CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206940Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ADDENDUM to OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	**206-940**
Submission Date(s)	**06/26/2014**
Brand Name	**Viberzi**
Generic Name	**Eluxadoline**
OCP Reviewer	**Dilara Jappar, Ph.D.**
OCP Team Leader	**Sue-Chih Lee, Ph.D.**
GTTG Reviewer	**Jeffrey Kraft, PhD**
GTTG Team Leader	**Christian Grimstein, PhD**
OCP Division	**Division of Clinical Pharmacology 3**
OND Division	**Division of Gastroenterology and Inborn Errors Products**
Sponsor	**Furiex Pharmaceuticals,**
Relevant IND(s)	**79,214**
Submission Type	**Original, Priority Review, 505(b)(1), NME,**
Formulation, Strength	**Immediate Release Tablet, 75 mg and 100 mg**
Proposed indication	**Irritable Bowel Syndrome with diarrhea (IBS-d) in adults.**
Recommended Dosing Regimen	**75 mg and 100 mg twice daily**

The dosing recommendations in the clinical pharmacology review dated 03/30/2015 was based on our understanding at the time of the safety profile of the drug, including CNS effect (i.e., euphoria) and cardiovascular safety concern for opioid receptor antagonists. Since then, clinical division has determined that eluxadoline under the clinical use conditions does not have a significant cardiovascular concern. In addition, Controlled Substance Staff (CSS) reviewer has concluded that eluxadoline has a dose-dependent increase in CNS effect (i.e., euphoria). After a discussion with the clinical division regarding the risk-benefit ratio of eluxadoline, we have modified dosing recommendations for patients with hepatic impairment and certain drug-drug interaction scenarios as listed below. The final label reflects the modified dosing recommendations.

Mild to moderated Hepatic Impairment

Labeling recommendation in review dated 03/30/2015:
Avoid the use of eluxadoline in patients with mild and moderate hepatic impairment if possible; If not, monitor for adverse reactions related to eluxadoline when eluxadoline is used in patients with mild and moderate hepatic impairment.

Current revised labeling recommendation:

Administer VIBERZI at a reduced dose of 75 mg twice daily to these patients. Monitor patients with any degree of hepatic impairment for impaired mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery and for other eluxadoline-related adverse reactions

Strong CYP inhibitors:

Labeling recommendation in review dated 03/30/2015:
Avoid concomitant use of strong CYP inhibitors with eluxadoline if possible; If not, monitor for adverse reactions related to eluxadoline.

Current revised labeling recommendation:
Monitor patients for impaired mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery and for other eluxadoline-related adverse reactions

Cyclosporine (OATP1B1 inhibitors)

Labeling recommendation in review dated 03/30/2015:
Avoid concomitant use of OATP1B1 inhibitors with eluxadoline if possible; if not, monitor for adverse reactions related to eluxadoline.

Current revised labeling recommendation:
Administer VIBERZI at a dose of 75 mg twice daily and monitor patients for impaired mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery and for other eluxadoline-related adverse reactions.

Typographical Correction:

There was a typographical error in the clinical pharmacology review for NDA 206940 dated 3/30/2015 on page 4 regarding the food effect.

The original review stated the following incorrect statement:
High fat meal <u>increased</u> eluxadoline Cmax by 50% and AUC by 60% at the 100 mg dose.

The correct version should be:
High fat meal <u>decreased</u> eluxadoline C_{max} by 50% and AUC by 60% at the 100 mg dose.

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

/s/

DILARA JAPPAR
05/27/2015

SUE CHIH H LEE
05/27/2015

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	**206-940**
Submission Date(s)	**06/26/2014**
Brand Name	**TBD**
Generic Name	**Eluxadoline**
OCP Reviewer	**Dilara Jappar, Ph.D.**
OCP Team Leader	**Sue-Chih Lee, Ph.D.**
GTTG Reviewer	**Jeffrey Kraft, PhD**
GTTG Team Leader	**Christian Grimstein, PhD**
OCP Division	**Division of Clinical Pharmacology 3**
OND Division	**Division of Gastroenterology and Inborn Errors Products**
Sponsor	**Furiex Pharmaceuticals,**
Relevant IND(s)	**79,214**
Submission Type	**Original, Priority Review, 505(b)(1), NME,**
Formulation, Strength	**Immediate Release Tablet, 75 mg and 100 mg**
Proposed indication	**Irritable Bowel Syndrome with diarrhea (IBS-d) in adults.**
Recommended Dosing Regimen	**75 mg and 100 mg twice daily**

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1. Executive Summary

Eluxadoline (also known as JNJ-27018966) is a new molecular entity (NME). It is a mixed mu-opioid receptor (μOR) agonist and delta-opioid receptor (δOR) antagonist designed to act locally in gastrointestinal tract for treatment of irritable bowel syndrome with diarrhea (IBS-d) in adults. The proposed oral dose is 100 mg twice daily (BID), but is lowered to 75 mg BID in patients who have had a prior cholecystectomy or are unable to tolerate 100 mg. Eluxadoline is being developed as immediate release oral tablets in 75 mg and 100 mg tablet strengths. In support of this NDA application, the sponsor had submitted 11 phase I studies to evaluate the pharmacokinetics, pharmacodynamics, drug-drug interactions, specific population PK, mass balance, QT prolongation potential, and food-effect of eluxadoline. A phase II dose-ranging study was conducted with 5 mg, 25 mg, 100 mg, and 200 mg BID doses in IBS-d patients where sparse PK samples were obtained for a population PK analysis. Two phase III studies were conducted to evaluate the safety and efficacy of 75 mg and 100 mg BID doses. In addition, 10 *in-vitro* studies were conducted to evaluate drug absorption-, distribution-, and metabolism-related characteristics, and drug-drug interaction potential of eluxadoline.

1.1 Recommendations

The Office of Clinical Pharmacology has found the submission acceptable from a clinical pharmacology standpoint provided a mutual agreement on labeling languages is reached. The current labeling recommendations are based on our current understanding of the safety profile of eluxadoline. If further additional safety information becomes available, our labeling recommendation will be re-evaluated. At this time, the labelling language is still being discussed with the sponsor.

A required office level briefing for this NDA was held on March 9, 2015

1.2 Recommended Post-Marketing Studies

We recommend that the sponsor commit to conduct the following post-approval studies:

1. *In –Vivo* Study
    a. A dedicated renal impairment study. A reduced study design (where the sponsor can conduct the study in patients with ESRD not yet on dialysis and subsequently decide on the necessity of a study in patients with lower degree of renal impairment) as discussed at pre-NDA stage will be acceptable.
    Rationale: A dedicated renal impairment study was not conducted in this submission.

2. *In-Vitro* Studies:
    a. *In-vitro* studies to adequately characterize the metabolism of eluxadoline in respect to various drug metabolizing enzymes. Depending on the results, further studies may be necessary.
    Rationale: 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. As such, the label will state "Avoid concomitant use of

strong CYP inhibitors with eluxadoline if possible; If not, monitor for adverse reactions related to eluxadoline." The metabolism information may allow elimination of some of these restrictions.

b. Further *in-vitro* studies to assess the *in-vivo* relevance of time-dependent inhibition of CYP3A4 by eluxadoline. Please refer to current "Guidance for Industry Drug Interaction Studies-Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations" for details. Depending on the results, an *in-vivo* study may be necessary.
Rationale: 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. Therefore, in the meantime until further data become available, the label will state "monitor the systemic level of narrow therapeutic index drugs that are CYP3A4 substrates when a concomitant use with eluxadoline is initiated or discontinued".

c. *In-vitro* study to estimate the IC_{50} (or Ki) value of eluxadoline toward P-gp and subsequently predict the *in-vivo* relevance of this interaction. Depending on the result, *in-vivo* study may be necessary.
Rationale: Inhibition potential of eluxadoline toward transporters was only evaluated at one concentration, 400 ng/mL (no inhibition was demonstrated), and thus, IC_{50} (or Ki) 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) can be about 1000-fold higher than the tested concentration. Therefore, further assessment is necessary.

d. *In-vitro* study to evaluate the potential of eluxadoline to inhibit CYP2C8 and induce CYP2B6.
Rationale: Potential of eluxadoline to inhibit CYP2C8 or induce CYP2B6 was not assessed in this submission.

1.3 Clinical Pharmacology Highlights

Dose-Response Relationship and Dose Selection

The phase II dose-ranging study assessed 5 mg, 25 mg, 100 mg, and 200 mg BID dosing regimens vs. placebo in IBS-d patients. Using the primary efficacy analysis consistent with that recommended in the current IBS guidance, the 5 mg and 25 mg BID doses were not efficacious while 100 mg and 200 mg doses had similar response rate. However, the 200 mg BID regimen was associated with a slightly increased rate of treatment related AEs, discontinuation rate, and GI related AE (most commonly reported AE). Therefore, 100 mg BID dose was carried into Phase 3 studies.

In the two phase III pivotal efficacy and safety studies, 75 mg and 100 mg BID regimens were evaluated against placebo. The response rates for placebo, 75 mg BID, and 100 mg BID dosing were 17.1%, 23.9%, and 25.1%, respectively, in Study IBS-3001 and 16.2%, 28.9%, and 29.6%, respectively in Study IBS-3002. According to Dr. Laurie Muldowney, Medical Officer of DGIEP, although 75 mg and 100 mg BID regimens appear to have comparable overall safety profiles, 100 mg BID regimen appears to have somewhat increased AEs of abdominal pain, especially in patients with prior cholecystectomy (4.8% vs. 9.8%). Therefore, even though the sponsor initially only proposed a dosing regimen of 100 mg BID for the indication, both 75 mg and 100 mg BID regimens are being considered for a regulatory action.

QTc Prolongation Potential: The QT-IRT review team concluded that no significant QTc prolongation was observed when 100 mg and 1000 mg (supreatherapeutic dose) of eluxadoline was administered to healthy subjects.

Pharmacokinetics:

Eluxadoline has a dose proportional increase in C_{max} and slightly less than dose proportional increase in AUC. PK variability of eluxadoline was relatively high (51-98%). Daily BID dosing results in no evidence of accumulation.

Absorption: After single dose administration of 100 mg eluxadoline in healthy subjects, the peak plasma concentration was reached in about 2 hours with C_{max} of approximately 2-4 ng/mL. High fat meal increased eluxadoline C_{max} by 50% and AUC by 60% at the 100 mg dose. Because phase III trials were conducted under fed conditions, the label recommends taking eluxadoline with food. Absolute bioavailability of eluxadoline was not evaluated.

Distribution: The plasma protein binding was approximately 81% between concentrations of 200-5700 ng/mL.

Metabolism: Metabolism of eluxadoline is not clearly established. Based on the available human data, it appears that eluxadoline undergoes glucuronidation to form acyl glucuronide (M11) that is found in urine. The bioanalytical methods used in the metabolic profiling studies to monitor the metabolites in plasma and urine did not have adequate assay sensitivity. As such, metabolism information is not clear even though no other metabolites were detected in human biological samples. Furthermore, although no major metabolites were detected *in-vitro* (human hepatocytes, microsomes and S9), these test systems were not adequately verified in respect to various phase 1 and 2 enzymes prior to the study. Therefore, potential metabolism mediated via other enzymes cannot be ruled out.
As eluxadoline is considered primarily a locally acting drug where efficacy will primarily depend on the local concentration in the gut and most reported safety signal in phase III studies are GI related adverse events, this unclear metabolic pathway of eluxadoline will be addressed with appropriate labeling. We recommend that the sponsor conduct further *in-vitro* studies to characterize the metabolism of eluxadoline as a PMC. In the meantime until further data become available, we recommend to avoid concomitant use of strong CYP inhibitors with eluxadoline if possible; If not, monitor for adverse reactions related to eluxadoline.

Elimination: The terminal half-life of eluxadoline across various phase 1 studies ranged 3.7-6.0 hr. In the mass balance study, about 0.12% and 82% of the administered radioactive dose was recovered in urine and feces, respectively. From various studies in healthy subjects, the mean fraction of oral dose of eluxadoline excreted as unchanged drug in urine was less than 0.17 %.

Specific Populations:

Pediatric: No studies were conducted in pediatric patients. A waiver for <6 years of age and deferral ≥6 years to 17 and 11 months of age have been submitted in this application.

Gender: The exposure of eluxadoline is 35 % higher in females than in males. No dose adjustment is needed based on gender.

Hepatic Impairment: The exposure (both AUC and C_{max}) in patients with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment is 6- fold and 4-fold higher than the exposure in subjects with normal hepatic function. AUC and C_{max} in patients with severe (Child-Pugh Class C) hepatic impairment are about 16-fold and 19-fold higher than that of in subjects with normal hepatic function, respectively. The sponsor proposed to contraindicated eluxadoline in patients with hepatic impairment due to cirrhosis. However due to the difference in the level of change in systemic exposure of eluxadoline, we propose to only contraindicate eluxadoline in patients with severe hepatic impairment and avoid the use of eluxadoline in patients with mild and moderate hepatic impairment if possible; If not, monitor for adverse reactions related to eluxadoline when eluxadoline is used in patients with mild and moderate hepatic impairment.

Renal Impairment: There was no dedicated PK study to evaluate the effect of renal impairment on PK of eluxadoline. In the phase 3 studies, the % of patients with AEs were comparable between the patients with mild renal impairment and the overall population. In addition, in patients with mild renal impairment, the % patients with AEs were comparable for subjects who were treated with 75 mg or 100 mg eluxadoline vs. placebo. However, there is not an adequate number of subjects with moderate renal impairment to draw any conclusion (n=6). Therefore, a renal impairment study will be required as a post-marketing study.

Based on sponsor's population PK analysis, age (within the range of 18 to 65 years old), race, body weight and BMI had no impact on eluxadoline PK.

Genetics: Analyses of genotypes of SLCO1B1 (OATP1B1) from phase 2 study indicates that there is a relationship between increasing exposure of eluxadoline and decreasing OATP1B1 transporter function. However, extrapolation of this relationship and its clinical significance is complicated by very low numbers of poor transporters (n=5) with exposure data, very large inter-subject variability (CV of 50%-300%) in AUC, and inconsistencies in the relationship between dose groups.

In-vitro Drug-Drug Interaction Evaluation:

CYP Inhibition: In an *in-vitro* study, eluxadoline appears to show time-dependent inhibition of CYP3A4 at 50 μM, a concentration that can be achieved in the gut (I_{gut} is estimated to be 700 μM). Further *in-vitro* studies are necessary to assess the *in-vivo* relevance of this potential time-dependent inhibition of CYP3A4 by eluxadoline. Depending on the results, further *in-vivo* study may be necessary. In the meantime until further data become available, the label will state "monitor the systemic level of narrow therapeutic index drugs that are CYP3A4 substrates when a concomitant use with eluxadoline is initiated or discontinued". Eluxadoline up to 50 μM concentration did not show time-dependent inhibition toward CYP1A2, 2C9, 2C19 and 2D6.

Based on the *in-vitro* studies, *in-vivo* drug interactions of eluxadoline with CYP1A2, 2A6, 2B6, 2C9, 2C19.2D6, 2E1 and 3A4 via reversible inhibition at the clinical dose of 100 mg is unlikely. The potential of eluxadoline to inhibit of CYP2C8 was not evaluated in this submission.

CYP Induction: Eluxadoline up to 10 µM (5.7 µg/mL) do not induce CYP1A2, CY2C9, CYP2C19 and CY3A4/5 in *in-vitro*. The sponsor did not evaluate the potential of eluxadoline to induce CYP2B6.

Transporters Substrate: Based on *in-vitro* studies, eluxadoline appears to be a substrate for OAT3, OATP1B1, BSEP, and MRP2 and but not for OCT1, OCT2, OAT1, OATP1B3. Eluxadoline is not a good substrate for P-gp and BCRP.

Transporters Inhibition: Eluxadoline appears to be a weak inhibitor of OATP1B1, but no significant inhibition was observed for all other evaluated transporters, OAT1, OAT3, OCT1, OCT2, OATP1B3, P-gp, BCRP, BSEP, and MRP2 at 400 ng/mL concentration (C_{max} = 2-4 ng/mL). IC_{50} values were not determined. However, concentration in the gut, which has expression of P-gp and BCRP, can be much higher than the tested concentration (I_{gut} = dose/250 mL=400 µg/mL). Nonetheless, since no significant increase in exposure of rosuvastatin, a substrate for BCRP, was noted (AUC ↑ by 40 % and Cmax ↑ by 18%) when it was coadministered with eluxadoline, significant inhibition of BCRP in the gut by eluxadoline in not likely. Therefore, further *in-vitro* studies are needed to estimate the IC_{50} (or Ki) value of eluxadoline toward P-gp and subsequently predict the *in-vivo* relevance of this interaction. Depending on the result, further *in-vivo* study may be necessary.

In-vivo drug interactions:

Effect of other drugs on the PK of eluxadoline

- Probenecid: Coadministration of single oral dose of 500 mg probenecid (an inhibitor of MRP2 and OAT3) with single oral dose of 100 mg eluxadoline increased both AUC and C_{max} of eluxadoline by 30%, which is not considered to be clinically significant.

- Cyclosporine: Coadministration of single oral dose of 600 mg cyclosporine (an inhibitor of many transporters including OATP1B1 and MRP2) with single oral dose of 100 mg eluxadoline increased eluxadoline AUC by 4.4 fold and C_{max} by 6.2 fold. The sponsor proposed to monitor patients for adverse reaction when eluxadoline is prescribed concomitantly with OATP1B1 inhibitors in the proposed label. We recommend that patients to avoid concomitant use of OATP1B1 inhibitors with eluxadoline if possible; if not, monitor for adverse reactions related to eluxadoline.

Effect of eluxadoline on PK of other drugs

Rosuvastatin: Coadministration of multiple dose of 100 mg eluxadoline with single dose 20 mg rosuvastatin increased rosuvastatin AUC by approximately 40% and C_{max} by 18% compared to when rosuvastatin was administered alone. Caution should be exercised when rosuvastatin is coadministered with eluxadoline.

Oral contraceptive

Coadministration of multiple dose of 100 mg eluxadoline with multiple dose of oral contraceptive Brevicon (norethindrone 0.5 mg / ethinyl estradiol 0.035 mg) does not significantly change the exposure of either drug. . While eluxadoline has no impact on exposure of norethindrone and ethinyl estradiol of Brevicon, coadministration of Brecicon reduced the exposure (both C_{max} and

AUC) of eluxadoline by 10%. Dose adjustment for both eluxadoline and oral contraceptive are not needed.

