effect on June 30, 2015; however, at this time applicants may voluntarily convert labeling to the PLLR format.

Pregnancy

The data on the seven women who became pregnant in the clinical trials with eluxadoline do not clearly demonstrate the presence or absence of any teratogenic risk or adverse pregnancy outcome with eluxadoline exposure. All of these women were exposed during

¹⁵ Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies.

¹⁶ TERIS is the TERatology Information Service located at University of Washington. It is an online database designed to assist physicians or other healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women.
http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/

¹⁷ © 2014 Shepard's: A Catalog of Teratogenic Agents: An updated, automated version of Shepard's Catalog of Teratogenic Agents is distributed with TERIS. It's a comprehensive compilation of animal and human research on the teratogenicity of chemical and environmental agents. The Catalog contains information on over 2500 agents and includes many references for the Japanese as well as the American and European literature.

¹⁸ Dove L, Lembo A, *et al.* Eluxadoline benefits patients with irritable bowel syndrome with diarrhea in a phase 2 study. *Gastroenterology* 2013;145:329–338.

¹⁹ LACTMED®: The LactMed database is a National Library of Medicine database with information on drugs and lactation geared toward healthcare practitioners and nursing women.

²⁰ Hale's 2012 Medications and Mother's Milk, 15th Edition, Amarillo, TX

²¹ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

the first trimester for varying periods of time. There are no other sources of human data which might be used in the eluxadoline labeling to inform prescribers. The animal data in rats and rabbits did not show any teratogenic effect from exposure to eluxadoline during organogenesis at 51 and 115 times, respectively, the human exposure after a single oral dose of 100 mg. Given that there are no data indicating a safety risk associated with eluxadoline, DPMH-MHT does not suggest that a pregnancy registry or added post marketing surveillance be requested of the applicant at this time.

Lactation

There are no data on the presence of eluxadoline in human milk; however, the low oral bioavailability of eluxadoline diminishes the amount of drug reaching the maternal circulation such that the potential amount available to be transferred into the milk is likely to be low. DPMH-MHT advises that the benefits of breastfeeding and the potential risks of the drug to the breastfed infant be considered depending on the lactating woman's need for eluxadoline.

CONCLUSIONS

- The limited human data from the clinical trials and the animal data do not suggest that eluxadoline poses a teratogenic risk to the fetus.
- There are no data on any possible effects of eluxadoline exposure in the breastfeeding infant.

DPMH-MHT attended meetings in December, 2014, January and February, 2015.

RECOMMENDATIONS

The following are DPMH-MHT recommendations for the proposed eluxadoline label in PLLR format. Note: The trade name (b) (4) has been withdrawn and no new trade name has been agreed upon.

[TRADE NAME] (eluxadoline) tablets, for oral use
Initial U.S. Approval: YYYY

FULL PRESCRIBING INFORMATION CONTENTS*

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no studies with TRADENAME in pregnant women that inform any drug-associated risks. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically

recognized pregnancies. In animal reproduction studies, oral and subcutaneous administration of eluxadoline to rats and rabbits during organogenesis at doses with exposures approximately 51 and 115 times, respectively, the human exposure after a single oral dose of 100 mg demonstrated no teratogenic effects. In a pre- and postnatal development study in rats, no adverse effects were observed in offspring with oral administration of eluxadoline at doses with exposures approximately 10 times the human exposure [see Data].

Data

Animal Data

Eluxadoline administered during the period of organogenesis to rats and rabbits at oral/subcutaneous doses up to 1000/5 mg/kg/day (with exposures about 51 and 115 times, respectively, the human AUC of 24 ng.h/mL after a single oral dose of 100 mg) and did not cause any adverse effects on embryofetal development. A pre and postnatal development study in rats showed no evidence of any adverse effect on pre and postnatal development at oral doses of eluxadoline up to 1000 mg/kg/day (with exposures about 10 times the human AUC of 24 ng.h/mL after a single oral dose of 100 mg). In the same study, eluxadoline was detected in the milk of lactating rats administered oral doses of 100, 300 and 1000 mg/kg/day (with exposures about 1.8, 3 and 10 times, respectively, the human AUC of 24 ng.h/mL after a single oral dose of 100 mg). Milk samples were collected from six lactating females/group on lactation day 12 [REDACTED] (b) (4). Mean concentrations of eluxadoline in the milk of lactating rats on lactation day 12 were 2.78, 5.49 and 44.02 ng/mL at 100, 300 and 1000 mg/kg/day, respectively.

8.2 Lactation

Risk Summary

No data are available regarding the presence of eluxadoline in human milk, the effects of eluxadoline on the breast fed infant, or the effects of eluxadoline on milk production. However, eluxadoline is present in rat milk [see Use in Specific Populations (8.1)]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the breastfed infant from TRADENAME or from the underlying maternal condition.

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/s/

CAROL H KASTEN
02/26/2015

TAMARA N JOHNSON
02/26/2015

MELISSA S TASSINARI
02/26/2015
signed for L. Yao



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, ODE-IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
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MEMORANDUM TO FILE

From: Ethan D. Hausman, MD, Medical Officer
Division of Pediatric and Maternal Health (DPMH)

Through: Lynne P. Yao, MD, Acting Division Director
DPMH

NDA Number: 206,940

Sponsor: Furiex Pharmaceuticals, Inc

Drug: Eluxadoline (JNJ-27018966)

Dosage form and route of administration: Tablets; 75 and 100 mg

Dosing regimen: To be determined (TBD)

Proposed Pediatric dose regimen: TBD

Indication: Irritable bowel syndrome-diarrhea predominant (IBS-d)

Division Consult Request: The Division of Gastroenterology and Inborn Errors Products (DGIEP) requests a “labeling review, PeRC preparation assistance, and meeting attendance.”

Materials Reviewed

NDA 206,940; submitted June 27, 2014

Waiver request

Deferral request

Pediatric study plan

Draft labeling

IND 79,214

iPSP agreement letter including copy of iPSP, April 1, 2014

Minutes, sponsor meeting, October 25, 2013

Minutes, Pediatric Review Committee (PeRC)
March 26, 2014

Prior DPMH reviews

E. Hausman, October 21, 2013

E. Hausman, January 15, 2014

E. Hausman, March 24, 2014

Background

Eluxadoline is a locally active, mixed mu-opioid receptor agonist/delta-opioid receptor antagonist with low oral bioavailability under development for treatment of IBS-d. The NDA submission requests an indication in adults.

The Division of Gastroenterology and Inborn Errors Products (DGIEP) requests a “labeling review, PeRC preparation assistance, and meeting attendance.”

Introduction

The NDA submission includes a Pediatric Study Plan which consists of the previously agreed upon iPSP which includes plans for waiver in children from 0 to < 6 years of age, and deferral of studies in children from 6 to 17 years.

The pediatric development program and iPSP were previously (E. Hausman, October 21, 2013, January 15, 2014, and March 24, 2014), and recommendations were forwarded to the sponsor (A. Mulberg, February 3, 2014). On March 6, 2014, the sponsor submitted a revised iPSP. On review of the re-submitted iPSP, DGIEP and DPMH concluded that the recommendations outlined in the February 3, 2014, communication were incorporated into the revised iPSP. No additional meetings were held for internal review of the iPSP.

On March 26, 2014, the Pediatric Review Committee (PeRC) agreed to the plan for partial waiver of studies in children 0 to less than 6 years (G. Greeley, February 11, 2014) since the rarity of the condition in that age group would make studies impracticable.

Studies in children from 6 to 17 years of age will be deferred since the drug will be ready for approval in adults prior to completion of pediatric studies. (b) (4)

[REDACTED] (b) (4)

The three studies in the pediatric development plan are briefly summarized below. [Note: The sponsor has provided estimates that appear to support expected slow enrollment and the estimated report submission dates noted below.]

Study 1 (Dose Ranging Study): [REDACTED] (b) (4)

Estimate final report submission: August 15, 2019.

Study 2 (Confirmatory Efficacy and Safety Study): [REDACTED] (b) (4)

Estimate final report submission: October 15, 2025.

Study 3 (Safety Extension Study): [REDACTED] (b) (4)

[REDACTED] (b) (4)

Label Review

Eluxadoline is intended for treatment of adults with IBS-d and no pediatric data were submitted with the NDA. Therefore, the DPMH-Pediatric labeling review will focus on sections 1 (Indications and Usage) and 8.4 of labeling. For each section, the suggested labeling is presented first and is followed by suggested revisions which are noted in ***bold italics***.

1 INDICATIONS AND USAGE

Original labelling

(b) (4)

DPMH Comment: Since, to date, clinical studies submitted in support of the NDA contain adult information only, DPMH recommends the following revision to the indication which includes adult men and women and necessarily excludes children for whom clinical data has not been submitted.

Suggested labelling

“(b) (4)™ (eluxadoline) is indicated (b) (4) in *adults* (b) (4) irritable bowel syndrome (IBS-d).”

8.4 Pediatric Use

Original labelling

Safety and effectiveness in pediatric patients have not been established.

(b) (4)

DPMH Comment: DPMH agrees with this labeling description, but offers the following grammatical revision to enhance readability.

Recommended labelling

Safety and effectiveness in pediatric patients have not been established.

Juvenile Animal Data

(b) (4)

Based on these results, the ***NOAEL for general toxicity for male and female rats*** was 1500 mg/kg/day.

Additional comment: DPMH recommends that the first sentence of *Juvenile Animal Data* also include the human equivalent dose based on the juvenile rat exposure.

Other

On February 9, 2015, DPMH provided assistance with preparation for presentation to PeRC. The PeRC presentation is tentatively scheduled for March 18, 2015, and the PeRC minutes (pending) will include a summary of PeRC’s recommendations. Final labeling will be negotiated with the applicant and may contain additional changes not described in this document.

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/s/

ETHAN D HAUSMAN
02/17/2015

LYNNE P YAO
02/17/2015

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: February 11, 2014

TO: Jennifer Sarchet, Regulatory Project Manager
Laurie Muldowney, M.D., Medical Officer
Division of Gastroenterology and Inborn Errors Products

FROM: Susan Leibenhaut, M.D
Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 206940

APPLICANT: Furiex Pharmaceuticals

DRUG: eluxadoline (b) (4)
NME: Yes
THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Treatment of diarrhea and abdominal pain in men and women with
diarrhea predominant irritable bowel syndrome (IBS-d)

CONSULTATION REQUEST DATE: July 31, 2014
INSPECTION SUMMARY GOAL DATE: February 21, 2015
DIVISION ACTION GOAL DATE: May 27, 2015
PDUFA DATE: May 27, 2015

I. BACKGROUND:

Furiex Pharmaceuticals, Inc. submitted an NDA for the new molecular entity eluxadoline aka JNJ-27018966 (b) (4) for the indication of treatment of pain and diarrhea associated with diarrhea-predominant Irritable Bowel Syndrome (IBS-d). At the present time, there are no unrestricted prescription products on the market that are indicated to provide relief to patients who are suffering from IBS-d. Alosetron, a selective serotonin 5-HT₃ receptor antagonist marketed under the trade name Lotronex, is the only approved drug for IBS-d and its use is limited to women. Loperamide, a peripherally restricted mu-opioid receptor (μ OR) agonist, is widely used as an antidiarrheal. Both alosetron and loperamide are associated with constipation. JNJ-27018966 is a locally active mixed μ OR agonist and delta-opioid receptor (δ OR) antagonist that is being developed for the treatment of IBS-d. The applicant claims that eluxadoline has GI transit-inhibiting activity that is consistent with its primary pharmacological profile as a μ OR agonist; however, its additional δ OR antagonist activity may mitigate against the profound constipating effect of unopposed peripherally acting μ OR agonists (e.g., loperamide or diphenoxylate).

The sponsor submitted the following two studies in support of the application:

1. Protocol 27018966IBS3001 entitled, "A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-27018966 in the Treatment of Patients with Diarrhea-Predominant Irritable Bowel Syndrome". This study was conducted from May 2012 to July 2014 (total safety evaluation). A total of 1281 subjects were randomized at 295 sites in the US, Canada, and UK.
2. Protocol 27018966IBS3002 entitled, "A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-27018966 in the Treatment of Patients with Diarrhea- Predominant Irritable Bowel Syndrome". This study was conducted from May 2012 to January 2014. A total of 1146 subjects were enrolled at 261 clinical sites in the U.S., Canada, and the U.K.

The sponsor contracted with (b) (4) to develop an IVRS/IWRS system (also known as IXRS) that encompassed multiple functionalities including subject electronic diary, subject randomization, and study drug management (including dispensing, ordering, and returns).

The studies used an eDiary (IXRS) with direct subject entry to capture important subject symptoms such as daily pain response and stool consistency that determined eligibility and endpoints. The diary was developed and maintained by (b) (4). To prevent potential unblinding, the IXRS data entered by the patients was not provided to the investigative site staff at the time of randomization or during the study. The determination of whether a patient

met the eligibility criteria was made by the IXRS at the time of randomization. Periodic notifications were sent to the investigators during the double-blind treatment period to inform them of patient compliance with diary entries and to alert investigators if a patient had experienced episodes of constipation or required excessive loperamide rescue medication for acute treatment of uncontrolled diarrhea. Criteria for this notification were outlined in the protocols. In response to an IXRS notification for constipation or excessive loperamide rescue medication use, the investigator was required to contact the patient to review his/her status as soon as possible. An unscheduled visit to further evaluate the patient's status was to be arranged if deemed warranted by the Investigator.

The review division chose sites for inspection on the basis of several factors including high enrollment, previous inspections, complaints, and efficacy results. The sponsor was inspected because this application is for a new molecular entity. (b) (4) was inspected because of the central role of the central role of the IXRS systems in these clinical trials.