2 Question-Based Review

2.1 List of *In-vivo* and *In-vitro* Clinical Pharmacology Studies

Table 1: In-Vivo Studies:

Study #	**Objective(s)**	**Study Design**	**Test product; Dosage Regimen; Route of administration**	**Subjects**
27018966 EDI1002 (EDI-1002)	Food effect	Open label, single dose, crossover	Eluxadoline tablet; 500 mg single dose in fasted and fed state; PO	18 Healthy men
27018966 CPS1009 (CPS-1009)	Food effect	Open label, single dose, crossover	Eluxadoline tablet; 100 mg single dose in fasted and fed state; PO	28 Healthy men and women
27018966 EDI1001 (EDI-1001)	Initial tolerability, SAD/MAD	Randomized, double blind, 2 part, SAD, MAD Placebo control	Eluxadoline oral suspension; 30, 100, 300, 1000, 1500, or 2000 mg single dose; PO	18 Healthy men
			Eluxadoline oral suspension; 1000 mg single dose; PO	8 Healthy women
			Eluxadoline oral suspension; 100 mg QD; 150, 230, 300, or 500 mg BID; PO; 7 days treatment	40 Healthy men
			Eluxadoline oral suspension; 150 mg BID; PO; 7 days treatment	8 Healthy women
27018966 EDI1003 (EDI-1003)	Mass balance	Open label, single dose	Capsule containing 100 µCi [^{14}C]- eluxadoline; 300 mg single dose; PO	8 Healthy men
27018966 CPS1005 (CPS-1005)	Hepatic impairment	Open label, single dose, parallel group	Eluxadoline tablet; 100 mg single dose; PO	30 Hepatic impaired men and women (mild, moderate, and severe) and matched, healthy men and women
27018966 CPS1007 (CPS-1007)	Drug interaction with an oral contraceptive (Brevicon)	Open label, multiple dose, 3 period, single sequence	Eluxadoline tablet; 100 mg BID with and without steady- state Brevicon; PO 7 days treatment	53 Healthy women
27018966 CPS1011 (CPS-1011)	Drug interaction with cyclosporine or probenecid	Open label, single dose, 3 period, crossover	Eluxadoline tablet; 100 mg single dose alone and with cyclosporine (600 mg) or with probenecid (500 mg); PO	30 Healthy men and women

27018966 CPS1012 (CPS-1012)	Drug interaction with rosuvastatin	Open label, multiple dose, 2 period, crossover	Eluxadoline tablet; Rosuvastatin (20 mg) single dose alone and with 100 mg BID eluxadoline; PO 3 days treatment	28 Healthy men and women
27018966 CPS1008 (CPS-1008)	QTc	Randomized, evaluator blinded, single dose, 4 period, crossover Placebo and positive control (moxifloxacin)	Eluxadoline tablet; 100 and 1000 mg single dose; PO	64 Healthy men and women
27018966 CPS1006 (CPS-1006)	Oral abuse potential	Randomized, double blind, 6 period, crossover Placebo and active control (oxycodone)	Eluxadoline tablets; 100, 300, and 1000 mg single dose; PO, Oxycodone IR tablets; 30 and 60 mg single dose; PO	40 Nondependent recreational opioid users, otherwise healthy men and women
27018966 CPS1010 (CPS-1010)	Intranasal abuse potential	Randomized, double blind, 6 period, crossover Placebo and active control (oxycodone)	Eluxadoline tablets (crushed); 100 and 200 mg single dose; Intranasal Oxycodone IR tablets (crushed); 15 and 30 mg single dose; intranasal	36 Nondependent recreational opioid users, otherwise healthy men and women
27018966 IBS2001 (IBS-2001)	Dose ranging, efficacy, safety, and population PK	Randomized, double blind, parallel group, dose ranging Placebo control	Eluxadoline tablets; 5, 25, 100, or 200 mg BID; PO 12 weeks treatment	807 Men and women with IBS-d 1 week prior to randomization: • average daily pain scores ≥3.0 • average BSS ≥5.5 • diary compliance

Table 2: In-Vitro Studies

Study Identifier	**Type of Study**	**Objective(s) of the Study**
FK5826	*In-vitro* metabolism	To identify and estimate the *In-vitro* metabolites of the JNJ-27018966 produced by cryopreserved hepatocytes of rat, dog, monkey and human followed by comparison of metabolic profiles across the species to ensure all *In-vitro* metabolites of human are covered by the toxicological species
FK5944	*In-vitro* stability of acyl glucuronide of JNJ-27018966	To determine the configuration and chemical degradation half-life (t1/2) of the major acyl glucuronide of JNJ-27018966. Another objective is to investigate the *in-vitro* metabolism of JNJ-27018966 by human intestinal microsomes.
FK6533	*In-vivo* Metabolism	To identify and estimate the *in-vivo* metabolites of JNJ-27018966 following oral administration of 1000 mg dose to healthy male subjects enrolled in a single ascending dose study to assess safety and tolerability of JNJ-27018966.
FK6315	Protein Binding	To evaluate the binding of JNJ-27018966 to the proteins of rat, dog, mouse, monkey and human plasma
FK5731	CYP Induction	To evaluate potential for JNJ-27018966 to induce CYP1A2, CYP2C9, CYP2C19, and CYP3A4 in Cryo-Preserved Human Hepatocytes

FK5873	CYP Inhibition	To evaluate the reversible and mechanism-based inhibitory potentials of JNJ-27018966 on CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 in pooled, mixed gender, human liver microsomes
OPT-2012-063	Transporter inhibition	To determine whether or not JNJ-27018966 inhibit human Pgp, BCRP, BSEP, MRP2, OAT1, OAT3, OCT1, OCT2, OATP1B1 and OATP1B3-mediated transport.
OPT-2012-064	Transporters substrate	To determine whether JNJ-27018966 is substrate for human P-gp, BCRP, BSEP, MRP2, OAT1, OAT3, OCT1, OCT2, OATP1B1 or OATP1B3 mediated transport.
FK6635	P-gp and BCRP substrate/inhibition study	To examine whether JNJ-27018966 is a substrate and/or inhibitor of human P-gp or MRP2, using human MDR1- and MRP2-transfected MDCKII cell lines.
04-WJ.POl ~Report 5		to determine the solubility, metabolism, permeability, protein binding and red blood cell binding of JNJ-27018966

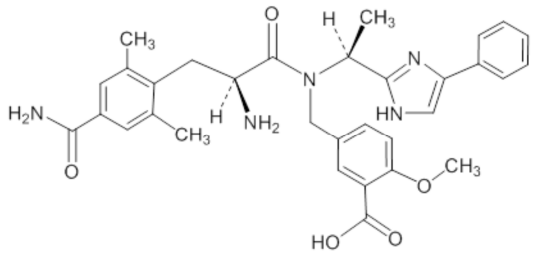
In addition to these clinical pharmacology studies, the sponsor had also conducted two phase III studies in IBS-d patients to evaluate the safety and efficacy of eluxadoline.

2.2 General Attributes of the drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Drug Substance: Eluxadoline is white crystalline powder with molecular formula of $C_{32}H_{35}N_5O_5$ and a molecular weight of 569.65 g/mol. (b) (4) Eluxadoline is slightly soluble in water (2.74 mg/mL). Eluxadoline is also referred by code name JNJ-27018966 in this review.

Figure 1: Structure of Eluxadoline



pKa1 = 7.11; pKa2 = 4.70; pKa3 = 3.77

Formulation: Eluxadoline is being developed as immediate release oral tablet in 75 mg and 100 mg tablet strength. (b) (4)

2.2.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

The proposed mechanism of action is that eluxadoline is a locally active drug that has mixed mu opioid receptor (μOR) agonist and delta opioid receptor (δOR) antagonist pharmacological activities.
The proposed indication is treatment of irritable bowel syndrome with diarrhea (IBS-d) in adults.

2.2.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dose of eluxadoline are 75 mg and 100 mg BID by oral route of administration with food.
The proposed oral dose is 100 mg twice daily (BID), and 75 mg BID regimen is recommended in patients who have had a prior cholecystectomy or are unable to tolerate 100 mg.

2.2.4 What drugs (substances, products) are approved in the US for the same indication?

Currently, Lotronex (alosetron), 5-HT3 receptor antagonist, is the only approved drug for chronic IBS-d in the USA. Lotronex was first approved in 2000, withdrawn from the market for safety concern (e.g., ischemic colitis, severe constipation) in 2001, and then reintroduced in 2002 only under restricted use (only doctors who have signed up with the company that makes LOTRONEX should write prescriptions for LOTRONEX) in women.
Note that Loperamide, a peripherally acting mu-opioid receptor (μOR) agonist, does not have an indication for IBS-d but is commonly used as an antidiarrheal. Loperamide was used as a rescue medication in the phase III trials.

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

In support of this NDA, the sponsor had submitted 11 phase I studies, one phase II dose-ranging study, two phase III efficacy and safety studies and 10 *in-vitro* studies. Please see table 1 and table 2 for more information.

Phase I clinical pharmacology program included single and multiple ascending dose pharmacokinetic study, mass balance study, food effect study, hepatic impairment study, drug-drug interaction studies with oral contraceptive, cyclosporine, probenecid and rosuvastatin, thorough QT study and drug abuse potential studies with PK components. *In-vitro* studies characterized the protein binding, substrate, inhibitor or inducer potential of eluxadoline for various enzymes and transporters. Additionally, six bioanalytical method validation reports in plasma and urine were submitted. Phase II dose-ranging study also had population PK analysis and population PK/PD analysis.

Two randomized, double-blinded, parallel-group, placebo-controlled, phase III studies (IBS-3001 and IBS-3002) evaluated efficacy and safety of 75 mg and 100 mg BID doses in IBS-d patients. Study IBS-3001 included safety evaluation up to 52 weeks to support the long-term safety of eluxadoline.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies?

The proposed indication is treatment of irritable bowel syndrome with diarrhea (IBS-d) which is characterized by symptoms of abdominal pain, loose stools (diarrhea) along with other symptoms such as sudden urges for bowel movement, gas, abdominal discomfort, . Accordingly, evaluation of clinical efficacy of eluxadoline focused on these two major symptoms of IBS-d, abdominal pain and stool consistency (diarrhea).

The primary efficacy endpoint used in two phase III trials was the proportion of composite responders over the initial 12 weeks of treatment. A patient was counted as a composite responder

if he or she met the daily composite response criteria (pain and stool consistency) for at least 50% of the days with diary entries during Weeks 1-12. A patient must have met both of the following criteria on any given day to be a daily responder:

- Daily pain response: worst abdominal pain scores in the past 24 hours improved by ≥30% compared to baseline pain.
  The worst abdominal pain in the past 24 hours was recorded on a 0 to 10 scale, where 0 corresponded to no pain and 10 corresponded to worst imaginable pain.
- Daily stool consistency response: Bristol Stool Score (BSS) score <5 or the absence of a bowel movement if accompanied by ≥30% improvement in worst abdominal pain compared to baseline.
  Stool consistency was measured with BSS based on a 1 to 7 scale where 1 corresponded to a hard stool and 7 corresponded to watery diarrhea.

The primary endpoint used in these two phase III studies was consistent with FDA's recommendation in the "Guidance for Industry Irritable Bowel Syndrome - Clinical Evaluation of Drugs for Treatment" (May 2012).

2.3.3 Are the active moieties in the plasma and urine appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?

Yes. Eluxadoline in plasma and urine were quantified by appropriately validate HPLC-MS/MS bioanalytical methods. Please see the analytical section 2.9 for more details.

2.4 Exposure-Response Evaluation

2.4.1 What are the characteristics of the exposure-response relationships for efficacy?

Phase 2 Trial

In the phase II study, four different doses regimens of eluxadoline (5 mg BID, 25 mg BID, 100 mg BID, and 200 mg BID) were evaluated against placebo over 12 weeks of treatment in IBS-d patients (study IBS-2001).

Only the dose –response relationship was reviewed. The sponsor had submitted PK/PD analysis report from the phase II study. However, pharmacometrics team determined that a review of this report is not necessary since this drug is considered to be primarily a locally acting drug, and thus systemic exposure is not relevant for the efficacy. In addition, based on the sponsor's analysis, no true PK/PD relationship was established to add any new information.

Initially, the primary endpoint used in phase II dose-ranging study, although still based on daily pain score and stool consistency, was slightly different than the one used in the phase III studies. Sponsor also conducted post-hoc analysis in this phase II study with endpoint that was consistent with the endpoint used in phase III studies and with the current FDA draft guidance on IBS. The results of this post-hoc analysis of phase II study were used for dose selection for the phase III studies.

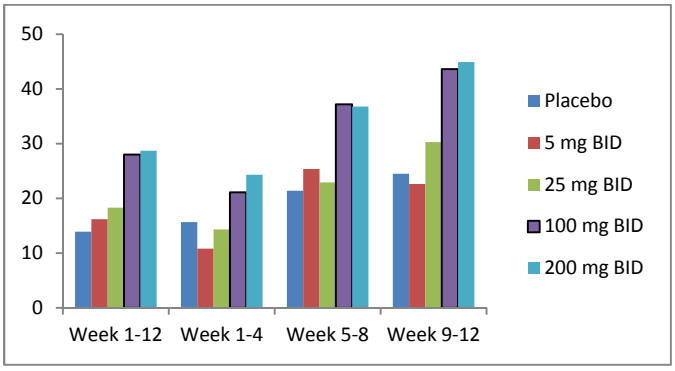
Based on post-hoc analysis, over the 12-week treatment period, both the 100-mg and 200-mg treatment groups had statistically significantly higher daily responders rate compared to placebo group (p=0.002). In addition, 200 mg BID dosing regimen did not enhance the efficacy compared to 100 mg BID dosing regimen. Furthermore, evaluation of monthly response rate over

the intervals of Weeks 5-8, and Weeks 9-12 showed a consistent result as the overall 12-week response rate.

Table 3: Study Response Rates Based on the Post Hoc Daily Responder Definition (IBS-2001)

	JNJ-27018966 5 mg BID (N = 105)	**JNJ-27018966 25 mg BID (N = 167)**	**JNJ-27018966 100 mg BID (N = 163)**	**JNJ-27018966 200 mg BID (N = 160)**	**Placebo (N = 159)**
Weeks 1-12					
n	105	167	163	160	159
Overall response rate	16.2%	18.3%	28.0%	28.7%	13.9%
P value	0.597	0.275	0.002	0.002	
Weeks 1-4					
n	105	167	163	160	159
Overall response rate	10.8%	14.3%	21.1%	24.3%	15.7%
P value	0.246	0.709	0.217	0.058	
Weeks 5-8					
n	95	149	139	136	143
Overall response rate	25.4%	22.9%	37.2%	36.8%	21.4%
P value	0.464	0.753	0.004	0.005	
Weeks 9-12					
n	77	140	131	112	131
Overall response rate	22.6%	30.3%	43.6%	44.9%	24.5%
P value	0.755	0.287	0.001	0.001	

Figure 2: Study Response Rates Based on the Post Hoc Daily Responder Definition (IBS-2001)



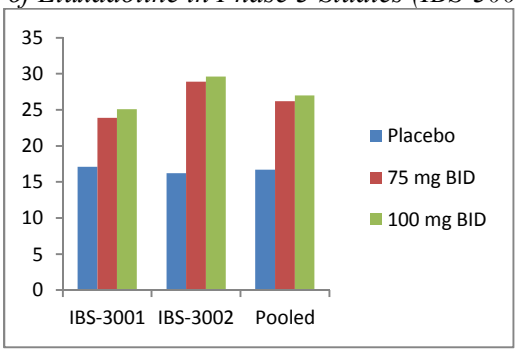
Phase 3 trials:

Two randomized, double-blind, placebo-controlled, parallel-group, phase III efficacy and safety trials of eluxadoline in IBS-d patients were conducted using 75 mg BID and 100 mg BID doses versus placebo. The 100 mg BID dose was chosen based on the observed risk benefit profile in the phase 2 study where the 5 mg BID and the 25 mg BID doses did not show adequate efficacy and 200 mg BID dose which had shown to be efficacious but was associated with higher incidence of GI related adverse events. 75 mg BID dose was included in phase 3 studies to identify a potentially lower effective dose. The primary efficacy endpoint used in two phase III trials was the proportion of composite responders over the initial 12-weeks of double-blind treatment. Please refer to section 2.3.2 for definition of responders. In the both phase III studies, both 75 mg and 100 mg BID doses have shown statistically significant improvement over placebo. Please refer to the clinical review by Dr. Laurie Muldowney and statistical reviews by Dr. Yeh-Fong Chen for a detailed review of study findings. Dr. Laurie Muldowney's and Dr. Yeh-Fong Chen's overall efficacy and safety finding were consistent with sponsor's analysis.

Table 4: Responders Rate of Eluxadoline in Phase 3 studies (IBS-3001 and IBS-3002)

Study	Dose	N	Responders Rate (%)	P-value
IBS-3001	Placebo	427	17.1	---
	75 mg BID	427	23.9	0.014
	100 mg BID	426	25.1	0.004
IBS-3002	Placebo	382	16.2	---
	75 mg BID	381	28.9	<0.001
	100 mg BID	382	29.6	<0.001
Pooled	Placebo	809	16.7	--
	75 mg BID	808	26.2	<0.001
	100 mg BID	806	27.0	<0.001

Figure 3: Responders Rate of Eluxadoline in Phase 3 Studies (IBS-3001 and IBS-3002)



2.4.2 What are the characteristics of the exposure-response relationships for safety?

In dose ranging phase II study (5 mg BID, 25 mg BID, 100 mg BID, and 200 mg BID), the incidence rates of treatment-emergent AEs were generally similar across the treatment groups, though patients in the 200-mg treatment group reported the most individual events.

Table 5: Adverse Event Summary (IBS-2001)

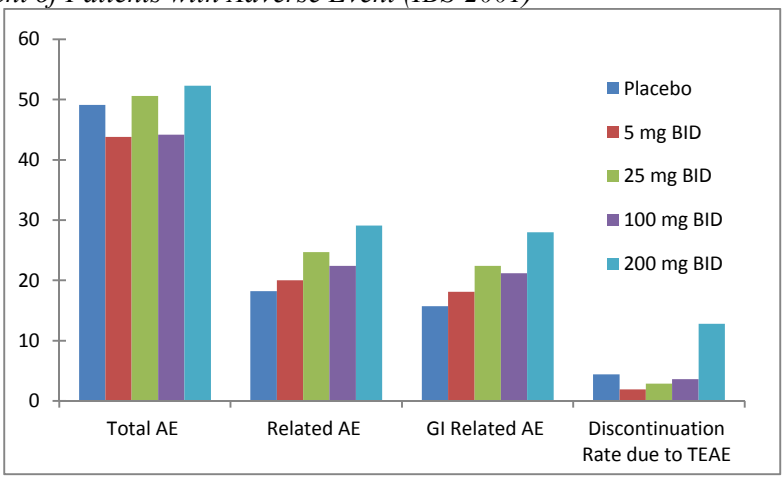
	JNJ-27018966 5 mg BID (N = 105)		JNJ-27018966 25 mg BID (N = 170)		JNJ-27018966 100 mg BID (N = 165)		JNJ-27018966 200 mg BID (N = 172)		Placebo (N = 159)	
	Patients n (%)	Total Events	Patients n (%)	Total Events	Patients n (%)	Total Events	Patients n (%)	Total Events	Patients n (%)	Total Events
Total number of TEAEs	46 (43.8)	97	86 (50.6)	212	73 (44.2)	167	90 (52.3)	233	78 (49.1)	174
Total number of serious TEAEs	1 (1.0)	1	2 (1.2)	2	0	0	2 (1.2)	2	1 (0.6)	2
Total number of related TEAEs	21 (20.0)	29	42 (24.7)	74	37 (22.4)	79	50 (29.1)	134	29 (18.2)	60
Total number of related serious TEAEs	0	0	0	0	0	0	0	0	0	0
Total number of deaths	0	0	0	0	0	0	0	0	0	0

Abbreviation: BID= twice daily; TEAE = treatment-emergent adverse event.

The rate of discontinuation due to treatment-emergent AEs was highest among the 200-mg group where the discontinuation rate was 4.4% in the placebo, 1.9% in the 5 mg, 2.9% in the 25 mg, 3.6% in the 100 mg, and 12.8% in the 200-mg treatment group;

Gastrointestinal (GI) disorders were the most commonly reported treatment-emergent AEs among all system organ classes, and its incidence rate was highest among patients 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 which was 15.7%.

Figure 4: Percent of Patients with Adverse Event (IBS-2001)



According to Dr. Laurie Muldowney, Medical Officer of DGIEP, in two phase III studies, the total number of adverse events, AEs leading to discontinuation, and GI related disorder (such as constipation, nausea and abdominal pain), which was the most commonly reported adverse event, were comparable between 75 mg BID dose and 100 mg BID doses. However, there is slight increase in adverse events of abdominal pain with 100 mg dose compared to 75 mg dose, especially in patient with prior cholecystectomy (4.8% vs. 9.8%). Therefore, although the sponsor initially only proposed a dosing regimen of 100 mg BID for the indication, 75 mg BID regimen is also being considered for a regulatory action in patients who have tolerability issues with 100 mg dose.

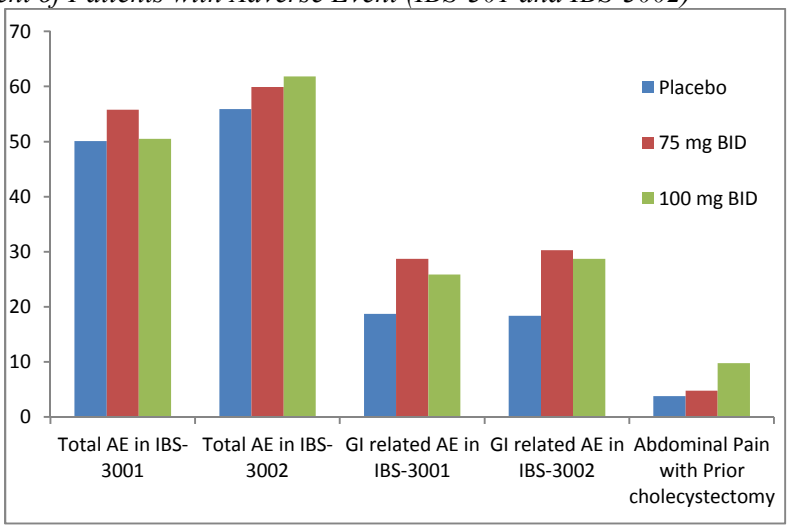
Table 6: Overview of adverse Events in study IBS-3001

	Eluxadoline 75 mg BID (N=428)		**Eluxadoline 100 mg BID (N=479)**		**Placebo BID (N=427)**	
	n (%) Patients	**Total Events**	**n(%) Patients**	**Total Events**	**n(%) Patients**	**Total Events**
Adverse events	239 (55.8)	775	242 (50.5)	836	214 (50.1)	667
Serious AEs	19 (4.4)	22	24 (5.0)	46	14 (3.3)	16
Related SAEs	2 (0.5)	2	3 (0.6)	5	0	0
AEs Leading to Discontinuations	31 (7.2)	31	42 (8.8)	42	15 (3.5)	15

Table 7: Overview of adverse Events in study IBS-3002

	Eluxadoline 75 mg BID (N=379)		**Eluxadoline 100 mg BID (N=380)**		**Placebo BID (N=381)**	
	n(%) Patients	**Total Events**	**n(%) Patients**	**Total Events**	**n(%) Patients**	**Total Events**
Adverse events	227 (59.9)	655	235 (61.8)	660	213 (55.9)	602
Serious AEs	9 (2.4)	11	14 (3.7)	16	8 (2.1)	8
Related SAEs	3 (0.8)	3	2 (0.5)	2	0	0
AEs leading to discontinuation	32 (8.4)	33	28 (7.4)	28	19 (5.0)	19

Figure 5: Percent of Patients with Adverse Event (IBS-301 and IBS-3002)



2.4.3 Does this drug prolong the QT or QTc interval?

Based on the review conducted by QT-IRT team, no significant QTc prolongation was observed when a 100 mg (clinical dose) and 1000 mg (supreatherapeutic dose) eluxadoline were administered to healthy subjects. The largest upper bounds of the 2-sided 90% CI for the mean differences between eluxadoline 100 mg and placebo, and between eluxadoline 1000 mg and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. Below is the brief summary of the study and analysis results. Please see IRT-QT team review of the thorough QT study dated 11/19/2014 for further detail.

Study CPS1008: QT prolongation was evaluated in randomized, evaluator-blinded, placebo- and positive-controlled, single-dose, 4-period crossover study in 64 healthy subjects with 100 mg eluxadoline, 1000 mg of eluxadoline, placebo, 400 mg of moxifloxacin. Plasma concentrations of eluxadoline were analyzed. Exposure of eluxadoline was approximately dose proportional where 1000 mg dose had about 10-fold higher C_{max} and about 8-fold higher AUC compared to 100 mg eluxadoline.

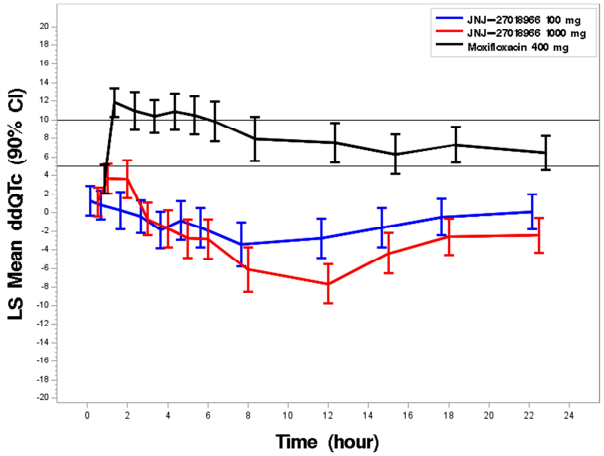
The supratherapeutic dose 1000 mg, which produced about 10-fold higher C_{max} compared to the therapeutic dose 100 mg, had covered the identified worst case clinical scenario with 1) drug interaction with cyclosporine, which produced 6.2-fold higher C_{max} and 2) exposure in mild and moderate hepatic impairment (Child-Pugh Class A and B), which produced 4-6-fold higher C_{max}. Although the C_{max} in severe hepatic impairment patients were higher (16-fold higher than healthy subjects), eluxadoline is being proposed to be contraindicated this group of subjects with severe hepatic impairment (Child-Pugh Class C). Therefore, QT prolongation potential in this group of population does not need to be addressed.

Table 8: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Eluxadoline (100 mg and 1000 mg) and the Largest Lower Bound for Moxifloxacin (from FDA QT-IRT team review)

Treatment	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
Eluxadoline 100 mg	0.5	1.3	(-0.3, 2.8)
Eluxadoline 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.

Figure 6: Mean and 90% CI ddQTcI Time Course Profile (from FDA IRT-QT review)



2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

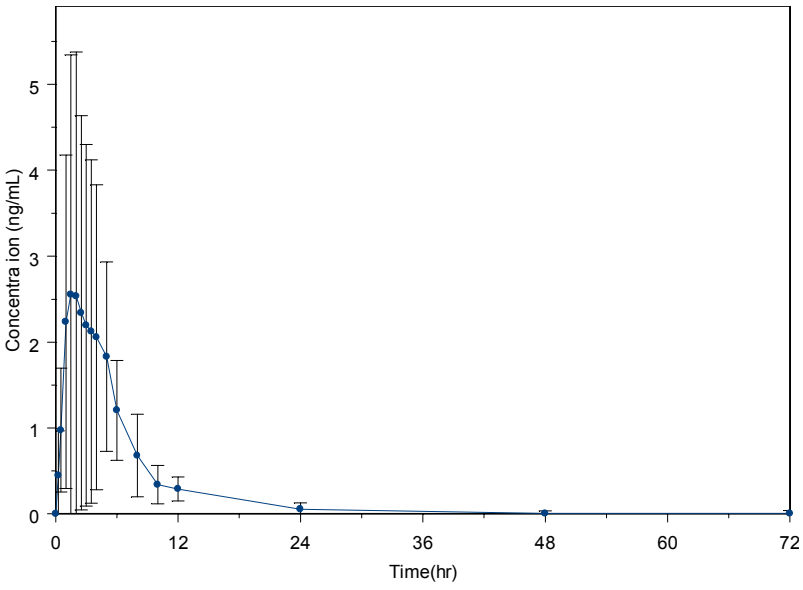
Yes, the sponsor's proposed doses of 75 mg and 100 mg appear to be reasonable based on dose-response relationship for both safety and efficacy that is supported by a phase II trial (IBS-2001) and two phase III trials (IBS-3001 and IBS-3002) in IBS-d patients.

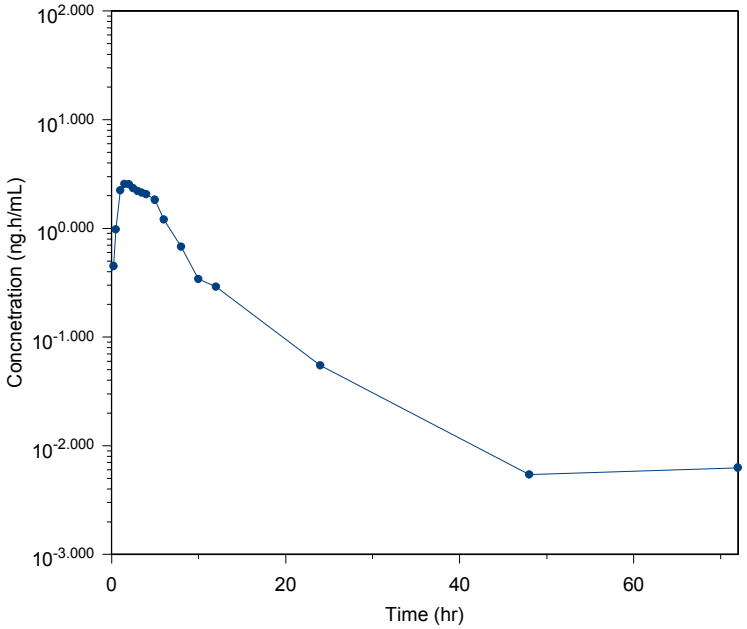
Phase II dose- ranging study had evaluated 5 mg, 25 mg, 100 mg, and 200 mg BID regimens and had shown that both 100 mg and 200 mg BID doses were efficacious compared to placebo while 5 mg and 25 mg BID regimens did not demonstrate efficacy. While 200 mg BID dosing did not enhance the efficacy of eluxadoline compared to 100 mg BID dosing, 200 mg BID dose was associated with slightly higher increased rate of treatment related AE, discontinuation rate, and GI related AE (most commonly reported AE). Therefore, 100 mg BID dose was carried into Phase III studies. To identify a potential lower effective dose, 75 mg BID dose was also included in the phase III studies. The phase III studies have shown that 75 mg and 100 mg BID doses have comparable efficacy and safety.

2.5. PK characteristics of drug

Following single dose administration of 100 mg eluxadoline, C_{max} was reached approximately at 2 hours with C_{max} of 2-4 ng/mL. It had dose-proportional increase in C_{max} and slightly less than dose proportional increase in AUC. Daily dosing does not result in accumulation. The plasma concentration of eluxadoline appears to decline in biphasic manner with mean terminal half-life of 3.7-6.0 hr. The apparent volume of distribution (Vz/F) ranged from approximately 36000 to over 58000 L. The apparent oral plasma clearance (CL/F) ranged from approximately 6400 to 8700 L/h, the renal clearance (CL_R) of eluxadoline ranged 6-12 L/h. In the mass balance study, about 0.12% and 82% of the administered radioactive dose was recovered in urine and feces, respectively. PK variability was high (51-98 %).

Figure 7: Mean (±SD) Plasma Concentration (ng/mL) Vs. Time Profiles after Single Oral Administration of 100 Mg Eluxadoline (CPS-1011)





2.5.1 What are the single dose and multiple dose PK parameters?

Single dose PK of 100 mg eluxadoline was characterized in multiple studies. PK parameters of 100 mg eluxadoline following single dose administration appear to be consistent across different studies. Multiple dose PK of 100 mg BID eluxadoline was evaluated only in one study (CPS1007) where single dose PK was not characterized in the same study to assess the potenail drug accumulation.

Table 9: Mean (%CV) Pharmacokinetic Parameters of 100 Mg Eluxadoline in Healthy Subjects Under Fasting Condition

Study #	C_{max} (ng/ml)	T_{max} (h)[a]	AUC_t (ng*h/ml)	AUC_{inf} (ng*h/ml)	$T_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)
Single Dose PK							

CPS1009 (n=28)	3.15 (78.7)	2.00 (0.50, 6.00)	16.95 (83.1)	19.91 (77.9)	4.47 (95.3)	7304.36 (63.0)	39025.65 (83.4)
CPS1005 (n=15)	4.13 (86.5)	2.00 (1.00, 6.00)	20.86 (63.7)	22.08 (79.2)	4.40 (136.8)	8752 (87.3)	36406 (85.4)
CPS1011 (n=29)	3.06 (92.2)	2.05 (0.25, 6.00)	16.47 (66.1)	17.95 (67.1)	3.67 (53.7)	7550.07 (54.2)	39318.01 (82.1)
CPS1008 (n=59)	3.03 (88.1)	3.00 (0.5-8.07)	21.91 (81.3)	23.54 (77.6)		6400.38 (63.2)	40605.9 (91.1)
CPS1006 (n=35)	2.33 (98.4)	2.08 (0.30, 8.05)	11.82 (86.6)	14.74 (75.6))			
*EDI1001 (n=6)	2.08 (53.7)	2.00 (0.25-6.00)	10.4 (59.8)				
Multiple dose PK on Day 7 following BID dosing							
CPS1007 (n=29)	3.02 (69.3)	2.00 (0.50 – 4.00)	22.34 (51.6)	25.29 (61.5)	6.00 (27.4)	7536.36 (56.2)	57715.92 (57.0)

[a] Median time to maximum concentration (range)

*Study EDI1001 had different formulation (suspension) and different bioanalytical method compared to rest of the studies in the table.

2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The PK parameters of eluxadoline and its variability are similar in IBS-d patients and healthy subjects.

Population PK analysis was conducted with data that was pooled from phase II dose-ranging study (IBS2001) in IBS-d patients population with sparse PK sampling and 2 phase I studies (EDI1001 and EDI1002) in healthy subjects with intensive PK sampling. A total of 410 subjects were included in population PK analysis. A two-compartment PK model with first order absorption and elimination was selected to describe the PK of eluxadoline. Please note that this population PK analysis report was not reviewed by pharmacometrics team as they determined that a review of this report is not necessary since this drug is considered to be primarily a locally acting drug, and thus, systemic exposure is not relevant for the efficacy. The following reported results are all based on the sponsor's analysis.