II. RESULTS (by Site):

Name, Address, and Type of Inspected Entity	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification*
CI: Dr. Mark Kutner 2128 West Flagler Street, 1st Floor Miami, FL 33135	27018966IBS3001 Site 359 60 subjects	August 18 to 28, 2014	NAI
	27018966IBS3002 Site 569 90 subjects		
CI: Dr. Armando Pineda-Velez 8300 West Flagler Street, Suite 210 Miami, FL 33144	27018966IBS3001 Site 373 22 subjects	September 15 to 18, 2014	NAI
	27018966IBS3002 Site 832 27 subjects		
CI: Dr. Leonel Perez-Limonte 6850 Coral Way, Suite 409 Miami, FL 33155	27018966IBS3001 Site 371 3 subjects	September 24 to October 6, 2014	NAI
	27018966IBS3002 Site 541 24 subjects		

Name, Address, and Type of Inspected Entity	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification*
CI: Dr. Ana Lorena Lewy Alterbaum 9700 Stirling Road Building C, Suite 111 and Suite 103 Cooper City, FL 33024	27018966IBS3001 Site 363 8 subjects 27018966IBS3002 Site 843 5 subjects	November 10 to 13, 2014	VAI
CI: Dr. Scott Wilson 106 Nate Whipple Highway, Suite 202 Cumberland, RI 2864	27018966IBS3001 Site 20 12 Subjects	September 2 and 10, 2014	VAI
CRO: (b) (4)	Protocol 27018966IBS3001 Protocol 27018966IBS3002	(b) (4)	Pending* (preliminary NAI)
Sponsor: Furiex Pharmaceuticals, Inc. 3900 Paramount Parkway, Suite 150 Morrisville, NC 27560	Protocol 27018966IBS3001 Protocol 27018966IBS3002	November 18 to 25, 2014	Pending* (preliminary NAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. Dr. Mark Kutner
2128 West Flagler Street, Miami, FL 33135

- a. **What was inspected:** At this site, for Protocol 3001, 102 subjects were screened, 60 subjects were enrolled, and 35 subjects completed the study. For Protocol 3002, 181 subjects were screened, 90 subjects were enrolled, and 70 subjects completed the study. Informed consent documents for all screened subjects for both studies were reviewed. Full source data was reviewed for 34 subjects in Protocol 3001 and for 43 subjects in Protocol 3002.

- b. **General Observations/Commentary:** No significant regulatory violations were noted, and no Form FDA 483 was issued. There was no evidence of under-reporting of adverse events.
- c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

2. Dr. Armando Pineda-Velez
8300 West Flagler Street, Miami, FL 33144

- a. **What was inspected:** At this site, for Protocol 3001, 22 subjects were screened, 22 subjects were enrolled, and 22 subjects completed the study. Full source data was reviewed for 11 subjects. For Protocol 3002, 34 subjects were screened, 27 subjects were enrolled and completed the study. Full source data was reviewed for 20 subjects in Protocol 3002.
- b. **General observations/commentary:** There was no evidence of under-reporting of adverse events. No discrepancies were noted between the line listings and the source documents and data.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the indication.

3. Dr. Leonel Perez-Limonte
6850 Coral Way, Miami, FL 33155

- a. **What was inspected:** At this site, for Protocol 3001, 3 subjects were screened, 3 subjects were enrolled, and no subjects completed the study. Full source data was reviewed for all 3 subjects. For Protocol 3002, 28 subjects were screened, 25 subjects were enrolled, and 24 subjects completed the study. Informed consent documents for 29 screened subjects were reviewed. Full source data was reviewed for 15 subjects in Protocol 3002.
- b. **General observations/commentary:** There was no evidence of under-reporting of adverse events. No discrepancies were noted between the line listings and the source documents and data.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the indication.

**4. Dr. Ana Lorena Lewy Alterbaum
9700 Stirling Road, Cooper City, FL 33024**

- a. **What was inspected:** At this site, for Protocol 3001, 27 subjects were screened, 8 subjects were enrolled, and 6 subjects completed the study. Full source data was reviewed for all 8 enrolled subjects. For Protocol 3002, 9 subjects were screened, 5 subjects were enrolled and completed the study. Full source data was reviewed for 5 subjects in Protocol 3002. The inspection included review of informed consent documents (ICDs), enrollment logs, institutional review board (IRB) correspondence and approvals, sponsor correspondence, investigator agreements (1572s), financial disclosure, adverse event reports, electronic case report forms (e-CRFs), device accountability records, Interactive Voice Response System (IVRS) information, and source documents.
- b. **General observations/commentary:** There was no evidence of under-reporting of adverse events. No discrepancies were noted between the line listings and the source documents and data. A Form FDA 483 was issued for failing to follow the protocol and not reporting changes in research activity to the IRB prior to implementation. While the trial was ongoing, the monitors determined that study personnel were entering data for the subjects. When this was brought to the attention of the clinical investigator (CI), she removed the study staff, discussed the issues with the subjects, and instituted corrective actions. The FDA inspection confirmed these allegations by the sponsor and the corrective actions by the CI. In addition, the site did not have IRB approval initially to give calling cards to subjects but approval was eventually obtained.

The clinical investigator acknowledged the observation and adequately responded to the inspection findings in a letter dated November 21, 2014.

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

**5. Dr. Scott Wilson
106 Nate Whipple Highway, Cumberland, RI 02864**

- a. **What was inspected:** At this site, for Protocol 3001 24 subjects were screened, 12 subjects were randomized, and 10 subjects completed the study. The inspection included review of informed consent documents (ICDs), enrollment logs, institutional review board (IRB) correspondence and approvals, sponsor correspondence, investigator agreements (1572s), financial disclosure, adverse event reports, electronic case report forms (e-CRFs), device accountability records, Interactive Voice Response System (IVRS) information, and source documents. Informed consent documents for all 24 screened subjects and the case histories for all 12 randomized subjects' were reviewed.

- b. **General observations/commentary:** The inspection found that the site was in general compliance with instructions from the sponsor, with the exception that Subject 0200021 was randomized in spite of having exclusion criterion of elevated lipase >2x upper limit of normal. This violation was noted by the sponsor while the study was ongoing, was noted in the NDA line listings as a protocol violation, and the subject was allowed to continue in the trial. This protocol violation was cited on the Form FDA 483 issued at the close of the inspection.

The clinical investigator acknowledged the observation and adequately responded to the inspection findings in a letter dated September 17, 2014.

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

6.  (b) (4)

Note: Observations below for the sponsor inspection are based on e-mail communications with the FDA field investigator and the FDA staff from headquarters that participated. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report (EIR).

- a. **What was inspected:** The IXRS system used for the clinical trial was inspected.

b. **General observations/commentary:**  (b) (4)

- c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data generated by this CRO appear acceptable in support of the respective indications.

**7. Furiex Pharmaceuticals, Inc.
3900 Paramount Parkway, Morrisville, NC 27560**

Note: Observations below for the sponsor inspection are based on review of a draft EIR and communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

- a. **What was inspected:** This inspection evaluated compliance with sponsor responsibilities including selection and oversight of contract research organizations, monitoring, financial disclosure, FDA Form 1572s, and quality assurance (QA) for the studies noted above. The inspection included review of general correspondence and study master files, site monitoring, handling of adverse events, and some information and procedures related to the IXRS subject diaries. Information was obtained concerning procedures for selection of clinical investigators, selection of monitors, IXRS, contract services used, and other sponsor/monitor related activities.
- b. **General observations/commentary:** The monitoring of investigators was adequate and the sponsor maintained adequate oversight of the trials. Data receipt and handling was considered adequate. Oversight of test article was considered adequate. No regulatory violations were noted and a Form FDA 483 was not issued. It was noted in the draft EIR that, on July 2, 2014 Furiex was acquired by Actavis. The firm is now a wholly owned subsidiary of Actavis, who will commercialize the product.
- c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data generated by these studies appear acceptable in support of the respective indications.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Five clinical investigator sites, the sponsor, and the CRO responsible for the IXRS were inspected for this NDA. Three clinical sites had the classification of NAI and two clinical sites had the classification of VAI with minor regulatory violations noted. For the sponsor and CRO inspections, the preliminary classifications are NAI. The studies appear to have been conducted adequately, and the data generated by these studies appear acceptable in support of the respective indications.

Note: Observations above for the sponsor and CRO site inspections are based on e-mail communications with the FDA field investigator (CRO) or a draft EIR (sponsor). An inspection summary addendum will be issued if conclusions change upon review of the final EIRs.

{See appended electronic signature page}

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

/s/

SUSAN LEIBENHAUT
02/11/2015

SUSAN D THOMPSON
02/11/2015

KASSA AYALEW
02/11/2015

LABEL AND LABELING REVIEW

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

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

Date of This Review: January 5, 2015
Requesting Office or Division: Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number: NDA 206940
Product Name and Strength: (b) (4) (eluxadoline) Tablets, 75 mg and 100 mg
Product Type: Single Ingredient
Rx or OTC: Rx
Applicant/Sponsor Name: Furiex Pharmaceuticals
Submission Date: June 26, 2014
OSE RCM #: 2014-1796
DMEPA Primary Reviewer: Sherly Abraham, R.Ph.
DMEPA Team Leader: Kendra Worthy, Pharm.D

1 REASON FOR REVIEW

This review is in response to a request by DGIEP to review proposed prescribing information and container labels for any areas that may cause medication errors. Furiex Pharmaceuticals submitted new molecular entity NDA on June 26, 2014 to DGIEP.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B-N/A
Previous DMEPA Reviews	C-N/A
Human Factors Study	D-N/A
ISMP Newsletters	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Furiex Pharmaceuticals is proposing 75 mg and/or 100 mg (b) (4) that will be packaged in a 60-count bottle, which is supported by the dosage and administration information for this product. We reviewed the proposed prescribing information and container labels. DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. We provide the recommendations in Section 4 to address the deficiencies.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

4.2 RECOMMENDATIONS FOR FURIEX PHARMACEUTICALS

Based on this review, we recommend the following be implemented prior to approval of this NDA:

Container Labels:

60 count bottles:

1. As currently displayed, NDC number is denoted as a placeholder (XXXXXX-XXXX-XX). Ensure that the NDC product code is different for both strengths.

Sample Packs:

1. As currently displayed, NDC number is denoted as a placeholder (XXXXXX-XXXX-XX). Ensure that the NDC product code is different for both strengths.
2. (b) (4) proprietary name, established drug name and strength. Ensure that each unit dose section presents these required information in the event the blister pack is separated.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for (b) (4) that Furiex Pharmaceuticals submitted on June 26, 2014, 2014.

Table 2. Relevant Product Information for (b) (4)	
Initial Approval Date	N/A
Active Ingredient	Eluxadoline
Indication	Treatment of diarrhea and abdominal pain in men and women with diarrhea predominant irritable bowel syndrome (IBS-d).
Route of Administration	Oral
Dosage Form	Tablets
Strengths	75 mg and 100 mg
Dose and Frequency	1 tablet twice daily
How Supplied	Bottle of 60 count
Storage	Store at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F).
Container Closure	Opaque HDPE container

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following (b) (4) labels and labeling submitted by Furiex Pharmaceuticals on June 26, 2014, 2014.

Container Labels

G.2 Label and Labeling Images



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

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

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

/s/

SHERLY ABRAHAM
01/05/2015

KENDRA C WORTHY
01/06/2015

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

NDA	206940
Brand Name	(b) (4)
Generic Name	Eluxadoline (JNJ-27018966)
Sponsor	Furiex Pharmaceuticals, Inc.
Indication	Treatment of diarrhea and abdominal pain in men and women with diarrhea predominant irritable bowel syndrome (IBS-d)
Dosage Form	Tablet, 100 mg
Drug Class	mixed mu opioid receptor (μ OR) agonist and delta opioid receptor (δ OR) antagonist
Therapeutic Dosing Regimen	100 mg twice daily
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	1500 mg single dose in man and 1000 mg single dose in woman
Submission Number and Date	SDN 001/ 26 June 2014
Review Division	DGIEP

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

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of JNJ-27018966 (100 mg and 1000 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between JNJ-27018966 100 mg and placebo, and between JNJ-27018966 1000 mg and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the $\Delta\Delta$ QTcI for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 3, indicating that assay sensitivity was established.

In this randomized, evaluator-blinded, placebo- and positive-controlled, 4-period crossover study, 64 healthy subjects received JNJ-27018966 100 mg, JNJ-27018966 1000 mg, placebo, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for JNJ-27018966 (100 mg and 1000 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta QTcI$ (ms)	90% CI (ms)
JNJ-27018966 100 mg	0.5	1.3	(-0.3, 2.8)
JNJ-27018966 1000 mg	2	3.6	(1.6, 5.6)
Moxifloxacin 400 mg*	1	11.9	(10.3, 13.4)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points are 9.7 ms.

The supratherapeutic dose (1000 mg) produced mean C_{max} values 10-fold the mean C_{max} for the therapeutic dose (100 mg). These concentrations are above those for the predicted worst case clinical scenario (drug interaction with cyclosporine). The results show that at these concentrations there are no detectable prolongations of the QT-interval. It is expected from drug interaction studies that co-administration of eluxadoline with cyclosporine can elevate eluxadoline's mean C_{max} 6.2-fold.

Hepatic impairment decreases eluxadoline's clearance, resulting in eluxadoline plasma levels 6-fold, 4-fold, and 16-fold in mild, moderate, and severe hepatic impaired subjects (Child Pugh Class A, B, C), respectively. Eluxadoline is proposed to be contraindicated in patients with a history of cirrhosis, diminishing the need to study QT interval prolongation at exposure levels observed in patients with hepatic impairment.

2 PROPOSED LABEL

The following is the sponsor's proposed labeling language related to QT.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

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

12.2. Pharmacodynamics

Cardiac Electrophysiology

The effect of (b) (4) on the QTc interval was evaluated in a Phase 1 randomized placebo and positive controlled double-blind, single-dose, crossover thorough QTc study in 64 healthy subjects. At the dose 10-fold the therapeutic dose, (b) (4) did not prolong QTc to any clinically relevant extent.