Table 10: Population PK Parameters

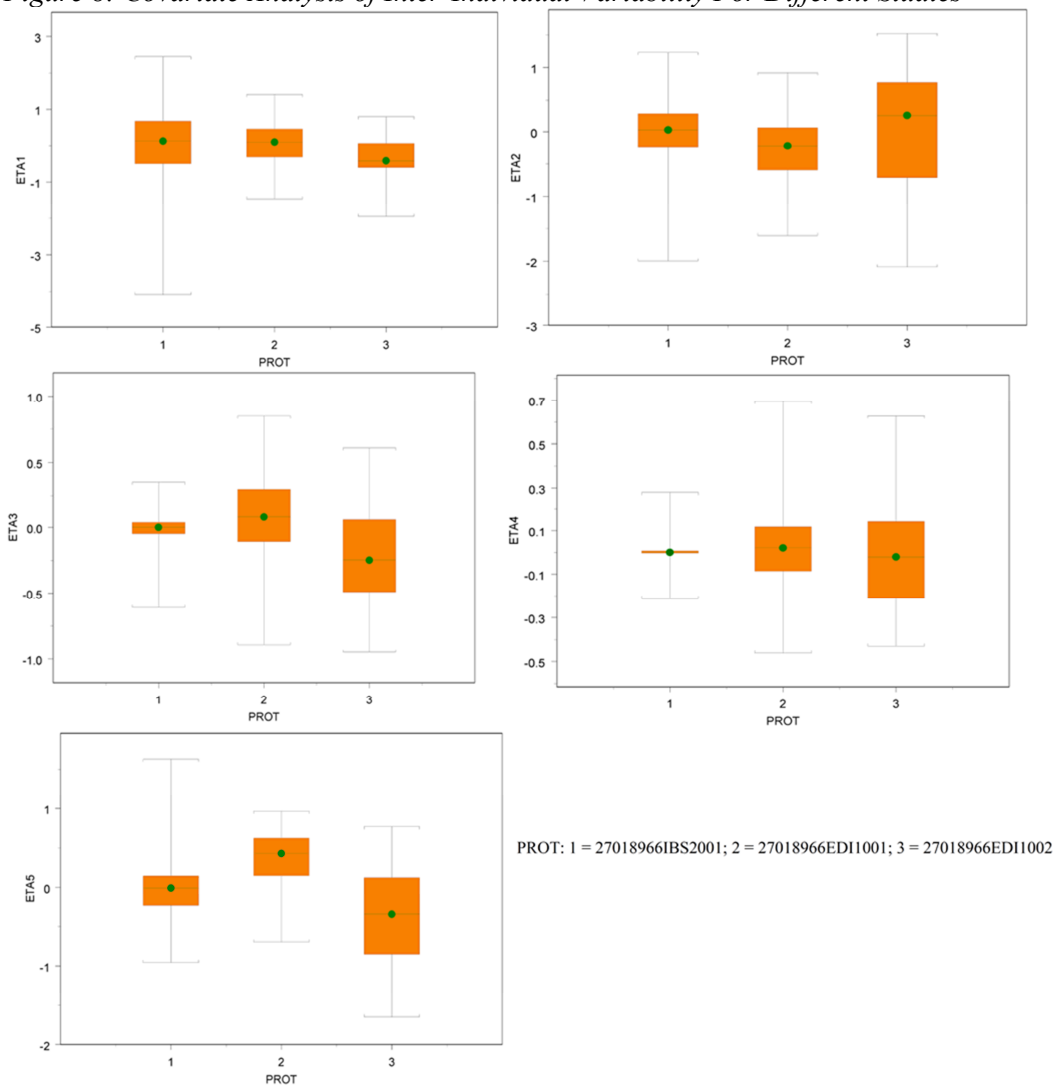
Parameters (Units)	Final Estimate	Bootstrap 95% CI		Between-individual Variability
		Lower	Upper	
CL/F (L/hr)	9030	8040	9910	96.8%
V/F (L)	27100	21400	36100	89.3%
K23 (1/hr)	0.264	0.223	0.345	59.2%
K32 (1/hr)	0.0331	0.0231	0.0395	47.9%
Ka (1/hr)	0.344	0.282	0.436	75.1%

The population PK parameters (pooled data from study IBS-2001, EDI1001 and EDI1002) that was obtained with data that consisted of both healthy subjects (n=88) and patients population (n=332) was not significantly different that the PK parameters that was obtained with only healthy subjects. The estimated CL/F in population PK was 9030 L/hr whereas the CL/F in healthy subjects was 6400-8750 L/h. In addition, variability of the PK parameters were comparable, 47-96% in population PK analysis and 54%-98% in healthy subjects.

In addition, in this population PK analysis, post-hoc AUC were estimated for patients with different OATP1B1 genotypes at different dose levels. The estimated post-hoc AUC for 100 mg dose for patients with normal OATP1B1 function was 9.88 ng.h/mL (CV of 89%) and for patients with intermediated OATP1B1 function was 19.89 ng.h/mL (CV of 152%), which were similar to the AUC observed in healthy subjects with 100 mg dose (ranging between 10.4-21.9 ng.h/mL).

Furthermore, a covariate analysis was conducted in population PK analysis with study ID where study IBS2001 only consisted of patient population and studies EDI1001 and EDI1002 consisted of only healthy subject. No major differences in PK parameters were observed between different studies to support that PK in patient population is similar to the PK in healthy subjects.

Figure 8: Covariate Analysis of Inter-Individual Variability For Different Studies



ETA1-ETA5 represents inter subject variability in CL/F, V/F, K23, K32, and Ka

PROT:

- 1= Study IBS2001 in IBS-d patient population (n= 332, with 4 samples per patients)
- 2 = Study EDI1001 in healthy subjects (n= 70, 12-21 blood samples per subjects)
- 3 = Study EDI1002 healthy subject (n= 18, 21 blood samples per subjects)

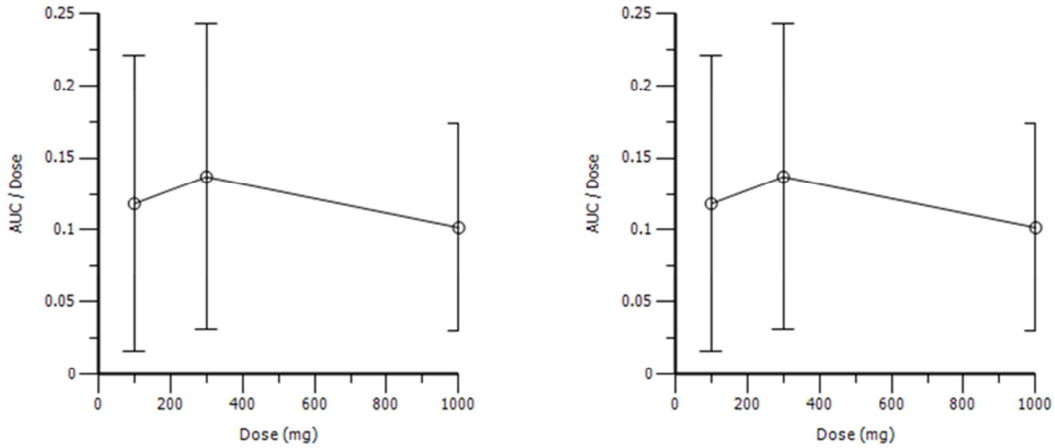
2.5.3 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

In healthy subjects, peak concentration (C_{max}) increased in dose-proportional manner and the total exposure (AUC) increased in slightly less than dose-proportional manner between 100 mg and 1000 mg dose where AUC of 1000 mg was approximately 7-8 fold higher than the AUC of 100 mg in healthy subjects (study CPS-1006 and CPS-1008 with cross-over study design).

Table 11: Mean (CV) Pharmacokinetic Parameters of Eluxadoline After Single Dose Administration In Healthy Subjects

Dose	Study CPS 1006 (n=35)			Study CPS-1008 (n=58)		
mg	C_{max} (ng/ml)	AUC_{0-t} (ng*h/ml)	AUC_{inf} (ng*h/ml)	C_{max} (ng/ml)	AUC_{0-t} (ng*h/ml)	AUC_{inf} (ng*h/ml)
100	2.33 (97.5)	11.82 (86.6)	14.74 (78)	3.03 (88.1)	21.94 (81.3)	23.54 (77.6)
300	7.64 (84.8)	41.11(77.2)	61.79 (50.5)			
1000	23.84 (74.4)	101.6 (70.4)	106.7 (59.9)	31.45 (66.9)	168.04 (54.3)	156.62 (64.2)

Figure 9: Dose Normalized AUC and C_{max} (SD) Of Eluxadoline Following Single Dose Administration vs. Dose in Healthy Subjects (CPS 1006)



Study EDI-1001 had also evaluated the single and multiple dose PK of various doses, 150 mg BID, 230 mg BID, 300 mg BID and 500 mg BID, of eluxadoline. Since this study had parallel group study in design, had too few subjects in each dose groups (n= 6) and used different formulation (suspension) than the proposed TBM formulation (tablet), this study was not used to assess the dose proportionality.

2.5.4 How do the PK parameters change with time following chronic dosing?

Following chronic dosing for 7 days, eluxadolien does not appear to have time-dependent PK.

Study EDI1001 had evaluated single dose and multiple doses PK of eluxadoline with suspension formulation. The evaluated multiple doses in this study includes 100 mg QD, 150 mg BID, 230 mg BID, 300 mg BID and 500 mg BID , but not the proposed dosing regimen of 100 mg BID. Nonetheless, accumulation potential of BID dosing regimen with higher dose (worse case) can be used to extrapolate to 100 mg BID dosing regimen. AUC_{12} on Day 7 seems to be similar to Day 1 where ratio of Day7/Day1 for AUC_{12} is around 1 for BID dosing regiment. However, C_{max} on Day 7 appears to be about 40% lower than the Day 1. The cause of the reduced C_{max} with multiple dosing is unknown. It is important to note that this study EDI1001 was conducted with different formulation (suspension) compared to TBM tablet formulation and had only 6 subjects per dose level to assess the accumulation potential.

Table 12: Mean (%CV) Pharmacokinetic Parameters of Eluxadoline After Single Dose And Multiple Dose Administration In Healthy Subjects (EDI1001)

Dose and Frequency	Day 1		Day 7		Ratio Day7/Day1	
	Cmax ng/mL Mean (CV%)	AUC12h ng.hr/mL Mean (CV%)	Cmax ng/mL Mean (CV%)	AUC12h ng.hr/mL Mean (CV%)	Cmax ng/mL Mean (CV%)	AUC12h ng.hr/mL Mean (CV%)
Part 2a: Males						
100 mg QD	2.46 (47%)	11.4 (41.7%)	1.35 (42.5%)	7.76 (39.8%)	0.606 (31%)	0.702 (26.9%)
150 mg BID	4.06 (52.2%)	14.7 (40.3%)	1.79 (29%)	10.8 (37.8%)	0.601 (69.3%)	0.815 (49.2%)
230 mg BID	6.80 (60.6%)	24.3 (48.1%)	3.28 (25.5%)	21.4 (30.5%)	0.571 (33.9%)	0.989 (39.1%)
300 mg BID	7.83 (35.6%)	24.8 (42.7%)	4.56 (37.9%)	25.9 (27%)	0.616 (41.1%)	1.12 (31%)
500 mg BID	7.12 (54.6%)	23.0 (32.3%)	3.84 (31.8%)	21.3 (27.7%)	0.605 (40.4%)	0.954 (23.8%)
Part 2b: Females						
150 mg BID	4.85 (71.1%)	16.5 (70.6%)	4.67 (95.8%)	24.9 (78.1%)	1.01 (42.5%)	1.51 (37.1%)

Multiple dose PK of 100 mg eluxadoline was evaluated on Day 7 in study CPS1007 where single dose PK was not characterized in the same study to assess the drug accumulation potential following multiple dosing. Based on cross-study comparison with Day 1 PK from other studies (table 10), there does not appear to be a significant drug accumulation for eluxadoline following chronic dose administration for both AUC and C_{max}.

In addition, the estimated CL/F in population PK (9030 L/hr) that was obtained with data after single and multiple dose administration appears to be comparable to the CL/F that was obtained after only single dose administration in healthy subjects (6400-8750 L/h) suggesting that there is no significant accumulation of eluxadoline following chronic dosing.

2.5.5 What is the variability of PK parameters of the drug and its relevant metabolites?

High variability of PK parameters of eluxadoline was observed with % CV of 51-98% for most of PK parameters in healthy subjects across studies, and it was similar after single dose administration and multiple dose administration. According to the population PK analysis, CV% for PK parameters ranged 48%-97% in IBS-d patients suggesting demonstrating similar degree of variability in healthy subjects.

Table 13: %CV PK Parameters of 100 mg Eluxadoline in Healthy Subjects

Study ID	Cmax	AUC_t	AUC_{inf}	CL/F
Single Dose PK				
CPS1009 (n=28)	78.7%	83.1%	77.9%	63.0%
CPS1005 (n=15)	86.5%	63.7%	79.2%	87.3%
CPS1011 (n=29)	92.2%	66.1%	67.1%	54.2%
CPS1008 (n=59)	88.1%	81.3%	77.6%	63.2%
CPS1006 (n=35)	98.4%	86.6%	75.6%	
*EDI1001 (n=6)	53.7%	59.8%		
Multiple dose PK on Day 7following BID dosing				
CPS1007 (n=29)	69.3%	51.6%	61.5%	56.2%

*Study EDI1001 had different formulation (suspension) and different bioanalytical method compared to rest of the

studies in the table.

Table 14: Inter-Individual Variability of PK Parameters of 100 mg Eluxadoline in Patients (based on population PK analysis)

Study #	CL/F	V2/F	K_{23}	K_{32}	K_a
IBS-2001	96.8%	89.3%	59.2%	47.9%	75.1%

2.5.6 Is there evidence for a circadian rhythm of the PK parameters?

Although the proposed dose is 100 mg BID, PK was only evaluated for morning dose, and but for the evening dose. Therefore, effect of circadian rhythm on PK parameters could not be assessed.

2.5.7 What are the ADME characteristics of the drug?

2.5.7.1 What are the characteristics of drug absorption?

Following single oral dose administration of eluxadoline, maximum concentration is reached approximately at median time of 2 hours (0.5-6 hr range) and C_{max} is 2-4 ng/mL. There appears to be double peaks in concentration-time profile in some subjects suggesting enterohepatic recirculation. Absolute bioavailability of eluxadoline was not evaluated as IV formulation was not developed for human use. In animal studies, the absolute bioavailability was estimated to be less than 0.2% in rats (study FK10138). Eluxadoline does not appear to be a good substrate for P-gp or BCRP.

2.5.7.2 What are the characteristics of drug distribution?

Eluxadoline is moderately bound to plasma protein (81%) and has negligible binding to red blood cells. The apparent volume of distribution of the terminal phase after administration of 100 mg eluxadoline ranged, on average, from approximately 36406 to 57715 L. In IBS-d patients, the apparent volume of distribution was estimated to be 27100 L based on population PK analysis. Inter- individual variability for V/F was high (89.3%).

The protein binding was evaluated by equilibrium dialysis at 37°C at concentration of 200 ng/mL and 2000 ng/mL in study KF6315 and at 10 µM (~5700 ng/ml) in study 04-RWJ.P01 in healthy human plasma. The eluxadoline is moderately bound to human plasma protein, and the binding was concentration independent between concentrations of 200-5700 ng/mL. The mean percent bound ±SD of eluxadoline to human plasma protein was 80.9 ±1.49 %, 81 ±1.79 %, and 82.2 ±0.54 % at 200, 2000, and 5700 ng/mL concentrations, respectively. However, the tested concentration of JNJ-27018966 (200 and 5700 ng/mL) is about 100-2000 fold higher than the expected therapeutic concentration in the human subject at the clinical dose of 100 mg where the observed C_{max} is approximately 2-4 ng/mL. Since dose linearity has been demonstrated in PK studies, plasma protein binding is unlikely to be different at lower concentration of 2-4 ng/mL. JNJ-27018966 did not bind to red blood cells at concentration of 10 µM in study 04-RWJ.P01.

2.5.7.3 What are the characteristics of *in-vitro* drug metabolism?

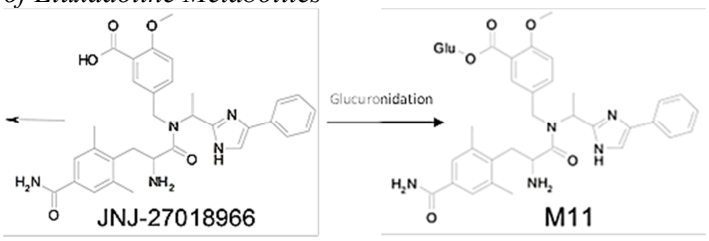
Based on the available in-vitro data (studies FK5826 and EDI1003), eluxadoline is not metabolized extensively where unchanged drug accounted for 97% of the drug-derived component and acyl glucuronides (M11) accounted for only 1% of the drug-derived component in human hepatocytes. However, test systems used to evaluate the in-vitro metabolism (human hepatocytes, microsomes and S9) 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. We recommend the sponsor to conduct further in-vitro studies to adequately characterize the

metabolism of eluxadoline in respect to various drug metabolizing enzymes as PMC. Depending on the results, further studies may be necessary. In the meanwhile, we will recommend avoiding concomitant use of strong CYP inhibitors with eluxadoline if possible; if not, monitor for adverse reactions related to eluxadoline when eluxadoline is concomitantly used with strong CYP inhibitors.

Study FK5826: Following 4 hours of incubation of 10 µM JNJ-27018966 in human pooled hepatocytes, JNJ-27018966 was not extensively metabolized in human hepatocytes. Unchanged drug accounts for majority (97%) of drug-derived component and metabolite M11 (acyl glucuronides) accounted for 1% of drug-derived component. The major metabolic pathway of JNJ-27018966 in human is direct glucuronidation of JNJ-27018966 to form acyl glucuronides. In this study, 10 µM diclofenac (CYP2C9 model substrate) was included as a positive control which only measures the CYP2C9 activity. Therefore, hepatocytes that were employed in this study were not adequately characterized in respect to all possible phase I and phase II enzymes prior to the study.

Study EDI1003: After incubation of JNJ27018966 in human microsome and S9 for up to 2 hours, only JNJ27018966 peak and no peaks for metabolites were identified in human microsome and S9. Sponsor states that midazolam was used as a positive control in S9, which only measures the CYP3A4 activity. No data was provided regarding performance of the positive control (midazolam) or the negative control. Therefore, both microsome and S9 were not adequately characterized with respect to phase I and II drug metabolizing enzymes or did not have proper positive controls during the study.

Figure 10: The Sponsor Proposed Metabolic Pathways for Eluxadoline and Chemical Structure of Eluxadoline Metabolites



Safety Analysis:
In the phase 2/3 studies, patient who concomitantly took strong CYP inhibitors with eluxadoline has higher % of patients with AEs (e.g., 97.3% vs. 52.6%) and SAEs (e.g., 17.3% vs. 3%) compared to subject who did not take strong CYP inhibitors. In addition, in patients who concomitantly took strong CYP inhibitors, patients in treatment arm with eluxadoline had higher % of patients with SEAs (e.g., 17.3% vs. 7.3%) compared to placebo group. However, theses safety data are difficult to interpret as it is not clear if these increase AE or SEAs are purely due to the increased systemic concentration of eluxadoline by strong CYP inhibitors.

Table 15: % of Patients with AEs or SAEs with Concomitant Use of Strong CYP Inhibitors

	Strong CYP inhibitors	75 mg	100 mg	Placebo
AEs	With	77.9 % (60/77)	97.3 % (73/75)	76.8% (63/82)
	Without	58.4 % (426/730)	52.6 % (503/957)	52.6% (470/893)
SAEs	With	13.0% (10/77)	17.3% (13/75)	7.3% (6/82)

	Without	3.4 % (25/730)	3.0% (29/957)	2.1% (19/893)

Strong CYP Inhibitor Compounds Taken Concomitantly Were: Bupropion, Ciprofloxacin, Clarithromycin, Fluconazole, Fluoxetine, Gemfibrozil, Itraconazole, Ketoconazole, Nefazodone, Paroxetine

2.5.7.4 What are the characteristics of drug excretion?

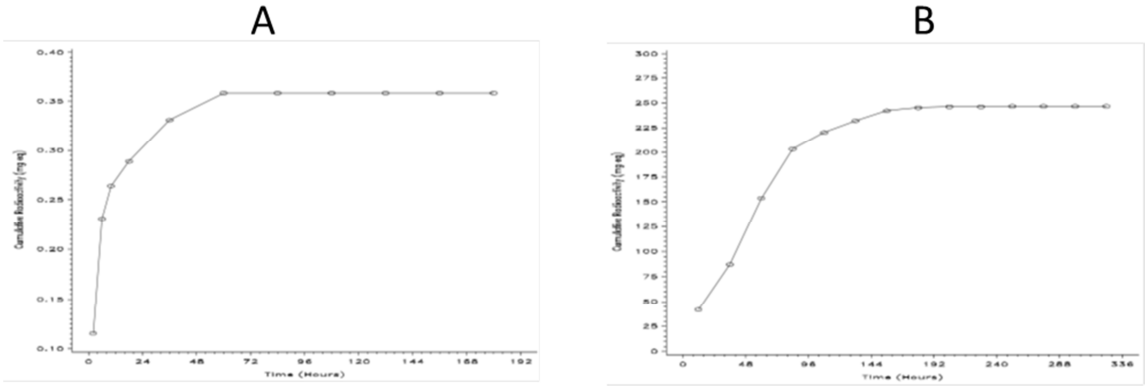
2.5.7.4.1 What are the results from the mass balance study?

Mass balance study was conducted in 8 healthy male subjects following single oral dose administration of 300 mg oral dose of 100 µCi [^{14}C] JNJ-27018966 (as capsule). Whole blood, plasma, urine, and fecal samples were collected through 168 hours after dosing and assessed for total radioactivity. Urine and fecal samples were collected until there was a combined radioactivity of less than 1% of the administered dose for 2 consecutive days.

On average, 0.12% of the administered dose was recovered from urine up to 192 hours post-dose and 82% was recovered from feces up to 336 hours post-dose. The percentage of radioactivity excreted as unchanged drug vs. metabolites in urine and feces was not assessed in this study.

Total radioactivity values from whole blood and plasma in all samples were BLQ. Therefore, the percentage of total radioactivity in plasma identified as unchanged parent drug and metabolites could not be assessed in this study either.

Figure 11: Cumulative Radioactivity in Urine (A) and Feces (B) vs. Time



2.5.7.4.2 What are the major metabolites in urine and/or plasma as presented (*In-vivo*)? Are they different from those measured *In-vitro*? If so, why?

Based on metabolic profiling of samples obtained from studies EDI1001 and EDI1003, no metabolite was detected in plasma and only one metabolite, acyl glucuronide (M11), was detected in urine. Metabolite found in urine was consistent with in-vitro data. However, due to low assay sensitivity in the bioanalytical methods used in the metabolic profiling studies, undetectable level of metabolites (e.g, acyl glucuronide, M11) in plasma does not rule out their possible presence in plasma at lower concentration compared to the parent drug.

Study EDI1001: Following oral administration of 1000 mg eluxadoline, unchanged drug accounted for all of detected drug-related compounds in pooled 0.25 to 8 hr plasma and was not detectable in pooled 12 to 48 hr plasma samples plasma. In the urine, unchanged drug accounted for 94% and 78% of total drug-derived materials in pooled 0 to 8, and 8 to 24 hr urine samples, respectively. The unchanged drug undergoes glucuronidation to form the acyl glucuronide M11,

which was undetectable in plasma samples but accounted for 6% and 22% of total drug-derived materials in pooled 0 to 8, and 8 to 24 hr urine samples, respectively. The bioanalytical method (LC/MS) employed in the metabolic profiling did not have good sensitivity where the LOQ values for potential metabolites of eluxadoline was estimated to be in between 1 to 5 ng/mL in the plasma or urine samples. Therefore, undetectable level of acyl glucuronide or other metabolites in plasma in metabolic profiling study does not rule out the possibility of their presence at lower concentration (<1 ng/mL) compared to parent drug JNJ-27018966 in plasma. Metabolic profiling was not assessed in fecal samples.

Table 16: In-Vivo Metabolism following 1000 mg Oral Dose of JNJ-27018966

Dose	1000mg			
Matrix	Plasma		Urine	
Time point (hr)	0.25-8	12-48	0-8	8-24
Compound				
JNJ-27018966 (UD)	100	ND	94	78
Acyl Glucuronide (M11)	ND	ND	6	22

Study EDI1003: Following oral administration of 300 mg eluxadoline, only small peak for eluxadoline was identified in plasma and urine samples and no predicted metabolites were detected in both plasma and urine samples. Most of signals for JNJ27018966 in human plasma and urine were at or just above the detection limits of the bioanalytical method (LC/MS/MS) employed in this metabolic profiling (the estimated LOQ of eluxadoline and metabolites were 10 ng/mL in metabolic profiling and C_{max} of 300 mg eluxadoline was 13.86 ng/mL). Therefore, any metabolites in the samples that are present at lower concentration (< 10 ng/mL) would not be detectable. Hence, presence of metabolites at lower concentrations relative to the concentration of parent drug eluxadoline in plasma or urine cannot be completely ruled out. Fecal samples were not analyzed for metabolic profiling.

2.5.7.4.3 What is the major route of elimination?

Based on the mass balance study, only 0.12% of the drug was excreted in the urine and 82% of the drug was recovered in feces. However, since absolute bioavailability of oral eluxadoline is unknown, contribution of renal clearance vs. hepatobiliary clearance cannot be estimated for the systemically absorbed drug.

2.5.7.4.4 What are the characteristics of drug excretion in urine?

The percent of drug recovered in urine as unchanged drug is less than 0.17% and the total amount of drug excreted in urine (based on mass balance study) was 0.12%. The renal clearance is estimated to be approximately 6.97 L/h (study CPS-1011 has the highest number of subjects, n= 29, at proposed dose of 100 mg with the proposed TMB tablet formulation)

Table 17: Mean (CV) Urine PK Parameters of Unchanged Parent Drug Eluxadoline in Healthy Subjects

Study ID	Formulation	Urine collection	Dose	N	%Fe	CLr (L/h)
EDI1001	Suspension	Up to 24 hr	30 mg	6	0.081 (64.87)	12.08 (97.01)
			100 mg	6	0.129 (72.38)	11.45 (27.75)
			300 mg	6	0.099 (23.84)	9.93 (40.2)
			1000 mg	12	0.062 (34.97)	10.14 (28.13)
			1500 mg	5	0.045 (7.17)	7.93 (21.91)
			2000 mg	5	0.044 (25.17)	8.89 (29.04)
EDI1003	^{14}C-Capsule	Up to 168 hr	300 mg	8	0.17 (69)	6.42 (18)
CPS-1011	Tablet (TBM)	UP to 72 hr	100 mg	29	0.12 (51.6)	6.97 (19.6)

%Fe = Fraction recovered as unchanged drug in urine

Based on *in-vitro* studies, eluxadoline is not a substrate for OCT1, OCT2, OAT1, but is a substrate for OAT3 and MRP2. Coadministration of probenecid (OAT3 and MRP2 inhibitors) reduced the renal clearance of eluxadoline almost by 50%, but overall exposure was only increased by 30% (study CPS 1011) suggesting that although OAT3 and MRP2 play a role in renal clearance of eluxadoline via renal secretion (OAT3-mediated basolateral uptake and MRP2-mediated efflux at the apical renal tubular epithelium), their role in overall clearance of eluxadoline is not major.

2.5.7.4.5 Is there evidence for excretion of parent drug and/or metabolites into bile?

There are no human data to assess the potential excretion of eluxadoline into bile. Biliary excretion of eluxadoline was observed in animals. In a bile cannulation study in rats (FK6432), an average of 1.70% of the dose was recovered from the bile of male SPF Sprague-Dawley rats collected during the 48-hours following oral dosing with ^{14}C-JNJ-27018966. In addition, following oral and subcutaneous administration of ^{14}C-eluxadoline to rats (FK5756), 97 % [PO] and 90 % [SC] of radioactive dose was excreted in feces, whereas only 0.5% [PO] and 7.3% [SC] of radioactive dose was excreted in urine suggesting that biliary route play important role in elimination of eluxadoline in rats.

It appears that transporter plays a role in hepato-billiary excretion of eluxadoline in human. *In-vitro* data suggest that eluxadoline is a substrate for OATP1B1 (expressed at sinusoidal [basolateral] membrane of liver hepatocytes), MRP2 and BSEP (both expressed at apical membrane of liver hepatocytes) with potential mechanism of OATP1B1 mediated basolateral uptake and MRP2 and BSEP mediated efflux of eluxadoline into bile. A follow-up *in-vivo* study confirmed that OATP1B1 (may be MRP2) plays a role in disposition of eluxadoline where exposure of eluxadoline was increased by 4-6-fold when it was coadministered with cyclosporine, an inhibitor of OATP1B1 and MRP2 (cyclosporine is also an inhibitor of P-g, BCRP and OATP1B3. But, there is no evidence that eluxadoline is good substrate for these transporters.). However, follow up *in-vivo* studies were not conducted to evaluate the clinical relevance of BSEP.

2.5.7.4.6 Is there evidence for enterohepatic recirculation for parent and/or metabolites?

Based on the individual plasma concentration profile, about 70% of the individuals displayed second peak in eluxadoline plasma concentration time profile suggesting possible enterohepatic recirculation via biliary excretion.

2.6 Intrinsic Factors

2.6.1 What intrinsic factors influence exposure (PK of parent and/or relevant metabolites) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.6.2 Based upon what is known about E-R relationships with respect to their variability and the groups studied (healthy volunteers vs. patients vs. specific populations), what dose adjustments, if any, are recommended for each of these groups? If dose adjustments are not based upon E-R relationships, describe the alternative basis for the recommendation.

- The effect of hepatic impairment on the systemic exposure was evaluated in a dedicated PK study.

- Effect of age, gender, race, weight (WT), body mass index (BMI), renal (creatinine clearance, CRCL) and hepatic (alanine amino transferease (ALT), aspartate amino transferease (AST), bilirubin (BIL), albumin (ALB)) conditions were evaluated in population PK analysis as covariates. Based on sponsor's analysis, none of these covariates were found to affect PK parameters of eluxadoline in the population PK analysis. Please refer to section 2.5.2 for detailed discussion of the population PK analysis.

- Eluxadoline PK data associated with 100-mg oral dose administration in healthy volunteers under fasting condition across phase 1 studies (CPS1005, CPS1008, CPS1009, and CPS1011) were pooled and analyzed for differences based on intrinsic factors of gender, age, race and BMI. No meaningful differences in the PK parameters among any of these intrinsic factors were observed.

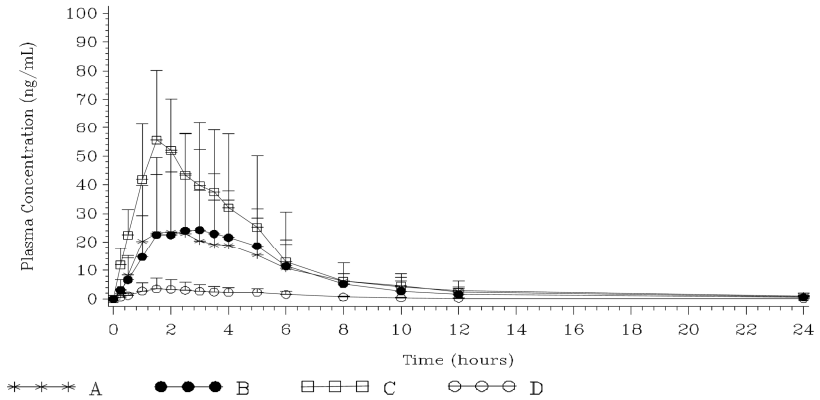
  Gender: Based on population PK analysis, gender was not identified as a covariate, and thus does not affect eluxadoline PK. In meta-analysis of 100 mg single oral dose PK data in healthy subjects pooled across phase 1 studies, eluxadoline exposure (both AUC and C_{max}) in female appear to be approximately 35% higher than the exposure in male. No dose adjustment is needed based on gender.

	Female (n=47)	Male (n=84)
AUC_{0-t} (ng*hr/mL)	23.73 (85.0)	17.2 (65.2)
C_{max} (ng/mL)	3.80 (90.1)	2.85 (80.0)

  Pediatric: No studies were conducted in pediatric patients. The sponsor requested a waiver for <6 years of age and deferral ≥6 years to 17 and 11 months of age.

  Hepatic impairment
  Following single oral dose administration of 100 mg eluxadoline under fasting conditions (study CPS-1005), the exposure of eluxadoline in subjects with hepatic impairment are significantly higher than the exposure in subjects with normal hepatic function. Subjects with mild hepatic impairment (Child-Pugh Class A) had about 6-fold higher, subjects with moderate hepatic impairment (Child-Pugh Class B) had 4-fold higher exposure (both AUC and C_{max}) compared to the subjects with normal hepatic function. Subjects with severe hepatic impairment (Child-Pugh Class C) had 16- and 19-fold higher AUC and C_{max}, respectively, compared to subjects with normal hepatic function. The sponsor proposed to contraindicated eluxadoline in patients with hepatic impairment due to cirrhosis. However, due to the difference in the degree of change in exposure, we propose to only contraindicate eluxadoline in patient with severe hepatic impairment (Child-Pugh Class C), and avoid the use of eluxadoline in patients with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment if possible. If it is not possible to avoid the use of eluxadoline in patients with mild and moderate hepatic impairment, monitor those patients for adverse reactions related to eluxadoline.

  Figure 12: Mean (±SD) Plasma Concentrations of Single Dose of 100 mg Eluxadoline Versus Time by Cohort in Subjects with Varying Degree of Hepatic Impairment



Cohort A = Mild hepatic impairment (Child-Pugh Class A).
Cohort B = Moderate hepatic impairment (Child-Pugh Class B).
Cohort C = Severe hepatic impairment (Child-Pugh Class C).
Cohort D = Normal hepatic function.

Table 18: Mean (CV) Plasma PK Parameters of 100mg Eluxadoline in Subjects with Varying Degree of Hepatic Impairment

Parameter (unit)	Mild Hepatic Impairment (N=6)	Moderate Hepatic Impairment (N=6)	Severe Hepatic Impairment (N=3)	Normal Hepatic Function (N=15)
AUC_{0-t} (ng•h/mL)	187.47 (103.5)	166.16 (132.6)	286.53 (42.8)	20.86 (63.7)
C_{max} (ng/mL)	27.56 (74.9)	29.88 (126.0)	58.83 (32.5)	4.13 (86.5)
T_{max} (h)[a]	2.25 (1.00, 5.00)	1.25 (0.50, 5.00)	1.50 (1.50, 2.50)	2.00 (1.00, 6.00)
	(N=4)	**(N=4)**	**(N=1)**	**(N=9)**
AUC_{0-inf} (ng•h/mL)[b]	268.12 (73.0)	104.82 (73.5)	237.22 (.)	22.08 (79.2)
$t_{1/2}$ (h)[b]	14.44 (48.4)	21.78 (50.8)	5.87 (.)	4.40 (136.8)
CL/F (L/h)[b]	490 (44.8)	1889 (101.1)	422 (.)	8752 (87.3)
V/F (L)[b]	10745 (75.4)	54851 (121.0)	3570 (.)	36406 (85.4)

Abbreviation: CV, coefficient of variation.
[a] For T_{max}, the median (minimum, maximum) values are presented.
[b] Terminal half-life and related parameters were not reportable for all subjects.

Table 19: Statistical Analysis of PK Parameters for 100 mg Eluxadoline in Subjects with Varying Degree of Hepatic Impairment

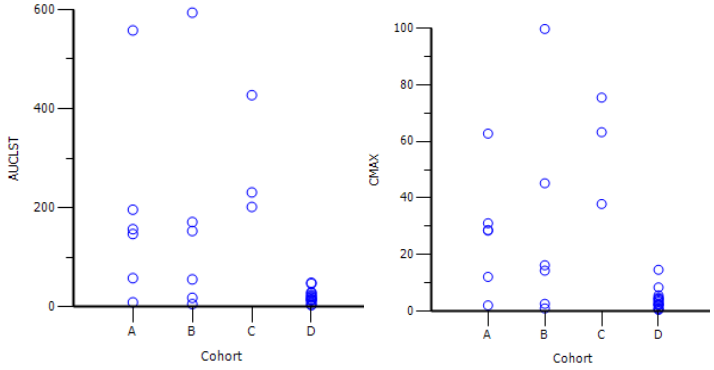
Parameter (unit)	Cohort[a]	N	Geometric LS Means	Cohort Comparison	Ratio of Geometric LS Means	90% CI of the Ratio
AUC_{0-t} (ng•h/mL)	A	6	105.122	A/D	6.250	(2.517, 15.520)
	B	6	66.859	B/D	3.975	(1.601, 9.871)
	C	3	270.925	C/D	16.109	(4.897, 52.992)
	D	15	16.819	–	–	–
C_{max} (ng/mL)	A	6	18.632	A/D	6.174	(2.479, 15.376)
	B	6	12.018	B/D	3.982	(1.599, 9.918)
	C	3	56.525	C/D	18.729	(5.670, 61.861)
	D	15	3.018	–	–	–

Cohort A = Mild hepatic impairment (Child-Pugh Class A).
Cohort B = Moderate hepatic impairment (Child-Pugh Class B).
Cohort C = Severe hepatic impairment (Child-Pugh Class C).
Cohort D = Normal hepatic function.