3 BACKGROUND

3.1 PRODUCT INFORMATION

JNJ-27018966 is a locally active, mixed mu opioid receptor (μ OR) agonist and delta opioid receptor (δ OR) antagonist that is being developed for the treatment of diarrhea-predominant irritable bowel syndrome (IBS-d).

3.2 MARKET APPROVAL STATUS

Eluxadoline is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

From IB (February 2012)

In in vitro cardiovascular safety studies, there were no notable effects of JNJ-27018966 on the IKr current in human ether-a-go-go related gene (hERG)-transfected human embryonic kidney (HEK) 293 cells up to a concentration of 3 μ M (Study CPF1226). There were no notable effects of JNJ-27018966 on the rate or force of contraction in the isolated guinea pig spontaneously beating right atrium (Studies DD07347 and EDMS-PSDB-6412461) and no significant or physiologically relevant effects after electrophysiological evaluation in isolated rabbit Purkinje fibers up to a concentration of 10 μ M (Study CPF1238).²⁰ This in vitro NOEL of 10 μ M correlates to a free plasma concentration of 5.7 μ g/mL, which is more than 3000-fold the estimated free exposure at the C_{max} after a mid- efficacious dose in mice. Table 4–3 presents a summary of findings for in vitro safety pharmacology studies with JNJ-27018966.

After IV administration of JNJ-27018966 to anesthetized guinea pigs (Study CPF1211)²² and conscious dogs (Study CPF1246), cardio-hemodynamic effects occurred (eg, changes in heart rate and blood pressure). These findings were very pronounced in conscious dogs, but coincided with behavioral findings (ie, licking, retching, heavy breathing). Therefore, JNJ-27018966 was given at increasing IV doses of 0.003 to 1 mg/kg (total cumulative dose of 1.443 mg/kg) to dogs that were anesthetized with α -chloralose (Study CPF1330). In this model, up to an IV cumulative dose of 0.143 mg/kg (free plasma level 117.6 ng/mL), no notable effects were found. After IV infusion of higher doses to anesthetized dogs (cumulative doses of 0.443 and 1.443 mg/kg), a tendency for a decrease in arterial blood pressure and heart rate occurred. The plasma level in dogs at the NOEL of 0.143 mg/kg after IV administration (117.6 ng/mL) represents a margin of 62, relative to the exposure at a mid-efficacious dose in mice (30 mg/kg; 1.88 ng/mL free). A non-dose-dependent decrease in arterial blood pressure that was not associated with an effect on heart rate was also found after SC administration at 5, 15, and 30 mg/kg to conscious telemetered monkeys (maximum decrease of 21% of the control value) (Study TOX8159). The exposure in monkeys at 30 minutes after a 5-mg/kg SC dose (free plasma concentrations of 234 ng/mL in males and 315 ng/mL in females) was 124- to 167-fold the C_{max} at a mid-efficacious dose in mice.

3.4 PREVIOUS CLINICAL EXPERIENCE

From IB (February 2012)

The clinical safety of JNJ-27018966 has been evaluated in 86 healthy volunteers administered JNJ-27018966 in the completed Phase 1 studies and 612 patients with IBS-d administered JNJ-27018966 in the completed Phase 2 study.

Study 27018966EDI1001: Single-and Multiple-Dose Safety

JNJ-27018966 appeared to be well tolerated after single doses in healthy male subjects and female subjects of nonchildbearing potential. No severe or serious AEs were reported and almost all were mild in severity; the incidence of AEs of moderate severity remained low and did not increase as a result of multiple dosing. Orthostatic changes in blood pressure occurred in several subjects in both the SAD and MAD phases on both placebo.

The most frequently reported AEs in males were dizziness, postural dizziness, headache, nausea, abdominal pain, and constipation, none of which appeared to be dose related. In Part 1a, the MTD was 1500 mg of JNJ-27018966 in men.

Reviewer's comments: No

seizures, sudden cardiac death or ventricular arrhythmias were reported in these studies. No clinically relevant ECG changes were reported.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of JNJ-27018966's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 79,214. The sponsor submitted the study report 27018966CPS1008 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Randomized, Evaluator-Blinded, Placebo- and Positive-Controlled, 4-Period Crossover Study to Evaluate the Effect of Single, Oral Doses of JNJ-27018966 on Cardiac Repolarization in Healthy Male and Female Adult Subjects

4.2.1 Protocol Number

27018966CPS1008

4.2.2 Study Dates

Study Initiation Date: 09 January 2013 (date of first subject informed consent)

Study Completion Date: 25 March 2013 (date of last subject contact)

4.2.3 Objectives

Primary Objective:

To assess the effects of JNJ-27018966 at therapeutic and suprathreshold doses on QT/corrected QT (QTc) intervals and electrocardiogram (ECG) morphology in healthy male and female adult subjects.

Secondary Objectives:

1. To evaluate the pharmacokinetics of JNJ-27018966.
2. To determine the relationship between the plasma concentration of JNJ-27018966 and QT/QTc interval changes.
3. To assess the safety and tolerability of JNJ-27018966 of a projected efficacious dose and a suprathreshold dose.

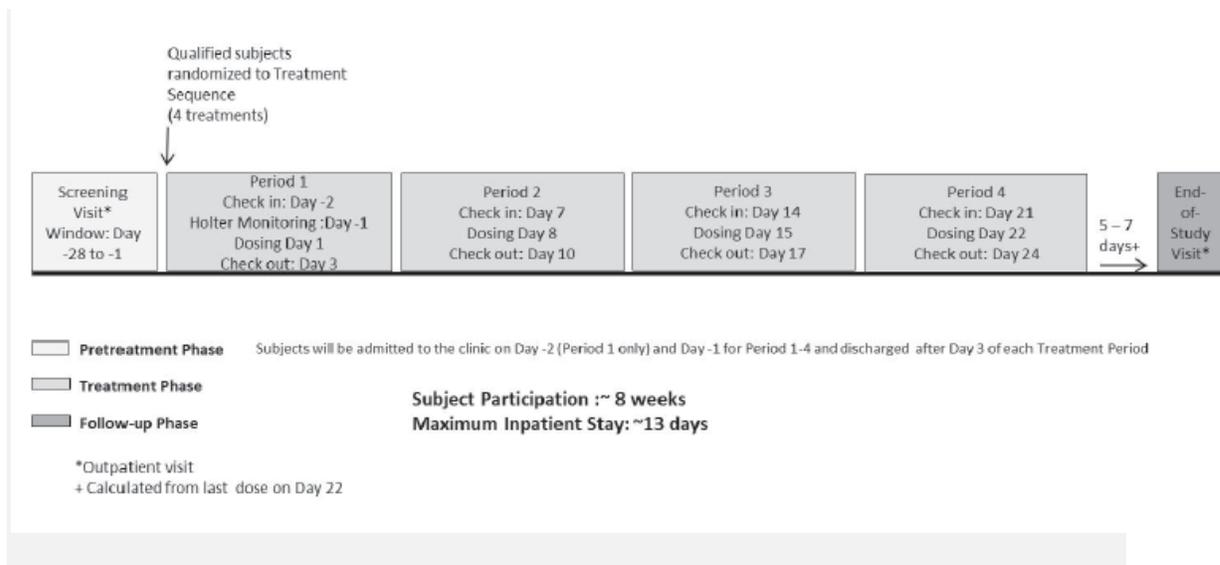
4.2.4 Study Description

4.2.4.1 Design

This is a randomized, evaluator-blinded, placebo- and positive-controlled, 4-period crossover study to evaluate the effect of JNJ-27018966 on cardiac repolarization. In each treatment period, the study drug will be administered as a single dose to subjects in a fasted state. The JNJ-27018966 doses to be evaluated in this study are 1000 mg (suprathreshold dose) and 100 mg (therapeutic dose in Phase 3 trials and anticipated for the market). A positive control, moxifloxacin 400-mg single dose that is known to prolong QT/QTc intervals, will be used to validate the assay sensitivity. A placebo control will be used to compare the effect of JNJ-27018966 on QT/QTc intervals.

For each subject, the study will consist of 3 phases: a screening phase (consisting of a Screening Visit that can occur up to 28 days prior to Period 1, Day 1), a treatment phase (4 treatment periods with a minimum 5-day washout interval between the last dose of study drug in a treatment period and the first dose of study drug in the next treatment period), and a post-treatment phase (that includes an End-of-Study Visit to occur 5-7 days after the last dose of study drug in Period 4). The total duration of study participation for each subject will be approximately 11 weeks (from the beginning of the screening phase to the post-treatment phase).

A diagram depicting subject participation was presented in Figure below:



4.2.4.1 Controls

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

4.2.4.2 Blinding

Moxifloxacin was administered as an open-label.

4.2.5 Treatment Regimen

4.2.5.1 Treatment Arms

The study was randomly assigned to 1 of 4 treatment sequences (sequences 1, 2, 3, and 4) and receive 1 of 4 treatments (Treatments A, B, C, and D) in each treatment period (Periods 1, 2, 3, and 4) in the order specified by the randomization schedule. The study and treatment sequences were:

Table 1: Treatment Sequences

Treatment Sequence	Period 1	Period 2	Period 3	Period 4
ADBC	A	D	B	C
BACD	B	A	C	D
CBDA	C	B	D	A
DCAB	D	C	A	B

Note: The Williams design-based treatment sequences shown are for illustration purposes only.

Table 2: Dose Administration

Treatment	Treatment Description	Description and Number of Dosage Units To Be Administered ^a			
		JNJ-27018966 100 mg	Moxifloxacin 400 mg	Matching Placebo	Total
A	JNJ-27018966 1000 mg	10	0	0	10
B	JNJ-27018966 100 mg	1	0	9	10
C	Placebo	0	0	10	10
D	Moxifloxacin 400 mg	0	1	0	1

^a To maintain blinding of JNJ-27018966 a matching placebo will be used in the Treatments A, B, and C so that each treatment has the same number of tablets per dose.

4.2.5.2 Sponsor's Justification for Doses

In each treatment period, the study drug was administered as a single dose because repeat dosing with JNJ-27018966 had been shown to reduce its C_{max} by approximately 40%. The ICH E14 guidance recommends that the study drug be tested at substantial multiples of the anticipated maximum therapeutic exposure to allow dose- or concentration-response for QT/QTc prolongation being thoroughly characterized. The doses selected for JNJ-27018966 in this thorough QT study were 100 mg (intended therapeutic dose) and 1000 mg (supratherapeutic dose). The supratherapeutic dose is 10 times the intended therapeutic dose and has a C_{max} that is approximately 8 times that seen with the therapeutic dose.

Reviewer's Comment: Acceptable. These concentrations are above those for the predicted worst case clinical scenario of use with cyclosporine. The results show that at these concentrations there are no detectable prolongations of the QT-interval. It is expected from drug interaction studies that co-administration of eluxadoline with cyclosporine can elevate eluxadoline's mean C_{max} 6.2-fold.

Hepatic impairment decreases eluxadoline's clearance, resulting in eluxadoline plasma levels 6-fold, 4-fold, and 16-fold in mild, moderate, and severe hepatic impaired subjects (Child Pugh Class A, B, C), respectively. Eluxadoline is proposed to be contraindicated in patients with a history of cirrhosis, diminishing the need to study QT interval prolongation at exposure levels observed in patients with hepatic impairment.

4.2.5.3 Instructions with Regard to Meals

In each treatment period, the study drug will be administered as a single dose to subjects in a fasted state.

Reviewer's Comment: Acceptable. (b) (4) food reduces C_{max} and AUC by ~50%. Administering the proposed product in a fasted state maximizes exposure and it therefore appropriate for the purpose of this study.

4.2.5.4 ECG and PK Assessments

ECG and PK was assessed at the following time points:

ECG: -1, -0.5, -0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 15, 18, and 22.5 hours after dosing

PK: Within 0.75 h before dosing, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 15, 18, 22.5, 24, 36, and 48.

Reviewer's Comment: The PK and ECG sampling times are adequate to capture the T_{max} of Eluxadoline.

4.2.5.5 Baseline

The sponsor used time- averaged pre-dose QTc as baseline values.

4.2.6 ECG Collection

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

4.2.7 Sponsor's Results

4.2.7.1 Study Subjects

Sixty-four healthy males or females, 18 to 55 years of age, with a normal 12-lead ECG and BMI (18 to 32 kg/m²) enrolled at a single center, 52 subjects complete the study.

4.2.7.2 Statistical Analyses

4.2.7.2.1 Primary Analysis

The primary endpoint was baseline-adjusted mean differences between JNJ-27018966 100 mg and placebo, and between JNJ-27018966 1000 mg and placebo in Δ QTcI. The model included sequence, subject within treatment sequence, treatment, period, time and time-by-treatment interaction as fixed effect terms, subjects as a random effect, and period-specific baseline QTcI as covariate. The sponsor concluded that maximally 4.10 ms at 1 hour after dosing for the 1000 mg eluxadoline treatment, with a 1-sided 95% upper confidence bound of 5.81 ms, did not reach the threshold for significance for QT interval prolongation. The largest mean time-matched difference in change from baseline from placebo for the eluxadoline 100 mg dose was 1.2 ms at 0.5 hours after dosing, with a 1-sided upper confident bound of 2.91 ms. Therefore, this was a negative QT/QTc study.