Two SAEs were reported; one subject in moderate hepatic impairment (subject 5010001) reported acute MI and coronary artery disease13 days after single-dose administration of 100 mg

eluxadoline, and this event was not considered to be related to the drug due to lack of temporal relationship to study drug administration; one subject in severe haptic impairment (subject 5030004) reported ileus 4 days after a single-dose administration of 100 mg eluxadoline, and this event was considered to be related to the study drug. These two subjects with SAEs had similar demographic compared to rest of the subjects but were on many of concomitant medications compared to other subjects in those cohorts.

Figure 13: Individual AUC and C_{max} of 100 mg Eluxadoline in Subjects with Varying Degree of Hepatic Impairment



The two subjects, subject 5010002 in mild hepatic impairment (cohort A) and subject 5010004 in moderate hepatic impairment (cohort B), had very high exposure compared to rest of the subjects in those cohorts. These two subjects seems to have comparable demographic compared to rest of subjects in those cohorts However, both subjects were taking many concomitant medications, some of which were weak-moderate CYP inhibitors compared to other subjects, which may have contributed to the elevated level of eluxadoline systemic exposure. In addition, the subject 5010002 in mild hepatic impairment cohort had no encephalopathy, no ascites, and had normal level of albumin, bilirubin, and prothrombin time. Subjects 5010004 in moderate hepatic impairment cohort had encephalopathy, slight ascites, elevated level of bilirubin, slightly lower level of albumin, and high prothrombin time. Overall, the individual parameters in hepatic impairment do not appear to explain the high exposure seen in these two subjects in mild and moderate hepatic impairment cohorts.

Renal impairment

A dedicated renal impairment (RI) study was not conducted in this submission. Although creatinine clearance was not found to be a covariate in population PK analysis, most of the subjects in this analysis had creatinine clearance in range of 60-200 mL/min which corresponds to mild renal impairment and normal renal function. Therefore, it does not assess the effect of moderate and severe renal impairment in exposure of eluxadoline. Phase 3 studies had excluded patients with unstable renal conditions. In the phase 3 studies, the % of patients with AEs were comparable between the patients with mild renal impairment and the overall population. In addition, in patients with mild renal impairment, the % of patients with AEs were comparable for subject who were treated with 75 mg or 100 mg eluxadoline vs. placebo. However, there is not adequate number of subjects with moderate renal impairment to draw any conclusion (n=6). Therefore, a renal impairment study will be required as a post-marketing study.

Table 20: % of Patients with AEs by Renal Functions

	75 mg	100 mg	Placebo

Overall Population	60.2% (486/807)	55.7% (575/1032)	54.7% (533/975)
Mild RI	61.5% (59/96)	55.5% (66/119)	56.1% (74/132)
Moderate RI	66.7% (4/6)	50.0% (3/6)	75.0% (9/12)

Genetics:
Since *in-vitro* and clinical drug interaction studies indicated that eluxadoline is transported by SLCO1B1 (OATP1B1), genotyping was performed in a phase 2 dose-ranging study (IBS2001) in order to investigate the effect of SLCO1B1 variation on the exposure of eluxadoline. This study report was reviewed by Dr. Jeffrey Kraft, Ph.D. in Genomics and Targeted Therapy Group (GTTG). Analyses by the sponsor seem to indicate that there is a relationship between increasing exposure of eluxadoline and decreasing OATP1B1 transporter function. However, extrapolation of this relationship and its clinical significance is complicated by very low numbers of poor transporters (n=5) with exposure data, very large inter-subject variability (CV of 50%-300%) in AUC (post-hoc AUC based on population PK analysis and sparse sampling), and inconsistencies in the relationship between dose groups.

*Table 21: Post Hoc AUC (ng/mL*h) Results by SLCO1B1 Haplotype and Dose*

Dose	***SLCO1B1 Function***	***N***	***Mean***	***Std. Deviation***	***CV%***
5 mg	Normal	12	4.01	6.05	150.6
	Intermediate	9	1.87	0.98	52.5
	Poor	1	2.82	---	---
25 mg	Normal	64	6.07	18.22	300.1
	Intermediate	24	4.07	2.06	50.6
	Poor	1	9.10	---	---
100 mg	Normal	66	9.88	8.79	89.1
	Intermediate	19	16.36	24.87	152.0
	Poor	2	19.89	1.02	5.2
200 mg	Normal	50	22.09	28.44	128.7
	Intermediate	17	23.95	19.68	82.2
	Poor	1	33.28	---	---

Source: IBS-2001 Study Report 8, Page 2, Table 1

2.6.2.1 What pregnancy and lactation use information is there in the application?

PK was not evaluated in pregnant or lactating females. No clinical studies were performed to determine if eluxadoline is excreted into human milk. However, eluxadoline was secreted in the milk of lactating rats in dose-dependent manner.

2.7 Extrinsic Factors

2.7.1 What extrinsic factors (*drugs, herbal products, diet, smoking, and alcohol use*) influence exposure (PK of parent and/or relevant metabolites) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?

Coadministration of single oral dose of 500 mg probenecid with single oral dose of 100 mg eluxadoline increased both AUC and C_{max} of eluxadoline by 30%. Coadministration of single oral dose of 600 mg cyclosporine with single oral dose of 100 mg eluxadoline increased the AUC of eluxadoline by 4.4-fold and C_{max} by 6.2-fold. Coadministration of eluxadoline with oral contraceptive Brevicon (norethindrone and ethinyl estradiol) do not significantly affect each

other's exposure. Coadministration of rosuvastatin with eluxadoline increased rosuvastatin AUC by approximately 40% and C_{max} by 18% compared to when rosuvastatin was administered alone.

There were no specific studies or analyses designed to evaluate the effects of factors such as herbal products, diet (other than high-fat meal), smoking or alcohol use on the PK of eluxadoline. The effect of a high fat meal is discussed in Section 2.8.6.

2.7.2 Drug-Drug Interactions

2.7.2.1 Is there an i*n-vitro* basis to suspect *In-vivo* drug-drug interactions?

Yes, based on *in-vitro* studies, eluxadoline is a mechanism based inhibitor of CYP3A4, a substrate for OAT3, OATP1B1, BSEP and MRP2 and a weak inhibitor of OATP1B. The sponsor had conducted *in-vivo* follow-up drug-drug interaction studies with cyclosporine (an inhibitor of many transporters including OATP1B1 and MRP2) and probenecid (MRP2 and OAT3 inhibitor), rosuvastatin (OATP1B1 substrate) to assess the clinical relevance of eluxadoline's interaction with OAT3, OATP1B1 and MRP2 as a substrate and with OATP1B1 as an inhibitor. However, the sponsor did not evaluate the clinical relevance of eluxadoline's potential of being CYP3A4 mechanism based inhibitor or its interaction with BSEP.

2.7.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Metabolism of eluxadoline is not clearly established. Therefore, it is unknown that if eluxadoline is substrate for CYP enzymes. Based on the *in-vitro* study in hepatocytes that is not validated with regard to various phase I and II enzymes, acyl glucuronides (M11) accounted for 1% of the drug-derived component. However no further studies were conducted to identify which UTG is involved in metabolism. Nonetheless, it is important to note that UGT1A1 which can possibility be responsible for production of acyl glucuronides (M11) is a polymorphic enzyme.

2.7.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes? Were relevant metabolites evaluated for inhibitor or induction potential, *in-vitro*?

Eluxadoline up to 100 μM does not inhibit CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, and 3A4 in human liver microsomes via reversible inhibition ($IC_{50} \geq 100$ μM). In-vivo drug interactions via reversible inhibition of CYP2E1 at the clinical dose of 100 mg eluxadoline (C_{max}=3 ng/mL ≈ 0.0053 μM) is unlikely based on very weak inhibition of CYP2E1 in an in-vitro study (IC_{50}= 20 μM). Eluxadoline has potential to inhibit CYP3A4 via mechanism-based inhibition and further in-vitro studies are recommended to predict the in-vivo relevance of this interaction. In addition, potential of eluxadoline to inhibit CYP2C8 was not evaluated in in-vitro studies.
Eluxadoline does not induce CYP1A2, CY2C9, CYP2C19 and CY3A4/5 enzyme in cryopreserved human hepatocytes at concentration up to 10 μM (5.7 μg/mL), which is much higher than the anticipated C_{max} at the clinical dose of eluxadoline 100 mg (C_{max} ≈ 3 ng/mL). The sponsor did not evaluate the potential of eluxadoline to induce CYP2B6 in in-vitro studies.

Induction (Study FK5731):
Cryopreserved human hepatocytes (3 donors) were incubated with 0.4, 2 and 10 μM of JNJ-27018966 or positive control inducers (β-napthoflavone for CYP1A2 and rifampicin for CYP2C9, 2C19 and 3A4) for 48 hours at 37°C in triplicates. Negative controls were incubated with vehicle (0.1% DMSO). The exposure medium was refreshed every 24 hours. At the end of the induction period, the activity of target enzyme CYP1A2, CYP2C9, CYP2C19 and CYP3A4 was assessed by incubating the hepatocytes with model probe substrates (phenacetin for CYP1A2, tolbutamide for CYP2C9, S-mephenytoin for CYP2C19, and testosterone for CYP3A4) for each target enzymes and measuring the appearance rate of their respective metabolites.

Increases in enzyme activity that were ≥40% of the respective positive control(s) were considered to be a significant induction. JNJ-27018966 does not induce CYP12, 2C19, 2C9 and 3A4 as the percent of change in target enzyme activities are not greater than 40% of the positive control with known inducer.

Table 22: Induction of Cytochrome P450 Enzymatic Activities in Cryo-preserved Human Hepatocytes after 48-hours of Treatment

Treatments	1A2	2C19	2C9	3A4
Rifampicin 10 μM (fold increase,[a] n=3 donors)	ND	2.2 – 3.9	1.7 – 2.4	1.9 – 6.2
β–Naphthoflavone 50 μM (fold increase,[a] n=3 donors)	8 - 18	ND	ND	ND
JNJ-27018966 0.4 μM (% of positive control[b])	-1.47 ± 2.35	8.08 ± 21.5	3.38 ± 33.9	-8.10 ± 18.7
JNJ-27018966 2 μM (% of positive control[b])	-0.48 ± 2.51	26.0 ± 28.2	11.5 ± 33.3	-6.72 ± 18.7
JNJ--27018966 10 μM (% of positive control[b])	-0.21 ± 1.85	17.9 ± 21.5	14.9 ± 35.5	-9.29 ± 22.9
Additional Information				
[a] Range of fold-increase over vehicle-treated samples in cells from three different donors [b] Induction expressed as the mean of % relative to positive control from three different donors ND = not done				

Inhibition (StudyFK5873):

Reversible Inhibition: Pooled human liver microsomal suspension was incubated with JNJ-27018966 (1, 10 and 100 μM) and the corresponding selective model substrates in duplicated at 37°C in the presence of NADPH for 15 minutes (5 minutes for midazolam). No pre-incubation was carried out to assess the time-dependent inhibition. Known inhibitors as positive controls for each isoform were also incubated at three serially diluted concentrations in duplicate.

Table 23: Percent Inhibition of the CYP Isoforms Following Incubation with 100 μM JNJ-27018966 and Estimated IC_{50} Values for JNJ-27018966 and Positive Controls

CYP	Substrate	% Inhibition	Est. IC_{50} (μM)	C_{max}/IC_{50}	I_{gut}/IC_{50}	Positive Control	Est. IC_{50} (μM)
1A2	30 μM Phenacetin	14	> 100	<0.000054	<7	α-Naphthoflavone	0.007
2A6	3 μM Coumarin	30	> 100	<0.000054	<7	Tranylcypromine	0.50
2B6	50 μM Bupropion	3	> 100	<0.000054	<7	Ticlopidine	0.13
2C9	100 μM Tolbutamide	26	> 100	<0.000054	<7	Sulphaphenazole	0.095
2C9	5 μM Diclofenac	14	> 100	<0.000054	<7	Sulphaphenazole	0.095
2C19	20 μM S-Mephenytoin	49	100	=0.000054	=7	Tranylcypromine	2.5
2D6	15 μM +/- Bufuraloll	48	100	=0.000054	=7	Quinidine	0.040
2E1	30 μM Chlorzoxazone	81	20	=0.00026	=35	4-Methylpyrazole	2.6
3A4	15 μM Testosterone	47	100	=0.000054	=7	Ketoconazole	0.021
3A4	2 μM Midazolam	48	100	=0.000054	=7	Ketoconazole	0.021

C_{max} at the clinical dose of 100 mg eluxadoline was 3 ng/mL ≈ 5.4 nM
I_{gut} = 100 mg dose/250 mL = 400 ug/mL= 700 μM

JNJ-27018966 only showed weak inhibition (reversible) toward CYP2E1 with estimated IC_{50} values of 20 μM. However, since C_{max}/IC_{50} = 4.4 nM/20000 nM <0.1, *in-vivo* relevance of this interaction is unlikely. Although I_{gut}/IC_{50} =35>10 for CYP2E1, there is no strong evidence that CYP2E1 present in intestine at significant level. Therefore, potential of eluxadoline to inhibit CYP2E1 in the gut does not raise a concern. JNJ-27018966 did not inhibit any other evaluated CYP enzymes up to 100 μM concentration.

Time-Dependent Inhibition (TDI): The human liver microsomal suspension were pre-incubated with JNJ-27018966 at 5 and 50 μM concentrations and CYP-specific positive controls separately with and without NADPH in duplicate as the primary incubations for 60 minutes. 15 μL of aliquots of primary incubation solution were then transferred to a 300 μL secondary incubation mixture (20-fold dilution) that contains one of the CYP-specific probe substrates, and the reaction

was initiated by the addition of NADPH and were incubated for 15 minutes (5 minutes for midazolam). All incubations were conducted at 37 °C.

Table 24: Percent Residual CYP-specific Activity Following Pre-Incubation of Human Liver Microsomes with JNJ-27018966 and Positive Controls, with and without NADPH Regenerating System (Blank pre-incubate = 100%)

		JNJ-27018966			Positive Control [a]		
CYP (Probe Substrate)		Blank	5 µM	50 µM	Blank	Low	High
1A2 (Phenacetin)	+ NRS	100	87	87	100	22	20
	- NRS	100	97	98	100	101	93
2C9 (Tolbutamide)	+ NRS	100	101	94	100	32	22
	- NRS	100	88	100	100	70	43
2C19 (Mephenytoin)	+ NRS	100	87	88	100	52	34
	- NRS	100	90	93	100	88	46
2D6 (Bufuralol)	+ NRS	100	92	92	100	24	17
	- NRS	100	99	96	100	89	64
3A4 (Testosterone)	+ NRS	100	93	68	100	22	5
	- NRS	100	98	99	100	94	89
3A4 (Midazolam)	+ NRS	100	89	58	100	23	9
	- NRS	100	101	105	100	120	117

[a] – Positive Controls and Low and High Concentrations: CYP1A2 – Furafylline (2 and 20 µM), CYP2C9 – Tienilic Acid (2 and 20 µM) CYP2C19 – Ticlopidine (2 and 20 µM), CYP2D6 – Paroxetine (2 and 20 µM) CYP3A4 – Mifepristone (0.5 and 5 µM)
NRS – NADPH Regenerating System

With pre-incubation for 60 minutes, JNJ-27018966 inhibited CYP3A4 activity in a concentration dependent and NADPH-dependent manner suggesting potential for mechanism-based inhibition of CYP3A4 by JNJ-27018966. At 50 µM, 30-40% of CYP3A4 activity was inhibited while about 10% of the activity was inhibited at 5 µM. JNJ-27018966 up to 50 µM concentration did not show significant mechanism based inhibition toward any other evaluated CYP enzymes, CYP1A2, 2C9, 2C19, and 2D6.

Although JNJ-27018966 has potential for mechanism based inhibition toward CYP3A4, the sponsor did not assess the *in-vivo* relevance of this interaction by assessing R_2 value nor had followed up with an *in-vivo* study. The sponsor confirmed that they did not estimate the R_2 value as *in-vitro* testing to compute K_i and K_{inact} was not performed.

TDI, $R_2 = (K_{obs}+K_{deg})/K_{deg}$ and $K_{obs}=k_{inact}X[I]/(K_I+[I])$

> Where K_{deg} is the apparent first order degradation rate constant of the affected enzyme; k_{inact} and K_I are maximal inactivation rate constant and apparent inactivation constant, respectively; K_{obs} is the apparent inactivation rate constant.

Although the systemic concentration of eluxadoline is relative low, the concentration of eluxadoline in the gut, which has expression of CYP3A4, can be very high. With rough estimation of IC_{50} value of 50 µM based on TDI and I_{gut} of 700 uM, I_{gut}/IC_{50} = 14 >10, potential inhibition of gut CYP3A4 by eluxadoline cannot be ruled out. Therefore, we recommend the sponsor to follow up with further *in-vitro* studies to estimate the R_2 (by estimating K_{inact} and K_I) value to assess the *in-vivo* relevance of this mechanism based inhibitory interaction with CYP3A4, and may be a subsequence *in-vivo* study with sensitive CYP3A4 substrate if suggested

by *in-vitro* data. In the meantime until further data become available, the label will state "monitor the systemic level of narrow therapeutic index drugs that are CYP3A4 substrates when a concomitant use with eluxadoline is initiated or discontinued*"*.

Safety Analysis: In the phase 2/3 studies, patient who concomitantly took sensitive CYP3A substrate and/or CYP3A substrates with narrow therapeutic index with eluxadoline had higher % of patients with AEs (e.g., 81.2% vs. 53.5%) and SAEs (e.g., 15.3 % vs. 3.1%) compared to subjects who did not take those drugs. In addition, in patients who concomitantly took sensitive CYP3A substrate and/or CYP3A substrates with narrow therapeutic index, patients in treatment arm with eluxadoline had higher % of patients with SEAs (e.g., 15.3% vs. 6.8%) compared to placebo group. However, theses safety data are difficult to interpret as it is not clear if these increase AE or SEAs are purely due to the increased systemic concentration of CYP substrates by inhibition of CYP enzymes by eluxadoline.