Table 2: Sponsor’s Results of Mean Change from Baseline of Δ QTcI and $\Delta\Delta$ QTcI of JNJ-27018966 100 mg and JNJ-27018966 1000 mg

Hours After Dosing	Placebo ^a		100 mg Eluxadoline ^a		1000 mg Eluxadoline ^a		100 mg – Placebo ^b		1000 mg – Placebo ^b	
	N	Mean	N	Mean	N	Mean	Mean	95% UCB	Mean	95% UCB
0.5	60	-1.23	60	-0.03	60	0.20	1.20	2.91	1.43	3.13
1.0	60	-0.94	60	-0.09	60	3.16	0.84	2.55	4.10	5.81
2.0	60	-1.58	60	-1.12	60	2.41	0.46	2.17	3.99	5.70
3.0	60	-0.15	60	-0.59	59	-0.31	-0.44	1.27	-0.15	1.56
4.0	60	0.05	60	-1.37	59	-0.90	-1.41	0.29	-0.95	0.76
5.0	60	1.08	60	0.16	59	-1.19	-0.92	0.79	-2.27	-0.55
6.0	60	1.71	60	0.03	59	-0.63	-1.69	0.02	-2.34	-0.63
8.0	60	-2.42	60	-5.97	59	-8.28	-3.55	-1.84	-5.85	-4.14
12.0	60	1.16	60	-1.64	59	-6.09	-2.79	-1.09	-7.25	-5.53
15.0	59	2.81	60	1.03	58	-1.12	-1.78	-0.07	-3.93	-2.20
18.0	60	6.60	60	6.02	59	4.41	-0.58	1.13	-2.20	-0.48
22.5	60	2.12	59	2.16	59	0.17	0.05	1.76	-1.94	-0.23

Abbreviations: msec, milliseconds; QTcI: corrected QT interval using the subject specific method; UCB, upper confidence bound.

^a Least squares means from the primary analysis model.

^b Double delta ($\Delta\Delta$) least squares means from the primary analysis model.

Reviewer’s Comments: We will provide our independent analysis result in Section 5.2. Our analysis results are similar to the sponsor’s results of QTcI.

4.2.7.2.2 Assay Sensitivity

This reviewer could not locate the sponsor’s moxifloxacin analyses results.

Reviewer’s Comments: We will provide our independent analysis result in Section 5.2.

4.2.7.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc \leq 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and $>$ 500 ms, and changes from baseline QTc \leq 30 ms, between 30 and 60 ms, and $>$ 60 ms. No subject’s absolute QTc $>$ 480 ms and Δ QTc $>$ 60 ms.

4.2.7.3 Clinical Pharmacology

4.2.7.3.1 Pharmacokinetic Analysis

The PK results are presented in Table 2. Following administration of 1000 mg eluxadoline C_{max} and AUC values in the thorough QT study were 10 and 7- to 8-fold values seen at the intended clinical dose of 100 mg

Table 2: Mean (CV%) plasma PK parameters for eluxadoline

Parameter (unit)	Eluxadoline Treatment Group	
	1000 mg Eluxadoline (N=58)	100 mg Eluxadoline (N=59)
AUC _{0-t} (ng·h/mL)	168.04 (54.3)	21.94 (81.3)
AUC _{0-inf} (ng·h/mL)	156.62 (64.2) ^b	23.54 (77.6) ^c
C _{max} (ng/mL)	31.45 (66.9)	3.03 (88.1)
T _{max} (h) ^a	1.00 (0.50, 6.00)	3.00 (0.50, 8.07)
t _{1/2} , alpha (h)	2.56 (27.8)	2.71 (37.4)
t _{1/2} , beta (h)	18.50 (38.7) ^b	5.03 (108.7) ^c
CL/F (L/h)	8786.10 (52.6) ^b	6400.38 (63.2) ^c
V _z /F (L)	234270.51 (76.3) ^b	40605.90 (91.1) ^c

Abbreviations: CV, coefficient of variation; h, hours; L, liters.

^a For T_{max}, the median (minimum, maximum) values are presented.

^b n=21.

^c n=55.

Source: Sponsor's QT study report table 11-5

Reviewer's comments: The PK sampling schedule was adequate for the purpose for this study.

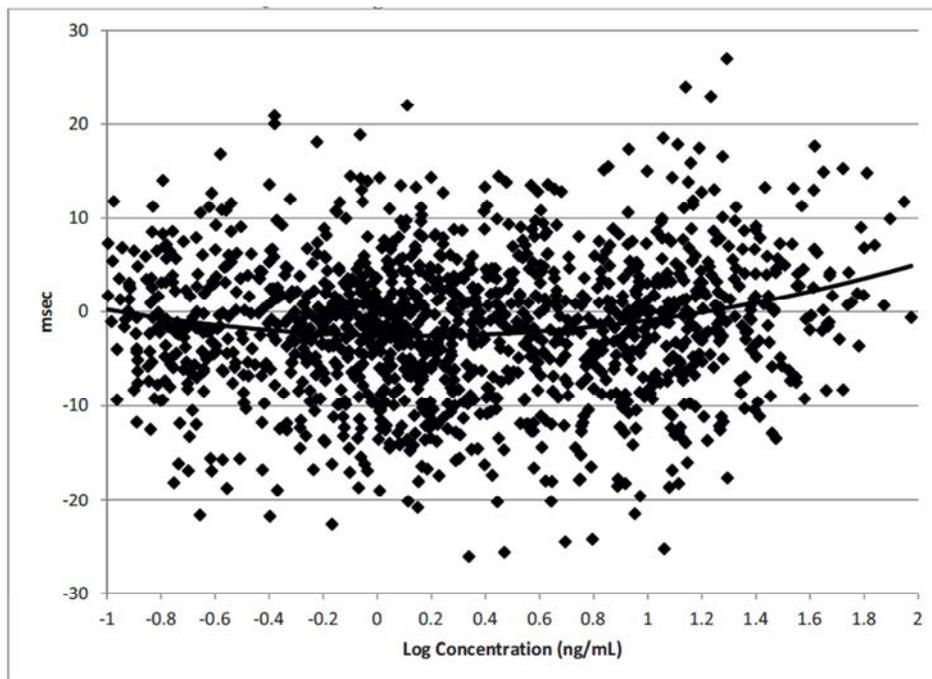
4.2.7.3.2 Exposure-Response Analysis

The sponsor has conducted a repeated measures analysis of placebo subtracted changes from baseline in QTcI vs. log₁₀ eluxadoline plasma concentrations. Sponsor investigated three models: 1) a linear model with intercept, 2) a model with intercept, slope, a quadratic term, 3) a model with intercept, slope, a quadratic, and a cubic term. The cube and quadratic terms were based on log₁₀ eluxadoline concentrations. Regression line from the final model (model 2) is shown in Figure 1.

The sponsor concludes the following :

Other than a trivial change, 0.2 msec, at the lowest concentration, there is an increase in placebo-subtracted change of QTcI, 4.9 msec, only at the highest concentration of JNJ-27018966, 94.1 ng/mL, and the upper confidence bound is 6.7 msec. Thus, the concentration analysis supports the negative findings of the other study endpoints.

Figure 1: Time-Matched Differences from Placebo in Changes from Predose Baseline in QTcI vs. Log JNJ-27018966 Concentration



Source: Sponsors QT report, Appendix 16.6, Figure 4.

Reviewer's Analysis: A plot of reviewer's analysis of $\Delta\Delta QTcI$ vs. drug concentrations is presented in Figure 5.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

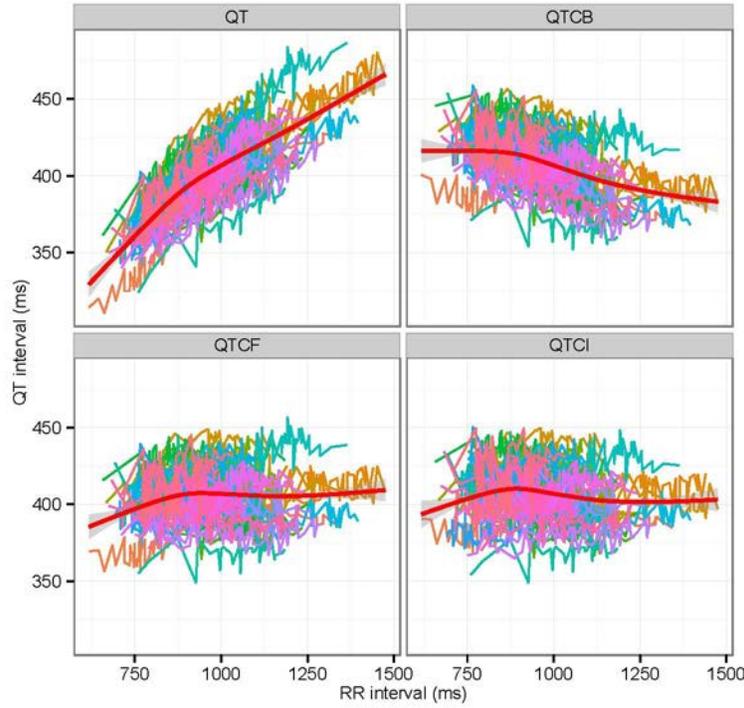
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 3, it appears that QTcI is better than QTcB and QTcF. To be consistent with the sponsor's analyses, this reviewer used QTcI for the primary statistical analysis.

Table 3: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method					
	QTcB		QTcF		QTcI	
	N	MSSS	N	MSSS	N	MSSS
JNJ-27018966 100 mg	60	0.0029	60	0.0021	60	0.0010
JNJ-27018966 1000 mg	60	0.0032	60	0.0033	60	0.0019
Moxifloxacin 400 mg	62	0.0022	62	0.0030	62	0.0013
Placebo	61	0.0033	61	0.0022	61	0.0014
All	64	0.0027	64	0.0018	64	0.0011

The relationship between different correction methods and RR is presented in Figure 2.

Figure 2: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the Δ QTcI effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 4. The largest upper bounds of the 2-sided 90% CI for the mean differences between JNJ-27018966 100 mg and placebo, and between JNJ-27018966 1000 mg and placebo are 2.8 ms and 5.6 ms, respectively.

Table 4: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI of JNJ-27018966 100 mg, JNJ-27018966 1000 mg, and Moxifloxacin 400 mg

Time (h)	Treatment Group													
	Placebo	JNJ-27018966 100 mg				JNJ-27018966 1000 mg				Moxifloxacin 400 mg				
	Δ QTcI	Δ QTcI		$\Delta\Delta$ QTcI		Δ QTcI		$\Delta\Delta$ QTcI		Δ QTcI		$\Delta\Delta$ QTcI		
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	90% CI
0.5	-1.0	60	0.2	1.3	(-0.3, 2.8)	60	0.1	1.1	(-0.4, 2.7)	61	2.6	3.6	(2.1, 5.2)	(1.5, 5.8)
1	-0.7	60	0.2	0.8	(-0.7, 2.4)	60	3.0	3.7	(2.1, 5.2)	62	11.2	11.9	(10.3, 13.4)	(9.7, 14.0)
2	-1.7	60	-1.4	0.2	(-1.8, 2.2)	60	2.0	3.6	(1.6, 5.6)	62	9.3	10.9	(8.9, 12.9)	(8.2, 13.7)
3	0.1	60	-0.3	-0.4	(-2.1, 1.3)	59	-0.6	-0.7	(-2.4, 1.1)	62	10.5	10.3	(8.6, 12.1)	(8.0, 12.7)
4	0.1	60	-1.7	-1.9	(-3.8, 0.1)	59	-1.6	-1.7	(-3.7, 0.2)	62	11.0	10.9	(8.9, 12.8)	(8.2, 13.5)
5	1.3	60	0.4	-0.9	(-2.9, 1.2)	59	-1.5	-2.8	(-4.8, -0.7)	62	11.8	10.5	(8.4, 12.5)	(7.7, 13.3)
6	2.0	60	0.3	-1.6	(-3.8, 0.5)	59	-0.8	-2.8	(-4.9, -0.7)	62	11.8	9.8	(7.7, 11.9)	(6.9, 12.7)
8	-1.3	60	-4.7	-3.4	(-5.8, -1.0)	60	-7.4	-6.1	(-8.5, -3.7)	62	6.6	7.9	(5.5, 10.3)	(4.7, 11.1)
12	1.4	60	-1.4	-2.7	(-4.9, -0.6)	59	-6.3	-7.6	(-9.8, -5.5)	62	8.9	7.5	(5.4, 9.6)	(4.6, 10.4)
15	3.0	60	1.3	-1.6	(-3.8, 0.5)	58	-1.4	-4.4	(-6.5, -2.2)	62	9.3	6.3	(4.2, 8.4)	(3.4, 9.2)
18	6.8	60	6.3	-0.5	(-2.4, 1.4)	59	4.2	-2.6	(-4.5, -0.6)	62	14.1	7.3	(5.4, 9.2)	(4.7, 10.0)
22.5	2.3	59	2.4	0.1	(-1.8, 2.0)	59	-0.1	-2.4	(-4.3, -0.5)	62	8.8	6.4	(4.6, 8.3)	(3.9, 9.0)

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

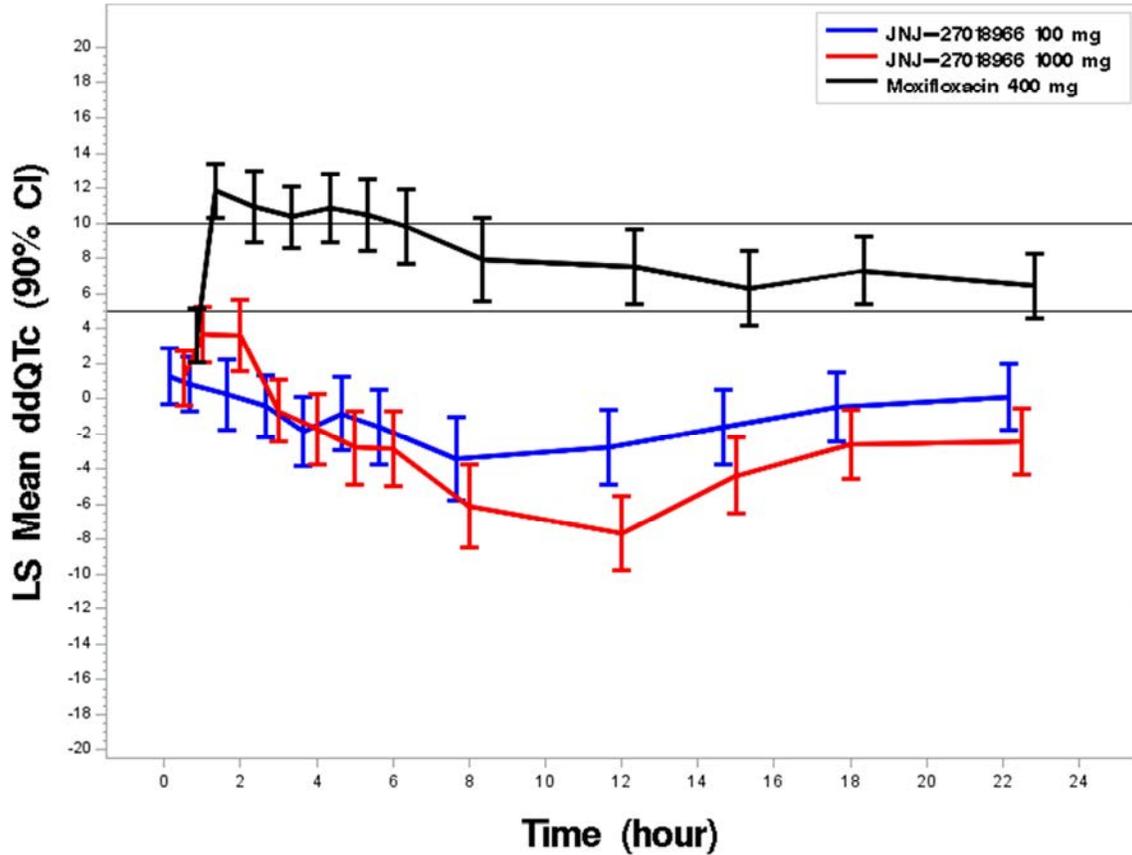
5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 4. The largest unadjusted 90% lower confidence interval is 10.3 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 9.7 ms, which indicates that an at least 5 ms QTcI effect due to moxifloxacin can be detected from the study.

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

Figure 3 displays the time profile of $\Delta\Delta$ QTcI for different treatment groups and moxifloxacin 400 mg.

Figure 3: Mean and 90% CI $\Delta\Delta\text{QTcI}$ Time Course for and Moxifloxacin 400 mg



5.2.1.4 Categorical Analysis

Table 5 lists the number of subjects as well as the number of observations whose QTcI values are ≤ 450 ms, between 450 ms and 480 ms, and between 480 ms and 500 ms. No subject's QTcI is above 480 ms.

Table 5: Categorical Analysis for QTcI

Treatment Group	Total N	Value ≤ 450 ms	450 ms < Value ≤ 480 ms
JNJ-27018966 100 mg	60	60 (100%)	0 (0.0%)
JNJ-27018966 1000 mg	60	59 (98.3%)	1 (1.7%)
Moxifloxacin 400 mg	62	56 (90.3%)	6 (9.7%)
Placebo	61	59 (96.7%)	2 (3.3%)

Table 6 lists the categorical analysis results for ΔQTcI . No subject's change from baseline is above 60 ms.

Table 6: Categorical Analysis for $\Delta QTcI$

Treatment Group	Total N	Value \leq 30 ms	30 ms<Value \leq 60 ms
JNJ-27018966 100 mg	60	60 (100%)	0 (0.0%)
JNJ-27018966 1000 mg	60	59 (98.3%)	1 (1.7%)
Moxifloxacin 400 mg	62	59 (95.2%)	3 (4.8%)
Placebo	60	60 (100%)	0 (0.0%)

5.2.2 HR Analysis

The statistical reviewer used mixed model to analyze the ΔHR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 7. The largest upper bounds of the 2-sided 90% CI for the mean differences between JNJ-27018966 100 mg and placebo, and between JNJ-27018966 1000 mg are 3.4 bpm and 7.8 bpm, respectively. Table 8 presents the categorical analysis of HR. No subject who experienced HR interval greater than 100 bpm is in JNJ-27018966 dosed-group.

Table 7: Analysis Results of ΔHR and $\Delta\Delta HR$ of JNJ-27018966 100 mg, JNJ-27018966 1000 mg, and Moxifloxacin 400 mg

Time (h)	Treatment Group												
	Placebo	JNJ-27018966 100 mg				JNJ-27018966 1000 mg				Moxifloxacin 400 mg			
	ΔHR	ΔHR		$\Delta\Delta HR$		ΔHR		$\Delta\Delta HR$		ΔHR		$\Delta\Delta HR$	
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	0.7	60	1.8	1.1	(-0.4, 2.6)	60	7.0	6.3	(4.8, 7.8)	61	1.5	0.8	(-0.7, 2.3)
1	0.3	60	1.4	1.0	(-0.5, 2.6)	60	5.7	5.4	(3.8, 6.9)	62	3.7	3.3	(1.8, 4.9)
2	-1.0	60	0.0	1.1	(-0.2, 2.3)	60	0.9	1.9	(0.6, 3.2)	62	0.5	1.5	(0.3, 2.8)
3	-0.5	60	-0.5	0.0	(-1.2, 1.3)	59	-1.3	-0.8	(-2.1, 0.4)	62	-0.3	0.2	(-1.0, 1.5)
4	-1.4	60	-1.7	-0.3	(-1.4, 0.9)	59	-1.9	-0.5	(-1.6, 0.7)	62	-0.4	1.0	(-0.1, 2.2)
5	-0.4	60	-1.3	-0.9	(-2.2, 0.3)	59	-1.1	-0.7	(-2.0, 0.6)	62	0.6	1.0	(-0.3, 2.3)
6	-0.4	60	-0.5	-0.1	(-1.6, 1.4)	59	-0.3	0.1	(-1.4, 1.6)	62	1.3	1.6	(0.2, 3.1)
8	6.6	60	6.7	0.1	(-1.5, 1.6)	60	4.9	-1.7	(-3.3, -0.2)	62	8.8	2.1	(0.6, 3.6)
12	9.1	60	10.6	1.5	(-0.3, 3.4)	59	9.2	0.0	(-1.8, 1.9)	62	11.0	1.9	(0.1, 3.7)
15	3.7	60	5.2	1.6	(-0.2, 3.3)	58	6.3	2.7	(0.9, 4.5)	62	5.4	1.8	(0.0, 3.5)
18	-0.2	60	0.7	0.9	(-0.5, 2.4)	59	1.5	1.8	(0.3, 3.2)	62	0.5	0.8	(-0.7, 2.2)
22.5	2.9	59	3.3	0.3	(-1.3, 1.9)	59	2.6	-0.3	(-1.9, 1.3)	62	2.4	-0.5	(-2.1, 1.1)

Table 8: Categorical Analysis for HR

Treatment Group	Total N	HR ≤ 100 bpm	HR >100 bpm
JNJ-27018966 100 mg	60	60 (100%)	0 (0.0%)
JNJ-27018966 1000 mg	60	60 (100%)	0 (0.0%)
Moxifloxacin 400 mg	62	62 (100%)	0 (0.0%)
Placebo	61	61 (100%)	0 (0.0%)

5.2.3 PR Analysis

The statistical reviewer used mixed model to analyze the Δ PR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 9. The largest upper bounds of the 2-sided 90% CI for the mean differences between JNJ-27018966 mg and placebo, and between JNJ-27018966 mg are 3.3 ms and 3.1 ms, respectively. Table 10 presents the categorical analysis of PR. Three subjects who experienced PR interval greater than 200 ms are in both JNJ-27018966 dosed-groups.

Table 9: Analysis Results of Δ PR and $\Delta\Delta$ PR of JNJ-27018966 100 mg, JNJ-27018966 1000 mg, and Moxifloxacin 400 mg

Time (h)	Treatment Group												
	Placebo	JNJ-27018966 100 mg				JNJ-27018966 1000 mg				Moxifloxacin 400 mg			
	Δ PR	Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR	
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	-0.3	60	0.1	0.4	(-1.3, 2.1)	60	-0.2	0.0	(-1.7, 1.7)	61	-0.2	0.0	(-1.7, 1.7)
1	0.9	60	0.1	-0.8	(-2.6, 1.0)	60	-2.5	-3.4	(-5.2, -1.7)	62	0.7	-0.3	(-2.0, 1.5)
2	-0.3	60	-1.0	-0.7	(-2.4, 0.9)	60	-3.2	-2.9	(-4.6, -1.3)	62	-1.0	-0.7	(-2.4, 0.9)
3	-0.9	60	-2.7	-1.8	(-3.8, 0.2)	59	-4.5	-3.6	(-5.6, -1.7)	62	-2.3	-1.4	(-3.4, 0.5)
4	-0.4	60	-1.4	-0.9	(-2.6, 0.8)	59	-4.0	-3.5	(-5.3, -1.8)	62	-2.8	-2.4	(-4.1, -0.7)
5	-1.4	60	-1.4	0.0	(-1.7, 1.7)	59	-3.7	-2.3	(-4.0, -0.6)	62	-2.5	-1.1	(-2.7, 0.6)
6	-1.7	60	-2.6	-0.9	(-2.9, 1.1)	59	-3.8	-2.1	(-4.1, -0.1)	62	-3.8	-2.1	(-4.1, -0.2)
8	-2.5	60	-2.2	0.3	(-1.9, 2.6)	60	-1.6	0.9	(-1.4, 3.1)	62	-3.1	-0.6	(-2.8, 1.6)
12	-2.8	60	-3.3	-0.4	(-2.7, 1.8)	59	-3.3	-0.5	(-2.7, 1.8)	62	-3.9	-1.1	(-3.3, 1.1)
15	-0.1	60	-1.3	-1.2	(-3.3, 0.9)	58	-1.1	-1.0	(-3.1, 1.2)	62	-0.3	-0.2	(-2.3, 1.9)
18	2.8	60	3.7	0.9	(-1.3, 3.2)	59	0.9	-1.9	(-4.1, 0.4)	62	3.0	0.3	(-2.0, 2.5)
22.5	0.2	59	1.7	1.5	(-0.4, 3.3)	59	0.6	0.4	(-1.5, 2.3)	62	0.7	0.5	(-1.4, 2.3)

Table 10: Categorical Analysis for PR

Treatment Group	Total N	PR ≤ 200 ms	PR >200 ms
JNJ-27018966 100 mg	60	58 (96.7%)	2 (3.3%)
JNJ-27018966 1000 mg	60	57 (95.0%)	3 (5.0%)
Moxifloxacin 400 mg	62	60 (96.8%)	2 (3.2%)
Placebo	61	57 (93.4%)	4 (6.6%)

5.2.4 QRS Analysis

The statistical reviewer used mixed model to analyze the Δ QRS effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 11. The largest upper bounds of the 2-sided 90% CI for the mean differences between JNJ-27018966 mg and placebo, and between JNJ-27018966 mg are 1.1 ms and 1.1 ms, respectively. Table 12 presents the categorical analysis of QRS. No subject who experienced QRS interval greater than 110 ms was on JNJ-27018966.

Table 11: Analysis Results of Δ QRS and $\Delta\Delta$ QRS of JNJ-27018966 100 mg, JNJ-27018966 1000 mg, and Moxifloxacin 400 mg

Time (h)	Treatment Group												
	Placebo	JNJ-27018966 100 mg				JNJ-27018966 1000 mg				Moxifloxacin 400 mg			
	Δ QRS	Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS	
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	0.4	60	-0.2	-0.6	(-1.2, 0.0)	60	-0.6	-0.9	(-1.5, -0.3)	61	0.0	-0.4	(-1.0, 0.3)
1	-0.1	60	-0.4	-0.3	(-1.0, 0.4)	60	-0.0	0.1	(-0.6, 0.8)	62	0.5	0.6	(-0.0, 1.3)
2	2.1	60	1.6	-0.5	(-1.3, 0.3)	60	2.4	0.3	(-0.4, 1.1)	62	2.6	0.5	(-0.2, 1.3)
3	0.1	60	-0.1	-0.3	(-0.9, 0.4)	59	-0.3	-0.4	(-1.0, 0.3)	62	0.2	0.1	(-0.5, 0.7)
4	2.2	60	1.9	-0.3	(-1.0, 0.4)	59	2.1	-0.1	(-0.8, 0.7)	62	2.4	0.3	(-0.5, 1.0)
5	-0.2	60	0.1	0.3	(-0.4, 1.1)	59	-0.0	0.2	(-0.6, 1.0)	62	-0.1	0.1	(-0.7, 0.9)
6	-0.3	60	-0.3	-0.0	(-0.8, 0.8)	59	-0.4	-0.1	(-0.8, 0.7)	62	0.1	0.4	(-0.3, 1.2)
8	2.9	60	2.4	-0.5	(-1.5, 0.4)	60	2.5	-0.4	(-1.4, 0.6)	62	2.3	-0.6	(-1.6, 0.3)
12	-0.7	60	-0.7	-0.0	(-0.9, 0.9)	59	-0.1	0.6	(-0.3, 1.5)	62	-0.1	0.6	(-0.3, 1.5)
15	-0.1	60	-0.1	0.0	(-0.9, 0.9)	58	0.4	0.5	(-0.4, 1.4)	62	0.5	0.6	(-0.3, 1.5)
18	0.8	60	0.0	-0.7	(-1.6, 0.1)	59	0.8	-0.0	(-0.9, 0.9)	62	0.8	-0.0	(-0.9, 0.9)
22.5	-0.1	59	-0.2	-0.1	(-1.0, 0.7)	59	0.2	0.2	(-0.7, 1.1)	62	0.6	0.7	(-0.2, 1.5)