Table 25: % of Patients with AEs or SAEs with Concomitant Use of Sensitive CYP3A substrates or CYP3A substrates with narrow therapeutic index drugs

	Sensitive CYP 3A4 substrate and /or NTI	75 mg	100 mg	Placebo
AEs	With	65.3% (47/72)	81.2 % (69/85)	70.5 % (62/88)
	Without	59.7 % (439/735)	53.5% (507/947)	53.1% (471/887)
SAEs	With	15.3% (11/72)	15.3% (13/85)	6.8% (6/88)
	Without	3.3% (24/735)	3.1% (29/947)	2.1% (19/887)

Sensitive/ NTI CYP3A Substrate Compounds Taken Concomitantly Were: Aprepitant, Budesonide, Buspirone, Darifenacin, Dronedarone, Felodipine, Fentanyl, Fluticasone, Lovastatin, Midazolam, Quetiapine, Sildenafil, Simvastatin, Tacrolimus, Triazolam

Note: the sponsor did not count patients who were concomitantly taking Dihydroergotamine mesilate as CYP3A substrates with narrow therapeutic index drugs and Eletriptan Hydrobromide as sensitive CYP3A substrates. Since the number of subject who were taking those drugs were small, this will not affect the safety conclusion.

2.7.2.4 Is the drug a substrate and/or an inhibitor of transport processes?

Eluxadoline appears to be a substrate for OAT3, OATP1B1, BSEP and MRP2 but not for OCT1, OCT2, OAT1, and OATP1B3. Eluxadoline is not a good substrate for P-gp and BCRP either. As a follow-up, the sponsor had conducted in-vivo drug-drug interaction studies with cyclosporine (an inhibitor of many transporters including OATP1B1 and MRP2) and probenecid (inhibitor of MRP2 and OAT3) to address the clinical relevance of interaction with OAT3, OATP1B1 and MRP2. However, clinical relevance of eluxadoline's interaction with BSEP was not evaluated.
Based on the in-vitro data, eluxadoline appears to be a weak inhibitor of OATP1B1, and a follow up in-vivo study was conducted with an OATP1B1 substrate rosuvastatin. No significant inhibitory effect of eluxadoline up to 400 ng/mL concentration (C_{max}≈3 ng/mL at clinical dose of 100 mg) was noted for OAT1, OAT3, OCT1, OCT2, , OATP1B3, P-gp BCRP, BSEP, and MRP2 (< 12% inhibition). However, inhibition potential of eluxadoline toward P-gp in the gut (where I_{gut} =400 μg/mL) could not be assessed.

Substrate:
Study OPT-2012-64 assessed the potential of JNJ-27018966 being a substrate for transporters at 4, 40, 400 ng/mL concentrations at 37 °C in triplicates in *in-vitro* system. For uptake of solute carrier transporter, JNJ-27018966 was incubated for 5 minutes with MDCK cells overexpressing solute carriers transporters OAT1, OAT3, OCT1, OCT2, OATP1B1 and OATP1B3 and control

cells that were grown on permeable support. For Efflux transporters, bidirectional (both A-B and B-A) transport of JNJ-27018966 or the model substrates (positive controls) were evaluated through Caco-2 monolayer for BCRP and MDCK-MDR1 monolayer for P-gp monolayers after 2 hours of incubation. For BSEP and MRP2, JNJ-27018966 or the model substrates (positive controls) were incubated with Sf9 membrane vesicle expressing human BSEP or MRP2 suspension for 5 minutes for MRP2 and for 15 minutes for BSEP in the presence of ATP or AMP to distinguish between transporter-mediated uptake and passive diffusion into the vesicles.

Table 26: Transporter Mediated Transport of Eluxadoline (JNJ-27018966)

Transporters	**Probe Substrates (positive control)**	**Positive control**	**JNJ-27018966 4 ng/mL**	**JNJ-27018966 40 ng/mL**	**JNJ-27018966 400 ng/mL**
Ratio of Uptake in transporter overexpressing cell vs. control cells					
OCT1	10 µM metformin	3.48	1.08	0.68	1.15
OCT2	10 µM metformin	5.28	0.89	1.04	0.88
OAT1	2 µM p-aminohippurate	7.82	0.07	0.0	1.12
OAT3	0.75 µM estrone-3-sulfate	6.11	2.0	1.69	3.53
OATP1B1	2 µM estradiol-17β-D-glucuronide	4.11	4.25	1.04	1.63
OATP1B3	10 µM CCK-8	3.15	1.15	0.86	1.42
Efflux Ratio (P_{B-A}/P_{A-B})					
P-gp	100 µM digoxin	19.2 ±0.998	1.89 ±1.47	2.29 ±0.357	1.63 ±0.281
BCRP	genistein	4.80 ±0.286	2.04 ± 0.537	1.36 ±0.165	1.57 ±0.268
Ratio of Vesicular Accumulation in ATP / AMP					
BSEP	taurocholate	15.84	0.97	2.22	2.12
MRP2	estradiol-17β-D-glucuronide	22.34	3.50	5.66	6.63

JNJ-27018966 appears to be transported via OAT3, OATP1B1, BSEP and MRP2 as the ratio of cellular or vesicular accumulation of JNJ-27018966 is almost 2 fold in systems that overexpresses those transporters compared to controls at certain concentrations.

P-gp and BCRP: Efflux ratio of JNJ-27018966 in MDCK-MDR1 cell monolayer is 2.29 at 40 ng/mL and less than 2 at 4 ng/mL and 400 ng/mL. In addition, on Caco-2 cell monolayer, which accounts for both P-gp and BCRP, the efflux ratio is at border line 2 at 4 ng/mL and less than 2 at 40 and 400 ng/mL. Furthermore, in study 04-RWJ.P01, the efflux ratio of JNJ-27018966 at 10 µM (5700 ng/mL) in Caco-2 cell monolayer was 1.57. Taken together, JNJ-27018966 not likely a good substrate for P-gp and BCRP.

Inhibition:

Study OPT-2012-063 had evaluated the potential of JNJ-27018966 to inhibit transporters at a single concentration of 400 ng/mL (133-fold higher than C_{max} where the C_{max} at clinical dose of 100 mg is approximately 3 ng/mL) at 37 °C in triplicates in *in-vitro* system. For solute carrier uptake transporters, probe substrates were incubated for 5 minutes in the presence of absence of JNJ-27018966 or model inhibitors (positive controls) in MDCK cells overexpressing solute carriers transporters OAT1, OAT3, OCT1, OCT2, OATP1B1 and OATP1B3 and control cells that were grown on permeable support. For efflux transporter, bidirectional transport (both A-B and B-A) of a probe substrates through Caco-2 monolayer for BCRP and MDCK-MDR1 monolayer for P-gp were assessed in the presence and absence of JNJ-27018966 or the model inhibitors (positive controls) for 120 minutes. For BSEP and MRP2, probe substrates were incubated with Sf9 membrane vesicle expressing human BSEP or MRP2 suspension in the presence and absence of JNJ-27018966 or model inhibitors (positive control). Incubations, 5 minutes for MRP2 and 15 minutes for BSPE, were carried out in the presence of ATP or AMP to distinguish between transporter-mediated uptake and passive diffusion into the vesicles.

Table 27: In-Vitro Inhibition of Transporter by 400 ng/mL Eluxadoline

Transporter	**Probe Substrates**	**% inhibition by JNJ-27018966**	**Model inhibitors (positive control)**	**% inhibition by model inhibitor**

OCT1	10 μM metformin	12.1 ± 8.68	100 μM Quinidine	86.0 ± 2.35
OCT2	10 μM metformin	12.5 ±19.0	100 μM Quinidine	79.1± 2.11
OAT1	2 μM p-aminohippurate	8.17 ± 7.84	100 μM probenecid	88.6 ± 0.51
OAT3	0.75 μM estrone-3-sulfate	-12.2 ± 7.41	100 μM probenecid	91.2 ± 4.00
OATP1B1	2 μM estradiol-17β-D-glucuronide	32.6 ± 5.39	100 μM rifampicin	104 ± 3.00
OATP1B3	10 μM CCK-8	8.22 ± 4.95	100 μM rifampicin	98.4 ± 2.50
P-gp	100 nM digoxin	6.25 ± 0.633	100 μM verapamil	80.4 ± 1.18
BCRP	25 nM genistein	-3.74 ± 5.79	100 μM chrysin	98.8 ± 1.93
BSEP	1 μM taurocholate	2.18 ± 1.46	300 μM rifampicin	96.0 ± 0.751
MRP2	50 μM estradiol-17β-D-glucuronide	4.27 ± 5.83	300 μM benzbromarone	95.8 ± 2.45

JNJ-27018966 does not appear to inhibit OCT1, OCT2, OAT1, OAT3, OATP1B3, BCRP, P-gp, BSEP and MRP2 significantly at 400 ng/mL concentrations (< 12.5% inhibition). JNJ-27018966 showed weak inhibition toward OATP1B1 (inhibited by 33 % at 400 ng/mL concentration), and the sponsor had followed up with an *in-vivo* study with an OATP1B1 substrate rosuvastatin.

Because this study was only conducted at one concentration of JNJ-27018966 at 400 ng/mL, IC_{50} values were not determined. Although the selected concentration of 400 ng/mL was adequate to assess the inhibitory potential of JNJ-27018966 toward various transporters at systemic level as this concentration covers the expected C_{max} and 100 times the C_{max} value, this concentration is not adequate to assess the inhibitory potential of JNJ-27018966 toward transporters in the gut, i.e., P-gp and BCRP.. The I_{gut} is estimated to be 100 mg/250 mL = 400000 ng/mL, which is 1000 fold higher than the tested concentration in this study. Nonetheless, since no significant increase in exposure of rosuvastatin, a substrate for BCRP, was noted (AUC ↑ by 40 % and Cmax ↑ by 18%) when it was coadministered with eluxadoline, significant inhibition of BCRP in the gut by eluxadoline in not likely Therefore, we recommend that the sponsor follow-up with an *in-vitro* study to estimate the IC_{50} (or Ki) value of JNJ-27018966 toward P-gp only and subsequently estimate the *in-vivo* relevance of this interaction.

Safety Analysis:
In the phase 2/3 studies, patient who concomitantly took P-gp or BCRP substrates with eluxadoline has higher % of patients with AEs and SAEs compared to subject who did not take those drugs. However, similar trend was observed in subjects who took placebo. Within the subjects who were concomitantly taking P-gp or BCRP substrate, there was not difference AEs or SEAs in subjects in treatment arm vs. placebo.

Table 28: % of Patients with AEs or SAEs with Concomitant Use of P-gp Substrates

	P-gp Substrates	75 mg	100 mg	Placebo
AEs	With	88.0% (22/25)	89.2% (33/37)	88.2 % (15/17)
	Without	59.3% (464/782)	54.6% (543/995)	54.1% (518/958)
SAEs	With	0 % (0/25)	18.9% (7/37)	11.8% (2/17)
	Without	4.5% (35/782)	3.5% (35/995)	2.4% (23/958)

P-gp Substrate Compounds Taken Concomitantly Were: Colchicine, Digoxin, Fexofenadine, Loperamide
Note: The sponsor did not count Dabigatran Etexilate Mesilate, Metformin, Sitagliptin, Ranolazine, Saxagliptin, Sitagliptin Phosphate as the P-gp substrates in their analysis. Therefore, this analysis may not be reliable.

Table 29: % of Patients with AEs or SAEs with Concomitant Use of BCRP Substrates

	BCRP substrates	75 mg	100 mg	Placebo
AEs	With	65.0% (13/20)	72.2% (13/18)	77.8% (14/18)

	Without	60.1% (473/787)	55.5 % (563/1014)	54.2% (519/957)
SAEs	With	10.0% (2/20)	5.6% (1/18)	5.6% (1/18)
	Without	4.2% (33/787)	4.0 % (41/1014)	2.5% (24/957)

BCRP Substrate Compounds Taken Concomitantly Were: Methotrexate, Rosuvastatin
Note: The sponsor did not count sulfasalazine (with only 1 subject) as the BCRP substrate in their analysis. Due to small number, this will not affect the analysis.

Induction:
Potential of eluxadoline to induce transporters were not evaluated in this NDA submission. Potential of eluxadoline to induce P-gp transporter can be ruled out based on absence of induction of CYP3A4 by eluxadoline in *in-vitro* study.

2.7.2.5 Are there other metabolic/transporter pathways that may be important?

The sponsor did not explore the potential of eluxadoline to inhibit CYP2C8 or induce CYP2B6.

2.7.2.6 What In-vivo drug interaction studies were conducted based on *in-vitro* findings?

Based on the in-vivo studies results, the sponsor had conducted in-vivo drug-drug interaction studies with cyclosporine (an inhibitor of many transporters including OATP1B1 and MRP2) and probenecid (MRP2 and OAT3 inhibitor), rosuvastatin (OATP1B1 substrate). In addition, the sponsor had also conducted in-vivo drug-drug interaction to evaluate the effect of oral contraceptive and eluxadoline on each other as they are expected to be co-administered in clinical practice.

Rosuvastatin
Study CPS-1012 was an open-label, randomized, single-center, 2-period crossover PK study in 28 healthy subjects to evaluate the effect of 100 mg eluxadoline on the single-dose pharmacokinetics of rosuvastatin (substrate for OATP1B1, OATP1B3 and BCRP) and its active metabolite n-desmethyl rosuvastatin. In treatment A, subjects were dosed with a single dose of 20 mg rosuvastatin on Day 1. In treatment B, subject were dosed with a single dose of rosuvastatin plus a 100 mg dose of eluxadoline on Day 1, followed by a single 100 mg dose of eluxadoline approximately 12 hours later on Day 1, followed by BID dosing with 100 mg eluxadoline on Days 2 and 3 to ensure the maximal potential inhibition of OATP1BI by eluxadoline persisted throughout the PK profiling of rosuvastatin.

Figure 14: Mean (±SD) Plasma Concentrations of Rosuvastatin vs. Time

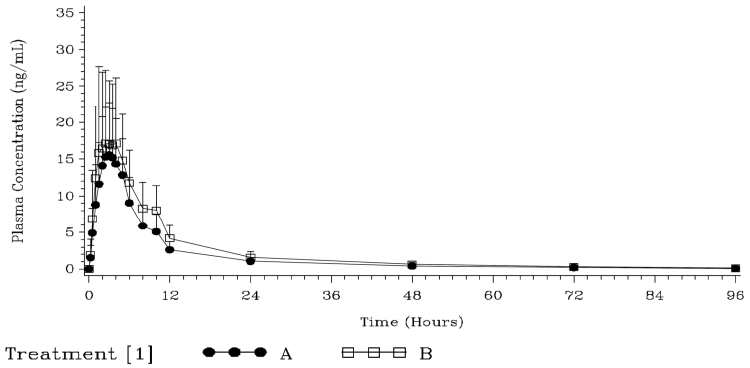
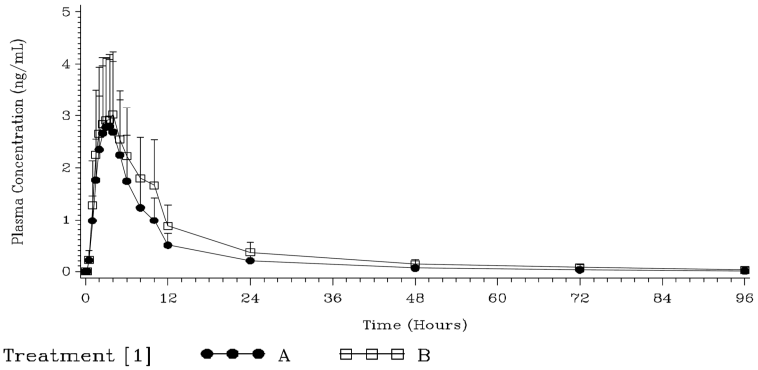


Figure 15: Mean (±SD) Plasma Concentrations of n-Desmethyl Rosuvastatin vs. Time



Treatment A = Single 20 mg dose of rosuvastatin on Day 1
Treatment B = Single 20 mg dose of rosuvastatin plus 100 mg dose of eluxadoline on Day 1, followed by a single 100 mg dose of eluxadoline approximately 12 hours later on Day 1, followed by twice daily dosing with 100 mg eluxadoline on Days 2 and 3

Table 30: Statistical Analysis of Plasma Pharmacokinetic Parameters for Rosuvastatin

Parameter (unit)	Treatment[a]	N	Geometric LS Means	Treatment Comparison	Ratio (%) of Geometric LS Means	90% CI of the Ratio
$AUC_{(0\text{-}inf)}$ (ng•h/mL)[b]	A	24	145.053			
	B	25	203.810	B/A	1.405	1.278 – 1.544
$AUC_{(0\text{-}t)}$ (ng•h/mL)	A	27	141.085			
	B	27	193.901	B/A	1.374	1.253 – 1.507
C_{max} (ng/mL)	A	27	14.941			
	B	27	17.663	B/A	1.182	1.037 – 1.348

Table 31: Statistical Analysis of Plasma Pharmacokinetic Parameters for n-Desmethyl Rosuvastatin

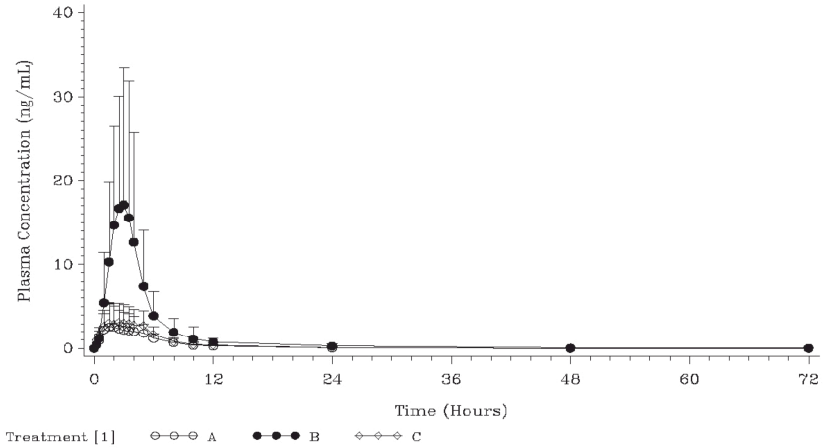
Parameter (unit)	Treatment[a]	N	Geometric LS Means	Treatment Comparison	Ratio (%) of Geometric LS Means	90% CI of the Ratio
$AUC_{(0\text{-}inf)}$ (ng•h/mL)[b]	A	22	25.343			
	B	26	38.780	B/A	1.530	1.374 – 1.704
$AUC_{(0\text{-}t)}$ (ng•h/mL)	A	27	24.058			
	B	27	36.455	B/A	1.515	1.364 – 1.684
C_{max} (ng/mL)	A	27	2.675			
	B	27	2.998	B/A	1.121	1.000 – 1.255

Coadministration of rosuvastatin with eluxadoline increased rosuvastatin AUC by approximately 40% and C_{max} by 18% compared to when rosuvastatin was administered alone, The active metabolite of rosuvastain , n-Desmethyl Rosuvastatin, also had shown similar trend of change in exposure as the parent drug rosuvastain. We recommend caution should be exercised when rosuvastatin is coadministered with eluxadoline.