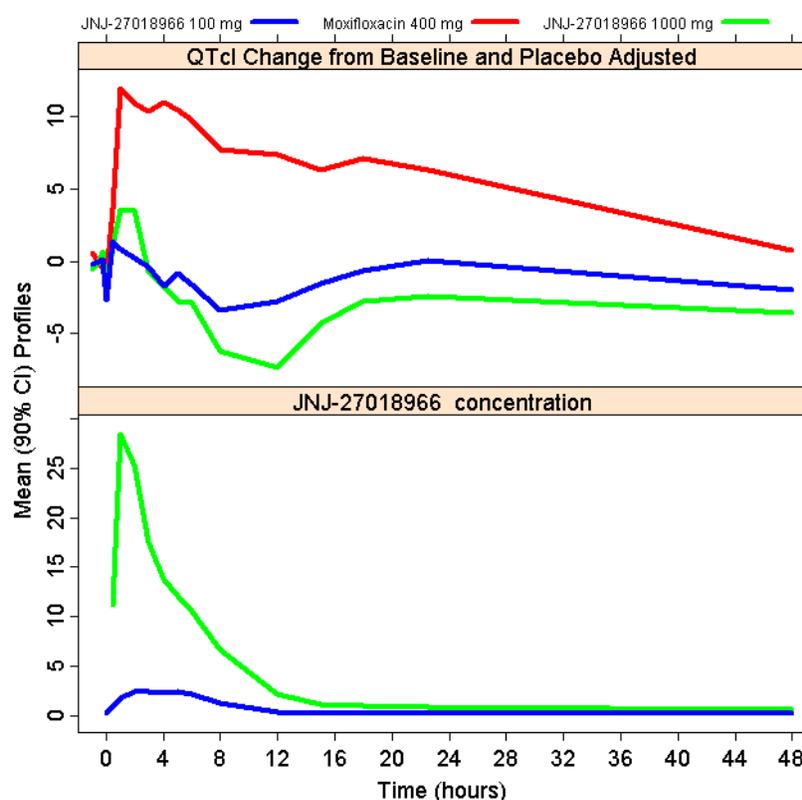
Table 12: Categorical Analysis for QRS

Treatment Group	Total N	QRS ≤ 110 ms	QRS > 110 ms
JNJ-27018966 100 mg	60	60 (100%)	0 (0.0%)
JNJ-27018966 1000 mg	60	60 (100%)	0 (0.0%)
Moxifloxacin 400 mg	62	62 (100%)	0 (0.0%)
Placebo	61	61 (100%)	0 (0.0%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

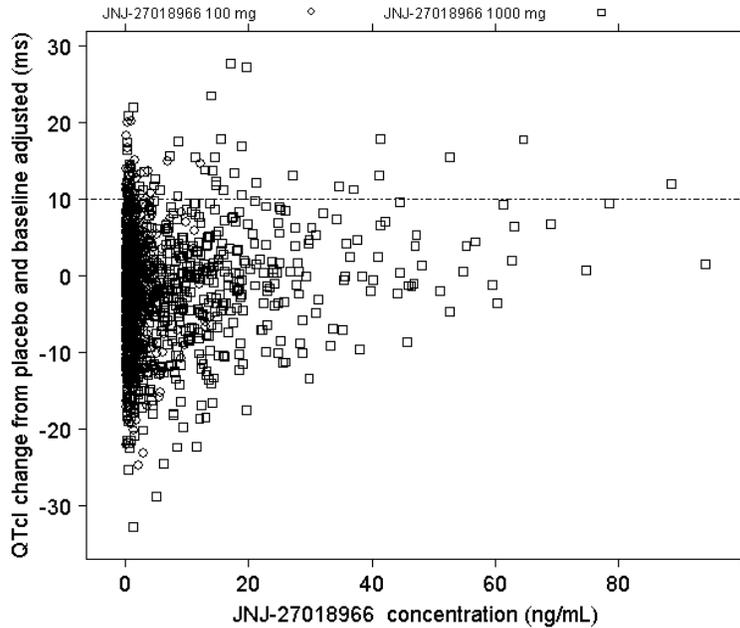
The mean drug concentration-time profile is illustrated in Figure 4.

Figure 4: Mean Eluxadoline Concentration-Time Profile (bottom) and $\Delta\Delta$ QTcI-Time Profile (top) for 100 mg (Blue) and 1000 mg Dose (Green Line)



The relationship between $\Delta\Delta$ QTcI and eluxadoline concentrations was analyzed with a linear mixed effects model that included intercept. The results are visualized in Figure 5. Although a statistically significant exposure-response relationship is seen, this is likely to be driven by the delayed QT shortening effect seen in Figure 4. The exposure response analysis cannot conclude that eluxadoline increases QT interval prolongation.

Figure 5: $\Delta\Delta$ QTcI vs. eluxadoline concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

The only cardiovascular adverse event was palpitations in one subject on the high dose.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

There was no clinically relevant effect on PR or QRS.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

The table below was submitted to the agency in 2012 when the QT protocol was originally reviewed. The protocol has been changed based on agencies recommendations (please see QT protocol review for IND 79214 by Dr. Qianyu Dang, Monica L Fiszman, Kevin M Krudys, and Norman L Stockbridge dated: October, 15 2012). The changes in the protocol may not be reflected in the table below.

Therapeutic dose	Maximum proposed clinical dosing regimen is 100mg orally BID
Maximum tolerated dose	<p>The NOAEL from the 9-month primate study (Study TOX8661¹) was considered to be 200 mg/kg/day, the highest dose level administered and the AUC₀₋₂₄ at this dose represents approximately a 15-fold margin relative to the estimated exposure following the 100 mg BID human dose. The NOAEL from the 6-month rodent study (Study 1808-007²) was 2000 mg/kg/day, the highest dose tested in this study.</p> <p>The maximum tolerated human single dose of JNJ-27018966 was 1500 mg in men and 1000 mg in women, though the 1000 mg dose was not tolerated well by 2 of 6 (33%) women due to AEs of moderate intermittent orthostatic hypotension (Study 27018966EDI1001³). A dosing regimen of 500mg BID for 7 days was well-tolerated in Part 2 of Study 270189661001³.</p>
Principal adverse events	<p>In the multiple-ascending dose phase in healthy volunteers (Study 27018966EDI1001³), the most frequently reported AEs upon 7 days of once- or twice-daily dosing were headache, abdominal pain, and pollakiuria in men and myalgia, dizziness, and abdominal pain in women.</p> <p>The most commonly reported adverse events experienced by IBS-d patients in the 3-month Phase 2 study (Study 27018966IBS2001⁴) were gastrointestinal disorders, which were reported most frequently in the 200-mg treatment group (27.9%), followed by the 25-mg (22.4%) and 100-mg treatment groups (21.2%) as compared with placebo (15.7%). The individual gastrointestinal adverse events most commonly reported were nausea, abdominal pain, vomiting, and constipation, with the incidence rate of each being higher among the 25-mg, 100-mg, and 200-mg treatment groups compared with placebo. The incidence of abdominal pain was approximately 4 times higher in the 200-mg group (7.6%) compared with placebo (1.9%). The incidence rates of abdominal pain among the other JNJ-27018966 treatment groups (range of 2.4% to 3.5%) were comparable to placebo. The incidence of nausea was also highest for the 200-mg treatment group (10.5%) but was comparable between the other JNJ-27018966 treatment groups (range of 5.5% to 6.5%) and placebo (4.4%). Vomiting was more common among the 25 mg (4.1%), 100-mg (4.2%), and 200-mg (7.0%) treatment groups compared with placebo (0.6%). Constipation was reported as an AE by 3.5% of patients overall in the study. Overall, no adverse events of constipation were rated severe in intensity or led to study drug discontinuation in the JNJ-27018966 treatment groups lower than 200 mg. While the incidence rate of reported constipation was highest in the 100-mg treatment group, the majority of events were mild and required no action.</p> <p>Other commonly reported adverse events were infections and infestations (reported by 17.1% of patients overall) and nervous system disorders (reported by 9.5% of patients overall). No dose-related trends were seen among adverse events related to infections or infestations. Nervous system disorders were highest among patients in the 200-mg treatment group (14.0%) followed by the 25-mg (10.0%), 100-mg (7.9%), 5-mg (7.6%), and placebo (6.9%) groups. The individual nervous system adverse events most commonly reported were headache and dizziness. While the incidence rate of headache was comparable across all treatment groups, the incidence of dizziness was approximately 2-fold higher in the 200-mg treatment group (6.4%) compared with either placebo (2.5%) or the other JNJ-27018966 treatment groups (range of 2.4% to 3.8%). Somnolence was also more commonly reported in the 200-mg treatment group (2.3%) compared with either placebo (not reported) or the other JNJ-27018966 treatment groups (range of 0.6% to 1.2%).</p>

Maximum dose tested	Single Dose	2000mg (men) and 1000mg (women) (Study 27018966EDI1001 ⁴)																	
	Multiple Dose	500mg BID for 7 days (men; Study 27018966EDI1001 ³) and 200mg BID for 3 months (men and women; Study 27018966IBS2001 ⁴)																	
Exposures achieved at maximum tested dose	Single Dose	Mean (SD, %CV) C_{max} (ng/mL), and AUC_{last} (ng•h/mL) from Study 27018966EDI1001 ³ : <ul style="list-style-type: none"> • 2000 mg (Men): 28.9 (SD12.2;%CV 42.1) and 139 (SD34.1;%CV 24.5), respectively • 1000 mg (Women): 20.3 (SD 9.39; %CV 46.3) and 81.5 (SD 22.5; %CV 27.6), respectively 																	
	Multiple Dose	Mean (SD %CV) C_{max} (ng/mL), and AUC_{last} (ng•h/mL) <ul style="list-style-type: none"> • 500 mg BID (Men): 3.84 (SD 1.22; %CV 31.8) and 34.9 (SD 11.7; %CV 33.5) on Day 7, respectively. • 150 mg BID (Women): 4.67 (SD 4.47; %CV 95.8) and 45.9 (SD 35.4; %CV 77.2) on Day 7, respectively. <p>Serial sampling for pharmacokinetic profiling not conducted in Phase 2 study with 3 months treatment and top dose of 200mg BID (Study 27018966EDI2001)</p>																	
Range of linear PK	<p>An analysis of dose proportionality using the power model approach shows that both AUC_{24} and C_{max} are marginally linear over a range of 30 mg to 2000 mg as shown in the table below:</p> <p>Table 1: Analysis of Dose Proportionality</p> <table border="1"> <thead> <tr> <th>Analyte</th> <th>Parameter</th> <th>Estimated Slope for ln(dose)</th> <th>Lower 90% Confidence Interval</th> <th>Upper 90% Confidence Interval</th> <th>P-value (b=1)</th> </tr> </thead> <tbody> <tr> <td rowspan="2">INJ-27018966</td> <td>LNAUC₂₄</td> <td>0.9167</td> <td>0.8324</td> <td>1.0010</td> <td>0.1040</td> </tr> <tr> <td>LNCMAX</td> <td>0.9299</td> <td>0.8397</td> <td>1.0201</td> <td>0.1986</td> </tr> </tbody> </table> <p>The upper bounds of the 90% confidence intervals contain unity by the smallest of margins, thus a visual representation (see figures 1 and 2) of dose normalized AUC and C_{max} are presented to more fully depict linearity. As seen in both figures linearity is clearly suspect over portions of the dose ranges since less than proportional increases in AUC_{24} and C_{max} are observable over the range of doses studied.</p> <p>AUC_{24} data in Figure 1 only includes the single dose arm of Study 27018966EDI1001³. The less than proportional increase that can be observed in C_{max} from Figure 2 is also observable in AUC_{last} results from Day 7 of the multiple dose portion of Study 27018966EDI1001³. From Table 2 the AUC_{last} mean (%CV) values are 37.5 (42.3%), 47.4 (32%) and 34.9 (33.5%) for 230 mg, 300 mg and 500 mg, respectively. Computing the dose normalized ratios gives values of 0.16, 0.16 and 0.07, showing less than proportional increase in this range. Of note from 500 mg to 2000 mg the dose normalized range appears to return to proportionality as does C_{max} in Figure 2.</p>		Analyte	Parameter	Estimated Slope for ln(dose)	Lower 90% Confidence Interval	Upper 90% Confidence Interval	P-value (b=1)	INJ-27018966	LNAUC ₂₄	0.9167	0.8324	1.0010	0.1040	LNCMAX	0.9299	0.8397	1.0201	0.1986
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Figure 1: Dose Normalized AUC₂₄ Versus Dose for JNJ-27018966 Following Single Doses of 30, 100, 300, 1000, 1500 and 2000 mg from Part 1 of Study 27018966EDI1001³

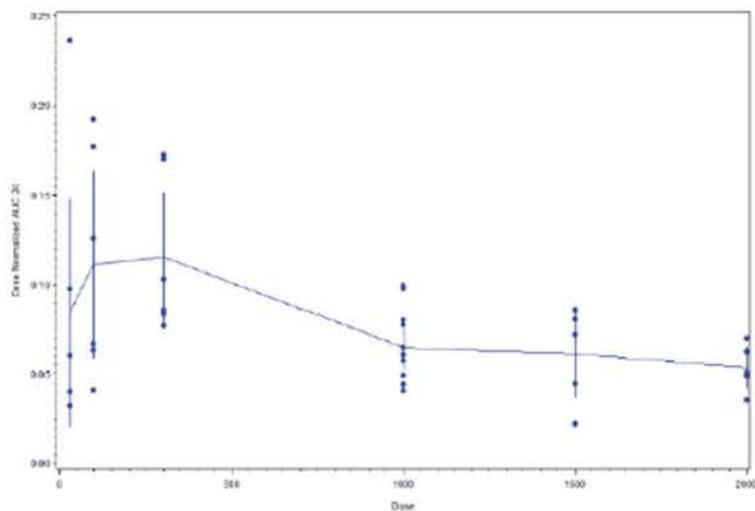
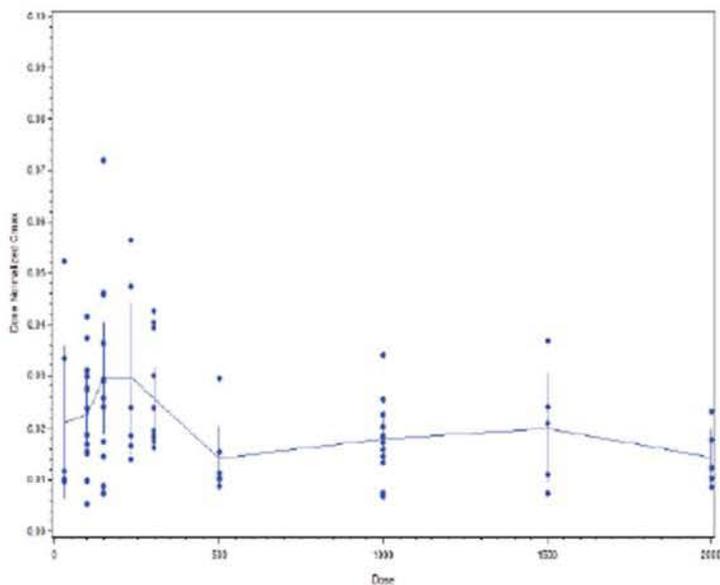


Figure 2: Dose Normalized C_{MAX} Versus Dose for JNJ-27018966 Following Single Doses of 30, 100, 150, 230, 300, 500, 1000, 1500, and 2000mg from Part 1 and Part 2, Day 1 of Study 27018966EDI1001⁵



Accumulation at steady state	<p>Little to no accumulation seen in humans and is summarized in the Table below:</p> <p>Table 2: Summary of Plasma Pharmacokinetic Parameters for JNJ-27018966 Following Multiple Dose Administration to Healthy Male (Part 2a) and Female (Part 2b) Adult Subjects (Study 27018966EDI1001³)</p> <table border="1"> <thead> <tr> <th rowspan="2">Dose (mg)/ Frequency</th> <th rowspan="2">Statistic</th> <th colspan="2">Day 1</th> <th colspan="3">Day 7</th> <th colspan="2">Accumulation Ratio Day 7/Day 1</th> </tr> <tr> <th>C_{max} (ng/mL)</th> <th>AUC_{12h} (ng•h/mL)</th> <th>C_{max} (ng/mL)</th> <th>AUC_{12h} (ng•h/mL)</th> <th>AUC_{last} (ng•h/mL)</th> <th>C_{max}</th> <th>AUC_{12h}</th> </tr> </thead> <tbody> <tr> <td colspan="9">Part 2a: Males</td> </tr> <tr> <td rowspan="2">100 mg QD^a</td> <td>Mean</td> <td>2.46</td> <td>11.4</td> <td>1.35</td> <td>7.76</td> <td>9.13</td> <td>0.606</td> <td>0.702</td> </tr> <tr> <td>(SD)</td> <td>(1.16)</td> <td>(4.75)</td> <td>(0.574)</td> <td>(3.09)</td> <td>(4.05)</td> <td>(0.188)</td> <td>(0.189)</td> </tr> <tr> <td></td> <td>CV</td> <td>47.0</td> <td>41.7</td> <td>42.5</td> <td>39.8</td> <td>44.4</td> <td>31.0</td> <td>26.9</td> </tr> <tr> <td rowspan="2">150 mg BID^b</td> <td>Mean</td> <td>4.06</td> <td>14.7</td> <td>1.79</td> <td>10.8</td> <td>23.1^c</td> <td>0.601</td> <td>0.815</td> </tr> <tr> <td>(SD)</td> <td>(2.12)</td> <td>(5.92)</td> <td>(0.518)</td> <td>(4.07)</td> <td>(8.90)</td> <td>(0.416)</td> <td>(0.401)</td> </tr> <tr> <td></td> <td>CV</td> <td>52.2</td> <td>40.3</td> <td>29.0</td> <td>37.8</td> <td>38.4</td> <td>69.3</td> <td>49.2</td> </tr> <tr> <td rowspan="2">230 mg BID^b</td> <td>Mean</td> <td>6.80</td> <td>24.3</td> <td>3.28</td> <td>21.4</td> <td>37.5</td> <td>0.571</td> <td>0.989</td> </tr> <tr> <td>(SD)</td> <td>(4.12)</td> <td>(11.7)</td> <td>(0.838)</td> <td>(6.53)</td> <td>(15.8)</td> <td>(0.194)</td> <td>(0.387)</td> </tr> <tr> <td></td> <td>CV</td> <td>60.6</td> <td>48.1</td> <td>25.5</td> <td>30.5</td> <td>42.3</td> <td>33.9</td> <td>39.1</td> </tr> <tr> <td rowspan="2">300 mg BID^a</td> <td>Mean</td> <td>7.83</td> <td>24.8</td> <td>4.56</td> <td>25.9</td> <td>47.4</td> <td>0.616</td> <td>1.12</td> </tr> <tr> <td>(SD)</td> <td>(2.78)</td> <td>(10.6)</td> <td>(1.73)</td> <td>(7.00)</td> <td>(15.2)</td> <td>(0.253)</td> <td>(0.349)</td> </tr> <tr> <td></td> <td>CV</td> <td>35.6</td> <td>42.7</td> <td>37.9</td> <td>27.0</td> <td>32.0</td> <td>41.1</td> <td>31.0</td> </tr> <tr> <td rowspan="2">500 mg BID^a</td> <td>Mean</td> <td>7.12</td> <td>23.0</td> <td>3.84</td> <td>21.3</td> <td>34.9</td> <td>0.605</td> <td>0.954</td> </tr> <tr> <td>(SD)</td> <td>(3.89)</td> <td>(7.43)</td> <td>(1.22)</td> <td>(5.90)</td> <td>(11.7)</td> <td>(0.244)</td> <td>(0.227)</td> </tr> <tr> <td></td> <td>CV</td> <td>54.6</td> <td>32.3</td> <td>31.8</td> <td>27.7</td> <td>33.5</td> <td>40.4</td> <td>23.8</td> </tr> <tr> <td colspan="9">Part 2b: Females</td> </tr> <tr> <td rowspan="2">150 mg BID</td> <td>Mean</td> <td>4.85</td> <td>16.5</td> <td>4.67</td> <td>24.9</td> <td>45.9</td> <td>1.01</td> <td>1.51</td> </tr> <tr> <td>(SD)</td> <td>(3.45)</td> <td>(11.7)</td> <td>(4.47)</td> <td>(19.5)</td> <td>(35.4)</td> <td>(0.429)</td> <td>(0.558)</td> </tr> <tr> <td></td> <td>CV</td> <td>71.1</td> <td>70.6</td> <td>95.8</td> <td>78.1</td> <td>77.2</td> <td>42.5</td> <td>37.1</td> </tr> </tbody> </table> <p>Abbreviations: BID = twice daily; CV = coefficient of variation; QD = once daily. ^a Single last dose administered in the morning of Day 7. ^b Two doses administered on Day 7 (one in the morning and the other in the evening) ^c This AUC_{last} includes a second dose in the evening of Day 7.</p>									Dose (mg)/ Frequency	Statistic	Day 1		Day 7			Accumulation Ratio Day 7/Day 1		C _{max} (ng/mL)	AUC _{12h} (ng•h/mL)	C _{max} (ng/mL)	AUC _{12h} (ng•h/mL)	AUC _{last} (ng•h/mL)	C _{max}	AUC _{12h}	Part 2a: Males									100 mg QD ^a	Mean	2.46	11.4	1.35	7.76	9.13	0.606	0.702	(SD)	(1.16)	(4.75)	(0.574)	(3.09)	(4.05)	(0.188)	(0.189)		CV	47.0	41.7	42.5	39.8	44.4	31.0	26.9	150 mg BID ^b	Mean	4.06	14.7	1.79	10.8	23.1 ^c	0.601	0.815	(SD)	(2.12)	(5.92)	(0.518)	(4.07)	(8.90)	(0.416)	(0.401)		CV	52.2	40.3	29.0	37.8	38.4	69.3	49.2	230 mg BID ^b	Mean	6.80	24.3	3.28	21.4	37.5	0.571	0.989	(SD)	(4.12)	(11.7)	(0.838)	(6.53)	(15.8)	(0.194)	(0.387)		CV	60.6	48.1	25.5	30.5	42.3	33.9	39.1	300 mg BID ^a	Mean	7.83	24.8	4.56	25.9	47.4	0.616	1.12	(SD)	(2.78)	(10.6)	(1.73)	(7.00)	(15.2)	(0.253)	(0.349)		CV	35.6	42.7	37.9	27.0	32.0	41.1	31.0	500 mg BID ^a	Mean	7.12	23.0	3.84	21.3	34.9	0.605	0.954	(SD)	(3.89)	(7.43)	(1.22)	(5.90)	(11.7)	(0.244)	(0.227)		CV	54.6	32.3	31.8	27.7	33.5	40.4	23.8	Part 2b: Females									150 mg BID	Mean	4.85	16.5	4.67	24.9	45.9	1.01	1.51	(SD)	(3.45)	(11.7)	(4.47)	(19.5)	(35.4)	(0.429)	(0.558)		CV	71.1	70.6	95.8	78.1	77.2	42.5	37.1
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	(SD)	(3.45)	(11.7)	(4.47)	(19.5)	(35.4)	(0.429)	(0.558)																																																																																																																																																																																															
	CV	71.1	70.6	95.8	78.1	77.2	42.5	37.1																																																																																																																																																																																															
Metabolites	<p>The in vivo metabolism of JNJ-27018966 was investigated in human plasma and urine following a 1000 mg oral dose in healthy male volunteers (Study FK6533⁷). Unchanged drug was the only drug-related component identified in the systemic circulation and accounted for 100% of total drug-derived materials in pooled 0.25- to 8 hour plasma samples. JNJ-27018966 was undetectable in pooled 12- to 48 hour plasma samples. In urine, unchanged drug accounted for 94% and 78% of total drug-derived materials in pooled 0- to 8- and 8- to 24 hour samples, respectively. M11 (acyl glucuronide; likely inactive) was the only metabolite detected in urine and accounted for 6% and 22% of total drug (<2% of total dose) derived materials in pooled 0- to 8- and 8- to 24 hour samples, respectively.</p>																																																																																																																																																																																																						
Absorption	Absolute/Relative Bioavailability	<p>Absolute bioavailability was low ($\leq 1.7\%$) in mice (Studies FK6179⁶ and DD07397⁷), rats (Study FK6180⁸), and cynomolgus monkeys (Study FK5721⁹). Consistent with the preclinical studies a human mass balance study (Study 27018966EDI1003¹⁰) showed that total radioactivity values from whole blood and plasma in all samples were below the limit of quantitation; approximately 82% was recovered in feces over 336 hours and 0.12% in urine after 192 hours.</p>																																																																																																																																																																																																					
	T _{max} (hours)	3.0 (1.50 – 4.00) , 150 mg BID dose																																																																																																																																																																																																					

Distribution	Vd/F or Vd	The terminal elimination rate constant was not estimable using noncompartmental methods. In a population PK sparse sampling approach the estimated population Vd/F was 27100 L. In general, there was a good agreement between AUCs calculated from the final population PK model and AUCs calculated by non-compartmental methods.
	% bound	JNJ-27018966 is 81.0% protein bound in human pooled plasma samples (Study FK6315 ¹⁴)
Elimination	Route	JNJ-27018966 remains located in the gut (rat distribution Study 5756 ¹²), very low levels of drug are found in portal vein (cannulation study in rat, Study DD07389 ¹⁵), 2% of radioactivity is found in bile duct (rat biliary excretion study FK6432 ¹⁴) and in vivo animal studies show >95% JNJ-27018966 is eliminated in the feces unchanged (FK5858 ¹⁵). Consistent with the preclinical studies a human mass balance study (Study 27018966EDI1003 ¹⁰) showed that approximately 82% was recovered in feces over 336 hours and 0.12% in urine after 192 hours.
	Terminal t _{1/2}	The terminal elimination rate constant was not estimable using noncompartmental methods. In the human mass balance study (Study 27018966EDI1003 ¹⁰) the apparent distribution half-life (t _{1/2} , alpha) mean (%CV) was estimated as 1.67 hours (50.7%).
	CL/F or CL	The terminal elimination rate constant was not estimable using noncompartmental methods. In a population PK sparse sampling approach the estimated population CL/F was 9030 L. In general, there was a good agreement between AUCs calculated from the final population PK model and AUCs calculated by non-compartmental methods.
Intrinsic factors	Age	Unknown
	Sex	Unknown
	Race	Unknown
	Hepatic and Renal Impairment	Unknown; studies not done (hepatic impairment study in progress)
Extrinsic factors	Drug Interactions	Studies are planned but have not yet been conducted. However, less than 3% of JNJ-27018966 is metabolized by human hepatocytes in vitro (FK5826 ¹⁶). JNJ-27018966 does not inhibit nor induce any of the major CYP450s (Studies FK5731 ¹⁷ and FK5873 ¹⁸) so there is little chance for drug-drug interactions via cytochrome P450s. Additionally, transporter studies have been conducted and JNJ-27018966 does not appear to be a substrate (Study OPT-2012-064 ¹⁹) or inhibitor (Study OPT-2012-063 ²⁰) for human P-gp, BCRP, BSEP, OAT1, OAT3, OCT1, OCT2, OATP1B1 and OATP1B3-mediated transport, with the exception that JNJ-27018966 is a substrate but not an inhibitor of MRP2.
	Food Effects	The absorption of JNJ-27018966 (tablet formulation) was rapid under fasting conditions, with a median T _{max} value of 2 hours. However, when JNJ-27018966 was administered to healthy male volunteers within 30 minutes of a high fat meal, there was a delay in reaching peak plasma concentrations. The median T _{max} value in the presence of a high fat meal

was 4 hours. The presence of food probably delays gastric emptying, thereby delaying absorption. Further, both AUC_{last} and C_{max} were reduced in the presence of food as shown in the summary table below. The mean ratios for fed versus fasting were 74.6 and 33.2 and both 90% confidence intervals fell outside the 80% to 125% range, displayed in the geometric mean table.

Table 3: Summary of Plasma PK Parameters Following Single Dose of 500 mg JNJ-27018966 to Healthy Normal Volunteers under Fed and Fasted Conditions

Dose (mg)/ Condition	Statistic	T_{max}^a (h)	C_{max} (ng/mL)	AUC_{last} (ng•h/mL)	T_{last}^a (h)
500 fasted	Mean	2.00	12.5	72.6 (26.5)	58.0
	(SD)	(1.00-6.00)	(8.27)		(26.0-58.0)
	CV	NA	66.0	36.5	NA
500 fed	Mean	4.00	3.80	51.1 (21.3)	58.0
	(SD)	(1.00-12.00)	(2.01)		(26.0-58.0)
	CV	NA	53.0	41.7	NA

Abbreviations: NA = not applicable.

Note: Descriptive statistics were based on 17 subjects that completed both treatment periods.

^a Median (range)

Source: Study 27018966EDI1002²¹

Table 4: Geometric Mean Ratios and 90% Confidence Intervals for JNJ-27018966 Fed versus Fasted Conditions

Treatment Comparison	Parameter	Geometric LS Mean	Mean Ratio Fed/Fasted	Lower Limit	Upper Limit
500 mg Fed versus 500 mg Fasted	C_{max} (ng/mL)	9.90	33.2	26.3	41.9
	AUC_{last} (ng•hr/mL)	64.0	74.6	60.4	92.0

Expected high clinical Exposure scenario

The table below summarizes the plasma pharmacokinetic parameters for JNJ-27018966 after single-dose administration to healthy male and female adult subjects (Study 27018966EDI1001 [Part 1]³). Repeat dosing demonstrated little to no accumulation (see Accumulation at Steady State Section). The suprathreshold dose proposed in the QTc study is 5 times the intended marketed dose and is the highest dosing regimen tested in a 7 day safety and tolerability study (Study 27018966EDI1001 [Part 2]³ in which the highest mean C_{max} and AUC_{last} were 7.12 ng/mL (SD 3.89; CV 54.6) and 34.9 (ng•h/mL) (SD 11.7; CV 33.5), respectively. Given JNJ-27018966 has no major metabolites, does not induce or inhibit any of the major CYP450s, is not metabolized in vivo to any extent, and individual

data indicated that approximately 90% or greater of the administered dose was recovered in 4 of 8 subjects¹, there is little chance for drug-drug interactions that will increase systemic levels of JNJ-27018966. Thus, a 500 mg BID dose should be more than adequate for measuring a suprathreshold effect in QTc prolongation if any such effect exists.

Table 5: Summary of Plasma Pharmacokinetic Parameters for JNJ-27018966 Following Single Dose Administration to Healthy Male (Part 1a) and Female (Part 1b) Adult Subjects (Study 27018966EDI1001)³

Gender	Dose (mg)	Statistic	C _{max} (ng/mL)	T _{max} (h) ²	T _{last} (h) ²	AUC _{0-∞} (ng•h/mL)
Part 1a						
Male	30	Mean	0.634	1.50 (1.00-	6.00 (4.00-	2.22
		(SD)	(0.536)	2.00)	12.0)	(2.02)
		CV	84.5	-	-	91.1
Male	100	Mean	2.08	2.00 (0.25-	18.0 (8.00-	10.4
		(SD)	(1.12)	6.00)	24.0)	(6.24)
		CV	53.7	-	-	59.8
Male	300	Mean	7.71	1.50 (1.00-	48.0 (24.0-	38.0
		(SD)	(3.31)	1.50)	48.0)	(13.0)
		CV	42.9	-	-	34.2
Male	1000	Mean	15.6	1.25 (1.00-	48.0 (48.0-	70.3
		(SD)	(4.75)	1.50)	48.0)	(14.7)
		CV	30.5	-	-	20.9
Male	1500	Mean	30.1	1.00 (0.58-	48.0 (48.0-	106 (49.5)
		(SD)	(17.5)	1.50)	48.0)	46.6
		CV	58.2	-	-	
Male	2000	Mean	28.9	1.50 (1.00-	48.0 (48.0-	139 (34.1)
		(SD)	(12.2)	2.00)	48.0)	24.5
		CV	42.1	-	-	
Part 1b						
Female	1000	Mean	20.3	1.25 (1.00-	48.0 (24.0-	81.5 (22.5)
		(SD)	(9.39)	2.00)	48.0)	27.6
		CV	46.3	-	-	

Abbreviations: CV = coefficient of variation.

²Median (Range)

Source: Study 27018966EDI1001³

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

/s/

MOH JEE NG
11/19/2014

QIANYU DANG
11/19/2014

DINKO REKIC
11/19/2014

JIANG LIU
11/19/2014

MICHAEL Y LI
11/19/2014

NORMAN L STOCKBRIDGE
11/19/2014

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 # 206940 BLA# N/A	NDA Supplement #:S- N/A BLA Supplement # N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: (b) (4) Established/Proper Name: eluxadoline Dosage Form: Tablet Strengths: 75 mg and 100 mg		
Applicant: Furiex Pharmaceuticals Agent for Applicant (if applicable): N/A		
Date of Application: Thursday, June 26, 2014 Date of Receipt: Friday, June 27, 2014 Date clock started after UN: N/A		
PDUFA Goal Date: Friday, February 27, 2015		Action Goal Date (if different): (Same)
Filing Date: Tuesday, August 26, 2014		Date of Filing Meeting: Thursday, August 14, 2014
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Treatment of diarrhea and abdominal pain in men and women with diarrhea predominant irritable bowel syndrome (IBS-d).		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</i>		
Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>		
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <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 (if OTC product): N/A				
List referenced IND Number(s): IND 079214				
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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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 New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.			N/A	
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>	N/A	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<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><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></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><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></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>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>	
<p><i>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</i></p>				
<p>If yes, please list below:</p>				
<p>Application No.</p>	<p>Drug Name</p>	<p>Exclusivity Code</p>	<p>Exclusivity Expiration</p>	
<p></p>	<p></p>	<p></p>	<p></p>	
<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 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input type="checkbox"/></p>	<p><input checked="" type="checkbox"/></p>		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 5 years <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
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)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content	
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?	

Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
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, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Signed by Gail McIntyre (different signatory than other forms).

1

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

Financial Disclosure	YES	NO	NA	Comment
<p>Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <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)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment

<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> Date of consult sent to Controlled Substance Staff :	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<u>BPCA (NDAs/NDA efficacy supplements only):</u> 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>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment

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

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

Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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 checked="" 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 applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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 applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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?	<input type="checkbox"/>	<input type="checkbox"/>		

4

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

<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent: DGCPC/OSI 7/11/2014; CSS 8/7/2014; PMHS 8/7/2014, Environmental Assessment 8/8/2014, ; OTS/OB/DBVI Human Abuse Potential 8/8/2014; Methods Validation 8/15/2014; QT-IRT 9/10/2014; PT Labeling pending</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): December 9, 2011	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): February 25, 2014, April 22, 2014	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): March 15, 2011	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 14, 2014

BLA/NDA/Supp #: 206940

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: Eluxadoline

DOSAGE FORM/STRENGTH: Tablet/100 mg

APPLICANT: Furiex Pharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Indicated for the treatment of diarrhea and abdominal pain in men and women with diarrhea predominant irritable bowel syndrome (IBS-d).

BACKGROUND: NDA 206940; (b) (4) (eluxadoline) is a new molecular entity submitted on June 26, 2014 and received on June 27, 2014. Regulatory history includes IND 079214 submitted on November 21, 2007. Fast track designation was granted on January 19, 2011. Currently the PDUFA goal date is February, 27, 2015.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jennifer Sarchet	Y
	CPMS/TL:	Brian Strongin	N
Cross-Discipline Team Leader (CDTL)	Ruyi He		Y
Clinical	Reviewer:	Laurie Muldowney	Y
	TL:	Ruyi He	Y
Social Scientist Review (for OTC products)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
OTC Labeling Review (for OTC products)	Reviewer:	N/A	N/A
	TL:	N/A	N/A

Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Clinical Pharmacology	Reviewer:	Dilara Jappar	Y
	TL:	Sue Chih Lee	Y
Biostatistics	Reviewer:	Yeh-Fong Chen	Y
	TL:	Freda Cooner	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Tamal Chakraborti	Y
	TL:	Sushanta Chakder	Y
Statistics (carcinogenicity)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Product Quality (CMC)	Reviewer:	Yichun Sun	N
	TL:	Marie Kowblansky	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
CMC Labeling Review	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Facility Review/Inspection	Reviewer:	Christina Capacc-Daniel	N
	TL:	Mahesh Ramandadham	N
OSE/DMEPA (proprietary name)	Reviewer:	Kendra Worthy	Y
	TL:	Sherly Abraham	N
OSE/DRISK (REMS)	Reviewer:	Nyedra Booker	N
	TL:	Jamie Wilkins	N

OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	N/A
	TL:	N/A	N/A
Bioresearch Monitoring (OSI)	Reviewer:	Kasssa Ayalew Susan Leibenhaut	Y
	TL:	Susan Thompson	N
Controlled Substance Staff (CSS)	Reviewer:	Chad Reissig	Y
	TL:	Silvia Calderon	N
PMHS – Maternal Health	Reviewer:	Ethan Hausman	N
	TL:	Hari Sachs	N
Other attendees		Julie Beitz, MD Donna Griebel, MD Andrew Mulberg, MD Maria Walsh CDR Stacy Barley, RN, M.S.N., M.S.H.A., Regulatory Project Manager	Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO N/A
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain: N/A</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments: N/A</p>	<input type="checkbox"/> Not Applicable

<p>CLINICAL</p> <p>Comments: 1. We note that complete safety data is included for all patients from Study IBS-3001 only up to Week 26 and that complete safety data (through 52 weeks of dosing and 2 weeks of post-treatment follow-up) was not provided for this study with your NDA submission. As previously agreed upon during the preNDA meeting on April 22, 2014 and follow-up communication to the pre NDA meeting dated May 7, 2014, the FDA considers the application fileable, however, the remaining IBS-3001 safety data should be provided as an amendment to the NDA and should comprise updated ISS tables and a complete update of the ISS text. As a reminder, this submission will trigger a “major amendment” adding three months to the review clock.</p> <p>2. Please update the AE datasets for studies 3001 and 3002 to include all levels of the MEDDRA hierarchy. Similarly, please include all levels of the MEDDRA hierarchy in the updated ISS datasets which will be submitted with the 120-day safety update.</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
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain: N/A</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments: CDTL Ruyi He stated there an Advisory Committee is not needed for NDA 206940.</p> <p>If no, for an NME NDA or original BLA , include the reason. For example:</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> <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> 	<input type="checkbox"/> YES Date if known: N/A <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: This application did not raise significant safety or efficacy issues, thus no Advisory Committee Meeting is expected.
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments: None.</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"> 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 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

health significance? Comments: None.	
CLINICAL MICROBIOLOGY Comments: N/A	<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
CLINICAL PHARMACOLOGY Comments: None.	<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 checked="" type="checkbox"/> YES <input type="checkbox"/> NO
BIOSTATISTICS Comments: None.	<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
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments: None.	<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
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments: N/A	<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
PRODUCT QUALITY (CMC) Comments: None.	<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
<u>Environmental Assessment</u> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments: None.</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Quality Microbiology (for sterile products)</p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: N/A</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Facility Inspection</p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments: None.</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>Facility/Microbiology Review (BLAs only)</p> <p>Comments: N/A</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>CMC Labeling Review</p> <p>Comments: N/A</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	None.
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Julie Beitz, M.D.

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 12/10/2014

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

Comments: None.

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>

ACTIONS ITEMS	
<input 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) • notify OMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

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

/s/

JENNIFER S SARCHET
09/10/2014

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

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 206940

Application Type: New NDA

Name of Drug/Dosage Form: (b) (4) (eluxadoline) and 100 mg tablets

Applicant: Furiex Pharmaceutical, Inc.

Receipt Date: June 27, 2014

Goal Date: February 27, 2015

1. Regulatory History and Applicant's Main Proposals

Regulatory history includes IND 79214 submitted on November 21, 2007. Fast track designation was provided January 19, 2011. The proposed indication is treatment of diarrhea and abdominal pain in men and women with IBS-d.

2. Review of the Prescribing Information

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

3. Conclusions/Recommendations

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

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by September 23, 2014. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

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

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- NO** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *In highlights section, under adverse reactions, line needs to be extended.*

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required

Selected Requirements of Prescribing Information

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

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Selected Requirements of Prescribing Information

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- NO** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment: *At this time there is no Established Pharmacologic Class. We will develop a proposal during our review.*

Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Selected Requirements of Prescribing Information

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment: *Need to add sponsor telephone number.*

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

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

- “**See 17 for PATIENT COUNSELING INFORMATION**”

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

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *Currently “MMM 201Y” is listed. The preferred format is “Revised: Month Year” or “Revised: M/YYYY” (i.e. Revised: April 2014 or Revised: 4/2014).*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment: I need to verify with another RPM what this question is exactly asking.
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- NO** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment: Subsections need indenting.
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- NO** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment: *The review team is in the process of determining if there is a reference label.*

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

JENNIFER S SARCHET
09/08/2014