Cyclosporine and Probenecid:

Study CPS-1011 was an open-label, randomized, single-center, single-dose, 3-period crossover PK study in 30 healthy subjects to evaluate the effects of cyclosporine (an inhibitor of many transporters including OATP1B1 and MRP2) and probenecid (MRP2 and OAT3 inhibitor) on the pharmacokinetics of eluxadoline.

Figure 16: Mean (±SD) Plasma Concentrations of Eluxadoline Versus Time



Treatment A = Single 100 mg dose of eluxadoline.
Treatment B = Single 100 mg dose of eluxadoline + single 600 mg dose of cyclosporine.
Treatment C = Single 100 mg dose of eluxadoline + single 500 mg dose of probenecid.

Table 32: Mean (CV) Plasma and Urine Pharmacokinetic Parameters of Eluxadoline

	Eluxadoline Treatment Group		
Parameter (unit)	**Eluxadoline 100 mg (N=29)**	**Eluxadoline 100 mg + Cyclosporine 600 mg (N=30)**	**Eluxadoline 100 mg + Probenecid 500 mg (N=29)**
$AUC_{(0\text{-}inf)}$ (ng•h/mL)[a]	17.95 (67.1)	75.32 (61.6)	22.99 (56.2)
$AUC_{(0\text{-}t)}$ (ng•h/mL)	16.47 (66.1)	77.31 (65.7)	21.45 (55.3)
$AUC_{(0\text{-}24)}$ (ng•h/mL)	17.04 (62.2)	76.40 (66.6)	22.23 (51.4)
C_{max} (ng/mL)	3.06 (92.2)	20.93 (85.0)	3.63 (59.4)
T_{max} (h)[b]	2.05 (0.25, 6.00)	2.50 (1.50, 4.00)	2.50 (0.25, 6.00)
$t_{1/2}$ (h)[a]	3.67 (53.7)	7.39 (79.8)	5.07 (77.4)
CL/F (L/h)[a]	7550.07 (54.2)	1943.03 (68.8)	5645.90 (53.3)
Vz/F (L)[a]	39318.01 (82.1)	20728.43 (87.9)	37145.09 (87.2)
$XU_{(0\text{-}24)}$ (mg)	0.10 (57.8)	0.43 (64.6)	0.06 (43.4)
$XU_{(0\text{-}72)}$ (mg)	0.12 (51.6)	0.46 (61.1)	0.08 (39.1)
%Fe	0.12 (51.6)	0.46 (61.1)	0.08 (39.1)
CLr (L/h)	6.97 (19.6)	5.82 (19.0)	3.65 (24.9)

Abbreviations: CV, coefficient of variation; h, hours; L, liters.
[a] n = 20 for eluxadoline alone; n = 19 for eluxadoline + cyclosporine ; n = 20 for eluxadoline + probenecid.
[b] For T_{max}, the median (minimum, maximum) values are presented.

Table 33: Statistical Analysis of Plasma Pharmacokinetic Parameters for Eluxadoline

Parameter (unit)	Treatment[a]	N	Geometric LS Means	Treatment Comparison	Ratio (%) of Geometric LS Means	90% CI of the Ratio
$AUC_{(0\text{-}inf)}$ (ng•h/mL)	A	7	15.692	–	–	–
	B	7	79.871	B/A	5.090	(3.807, 6.805)
	C	7	20.378	C/A	1.299	(0.971, 1.736)
$AUC_{(0\text{-}t)}$ (ng•h/mL)	A	29	13.940	–	–	–
	B	29	61.715	B/A	4.427	(3.842, 5.102)
	C	29	18.829	C/A	1.351	(1.172, 1.557)
$AUC_{(0\text{-}24)}$ (ng•h/mL)	A	29	14.803	–	–	–
	B	29	61.347	B/A	4.144	(3.634, 4.726)
	C	29	19.965	C/A	1.349	(1.183, 1.538)
C_{max} (ng/mL)	A	29	2.373	–	–	–
	B	29	14.668	B/A	6.182	(5.136, 7.441)
	C	29	3.118	C/A	1.314	(1.092, 1.582)

Treatment A = Single 100 mg dose of eluxadoline.
Treatment B = Single 100 mg dose of eluxadoline + single 600 mg dose of cyclosporine.
Treatment C = Single 100 mg dose of eluxadoline + single 500 mg dose of probenecid.

- Coadministration of a single oral dose of 100 mg eluxadoline with a single oral dose of 500 mg probenecid (MRP2 and OAT3 inhibitor) decreased the renal clearance of eluxadoline by 50% and increased AUC and C_{max} by 30% compared to when a single oral dose of 100 mg eluxadoline was administered alone. Absence of significant inhibition by probenecid when it was coadministered with eluxadoline suggests that MRP2 (expressed at apical membrane of intestine epithelia, liver hepatocytes and renal proximal tubule) and OAT3 (basolateral membrane of kidney) may play limited role in overall clearance of eluxadoline. However, their contribution to overall clearance cannot be ruled out. The change in eluxadoline exposure (30%) when coadministered with probenecid is not considered to be clinically significant and will not have labeling implication.

- Coadministration of a single oral dose of 100 mg eluxadoline with a single oral dose of 600 mg cyclosporine increased the AUC of eluxadoline by 4.4-fold and C_{max} by 6.2-fold compared to when a single oral dose of 100 mg eluxadoline was administered alone. Cyclosporine is not only an inhibitor of OATP1B1 and MRP2, but also an inhibitor of P-g, BCRP and OATP1B3. However, there is no evidence that eluxadoline is a good substrate for these transporters (P-gp, BCRP and OATP1B3). Therefore, the significant increase in AUC and C_{max} when eluxadoline was taken with cyclosporine suggests that OATP1B1 and possibility MRP2 play a role in disposition of eluxadoline where OATP1B1 is typically expressed at the sinusoidal (basolateral) membrane of liver hepatocytes and MRP2 is expressed at the apical membrane of liver hepatocytes.

- Overall, this study suggests that OATP1B1 (and possibility MRP2) plays an important role in disposition of eluxadoline. There was not enough number of subjects (n=6 in 100 mg BID and n=3 in placebo) in phase II and III studies who were coadministered eluxadoline with OATP1B1 inhibitors to assess the safety of eluxadoline when it is coadministered with OATP1B1 inhibitors. The sponsor proposed to monitor patients for adverse reaction when eluxadoline is prescribed concomitantly with OATP1B1 inhibitors in the proposed label. However, we recommend that patients should avoid concomitant use of OATP1B1 inhibitors with eluxadoline if possible; if not, monitor for adverse reactions related to eluxadoline.

Oral Contraceptive (Brevicon: norethindrone and ethinyl estradiol):

Study CPS1007 was an open-label, non-randomized, single-center, single-sequence study in 29 healthy female subjects to evaluate the effects of coadministration of 100 mg eluxadoline and Brevicon (norethindrone and ethinyl estradiol) on each other's pharmacokinetic profile. In Period 1, subjects took Brevicon (norethindrone 0.5 mg/ethinyl estradiol 0.035 mg) QD for 21 days (Treatment A). In period 2, subjects took Brevicon (norethindrone 0.5 mg/ethinyl estradiol 0.035 mg) QD on Day 1- 21 days + Eluxadoline 100 mg BID on Day 15-21 (Treatment B). In Period 3, subjects took Eluxadoline 100 mg BID for 7 Days (Treatment C).

Table 34: Statistical Analysis of Norethindrone and Ethinyl Estradiol Plasma PK Parameters

Analyte Parameter (unit)	Treatment[a]	N[b]	Geometric LS Means	Ratio (%) of Geometric LS Means (B/A)[a]	90% CI of the Ratio (%) (B/A)[a]
Norethindrone					
$AUC_{(0\text{-}tau)}$ (pg•h/mL)	A	33	103364.4	106.23	(103.33, 109.22)
	B	29	109807.8		
C_{max} (pg/mL)	A	33	14470.65	105.38	(98.82, 112.38)
	B	29	15249.43		
Ethinyl Estradiol					
$AUC_{(0\text{-}tau)}$ (pg•h/mL)	A	33	1142.38	105.19	(100.72, 109.86)
	B	29	1201.64		
C_{max} (pg/mL)	A	33	139.33	97.98	(92.01, 104.33)
	B	29	136.51		

Treatment A = Brevicon QD alone
Treatment B = Brevicon QD + Eluxadoline 100 mg BID.

Table 35: Statistical Analysis of Plasma PK Parameters for Eluxadoline

Analyte Parameter (unit)	Treatment[a]	N	Geometric LS Means	Ratio (%) of Geometric LS Means (B/C)	90% CI of the Ratio (%) (B/C)
Eluxadoline					
$AUC_{(0\text{-}tau)}$ (ng•h/mL)	B	29	13.786	90.297	(75.181, 108.452)
	C	29	15.267		
C_{max} (ng/mL)	B	29	2.227	90.661	(71.680, 114.668)
	C	29	2.456		

Treatment B = Brevicon QD + Eluxadoline 100 mg BID.
Treatment C = Eluxadoline 100 mg BID QD alone

Coadministration of eluxadoline with Brevicon does not impact the pharmacokinetic of norethindrone and ethinyl estradiol of Brevicon compared to when Brevicon was administered alone. Coadministration of Brevicon with eluxadoline reduced the exposure (AUC and C_{max}) of eluxadoline slightly by 10 % compared to when eluxadoline was administered alone. Oral contraceptive that contains norethindrone and ethinyl estradiol is one of the most commonly used oral contraceptive in US market. Oral contraceptives are considered to be weak inhibitors of CYP3A4. However, whether eluxadoline is metabolized by CYP3A4 is unclear. Based on the in-vitro studies, eluxadoline has potential for mechanism based inhibition toward CYP3A4. Although both norethindrone and ethinyl estradiol component of Brevicon are metabolized by CYP3A4, the relative contribution of CYP3A4 to overall metabolism of these two compounds are unknown. Therefore, this drug-drug interaction of eluxadoline with Brevicon does not adequately address the *in-vivo* potential of eluxadoline to inhibit CYP3A4 via mechanism based inhibition.

2.7.2.7 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

No, the label does not specify co-administration of eluxadoline with another drug.

2.7.2.8 What other co-medications are likely to be administered to the target patient population? Are they appropriately addressed in *In-vivo* drug interaction studies?

In the target IBS-d patient population, Loperamide is likely be used as a rescue medication. In the two phase III studies, loperamide was used as a rescue medication while patients continued to take eluxadoline. However, a dedicated clinical study to evaluate the potential drug-drug interaction between eluxadoline and loperamide was not conducted.

Loperamide is mainly metabolized by CYP3A4 and CYP2C8 and lesser extent by CYP2B6 and CYP2D6. In addition, loperamide is also a substrate for P-glycoprotein (P-gp) transport (this information was obtained from clinical pharmacology online and the label for loperamide is not available). Eluxadoline do not inhibit CYP2B6 (reversible inhibition), 2D6 (both reversible inhibition and mechanism based inhibition) and 3A4 (reversible inhibition) or P-gp or induced CYP2C8, CYP3A4 and P-gp. However, potential of eluxadoline to inhibit CYP2C8 is unknown. In addition, eluxadoline appears to inhibit CYP3A4 via mechanism based inhibition in *in-vitro* studies. Therefore, potential effect of eluxadoline on loperamide PK cannot be completely ruled out.

Metabolic pathway of eluxadoline is unclear. However, eluxadoline appear to be a substrate for OAT3, OATP1B1, BSEP and MRP2 in *in-vitro* studies, and *in-vivo* study had demonstrated that OATP1B1 plays a major role in disposition of eluxadoline. Loperamide's potential to inhibit OATP1B1 is unknown at this point. Therefore, potential effect of loperamide on eluxadoline cannot be completely ruled out either.

Nonetheless, according to the Medical Reviewer, Dr. Laurie Muldowney, the safety profiles of eluxadoline with and without the use of loperamide as a rescue medication appear to be comparable in the two phase III studies. There was a slightly increased incidence of GI related AEs in patients who used loperamide as a rescue medication; however, importantly there was no increase in SAEs or AEs resulting in study discontinuation. In addition, there was no clear association between the timing of loperamide rescue medication use and the reporting of GI adverse events. Therefore, although there is a theoretical concern for potential drug-drug interaction between eluxadoline and loperamide, this lack of significant safety signal with concomitant use of loperamide with eluxadoline may alleviate the need for a dedicated drug-drug interaction study between eluxadoline and loperamide.

2.7.2.9 Are there any other *In-vivo* drug-drug interaction studies indicating that exposure alone and/or E-R relationships are different when drugs are co-administered?

No.

2.7.2.10 Has modeling and simulation been used to project drug interactions?

No

2.7.2.11 What is the effect of other extrinsic factors (herbal products, diet, smoking, and alcohol use) on exposure and safety?

There were no specific studies or analyses designed to evaluate the effects of extrinsic factors such as herbal products, diet (other than high-fat meal), smoking or alcohol use on the exposure or safety of eluxadoline. The effect of a high fat meal is discussed in Section 2.8.6.

2.7.2.12 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

Eluxadoline, by having mu opioid agonistic effect, is design to slow down the gastrointestinal transit time. As a result, this may prolong the absorption time for other concomitant medications leading to increased absorption and exposure.

2.7.2.13 Were *In-vivo* PD drug interaction studies conducted?

No

2.7.2.14 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions?

Metabolism of eluxadoline is not clearly established. Please refer to section 2.5.7.3 for further detail.

2.7.3 Are there any issues related to dose, dosing regimens, or administration with respect to extrinsic factors that are unresolved and/or represent significant omissions??

None

2.8 General Biopharmaceutics

2.8.1 What are the solubility and the permeability of eluxadoline?

Solubility: Eluxadoline is slightly soluble in water. Both 75 and 100 mg tablet strengths dissolved (b) (4)% at 10 min time point (please refer to Biopharm review by Dr. Assadollah Noory).
Based on Dmax (defined as mg soluble per 250 mL) estimation, eluxadoline is expected to be soluble in all GI segments and not anticipated to be affected be co-administration of gastric acid reducing agents.

Table 36: Solubility Profile of Eluxadoline

Solution or Buffer	Starting pH	Final pH	Solubility mg/ml	Dmax (mg)
0.1N HCl	1.15	3.7	43.6	10900
Citrate	2	3.9	11.75	29375
Water (HCl)	3.5	3.65	8.83	2207.5
Water (HCl)	4	4.00	3.81	952.5
Citrate	4	4.32	4.69	1172.5
Water (HCl)	5	5.24	3.61	902.5
Water (HCl)	6	6.08	6.03	1507.5
Citrate	6	6.09	3.01	752.5
Water (NaOH)	7	6.90	14.91	3727.5
Borate	8	7.62	7.93	1982.5
Borate	10	7.84	31.5	7875
0.1N NaOH	13	8.01	108.7	27175
Simulated Intestinal Fluid		6.79	3.24	810

Permeability: The bidirectional permeability of 10 μM eluxadoline was evaluated in Caco-2 cell line from the apical to the basolateral (A→B) and from the basolateral to the apical (B→A) in duplicate in study 04-RWJ.P01. As controls, Lucifer Yellow, Atenolol, Propranolol and Digoxin were included in the assay to validate the Caco-2 test system. 27018966 has relatively low permeability with permeability of 0.18 x 10^{-6} cm/s (A-B) and 0.25 X 10^{-6} cm/s (B-A) (similar magnitude as Atenolol and Lucifer yellow, the low permeability drugs) and efflux ratio of 1.37.
In addition, study OPT-20112-064 had also assessed the permeability of JNJ-27018966 in Caco-2 cell monolayer at 4-400 ng/mL concentration range. The permeability values found in this study was consistent with the result of study 04-RWJ.P0 that JNJ-27018966 has relatively low permeability in Caco-2 cell monolayer. However, both of these studies are not adequate to categorize eluxadoline for BCS classification as the suitability of these study methods were not evaluated with sufficient number of model drugs.

Table 37: Permeability of Eluxadoline

Study ID	JNJ-27018966 concentration	Papp B->A (nm/s)	Papp A->B (nm/s)	Efflux ratio (B->A)/(A->B)
OPT-20112-064	4 ng/mL	2.26 ± 0.564	1.11 ± 0.0953	2.04 ± 0.537
	40 ng/mL	1.21 ± 0.140	0.892 ± 0.0342	1.36 ± 0.165
	400 ng/mL	1.15 ± 0.183	0.73 ± 0.0444	1.57 ± 0.268
04-RWJ.P01	5700 ng/mL (10 uM)	2.45±0.005	1.8±0	1.36±0.0278

2.8.2 What is the composition of the final to-be-marketed formulation (drug substance and drug product)? If there are multiple dose strengths, are the active and inactive ingredients proportionally similar in composition among different dose strengths?

Eluxadoline is formulated as 75 mg and 100 mg immediate release tablets, [redacted] b(4)

Table 38: Composition of To-Be Marketed (TMB) Formulation of Eluxadoline Tablets, 75-mg and 100-mg

Component and Quality Standard (and Grade)	Function	Strength (label claim) 75 mg Quantity per mg	%	100 mg Quantity per mg	%
Eluxadoline (Company Specification)	Active	75	[redacted]	100	[redacted]
Silicified Microcrystalline cellulose (NF, Ph. Eur.)	[redacted]	[redacted]			
Colloidal silica (NF, Ph. Eur.)					
Mannitol (USP, Ph. Eur.)					
Crospovidone [redacted] (NF, Ph. Eur.)					
Magnesium stearate (NF, Ph. Eur.)					
[redacted]					
Opadry II [redacted] (Company Specification)					
[redacted]					
Total	--	618	--	824	--
[redacted]					

b(4)

2.8.3 Were there any major changes to the drug substance and/or drug product during the development process? Are there *In-vivo* bioequivalence (BE) or comparability studies to compare PK or PD of various formulations?

Throughout the development process, the following formulations were used:

- Suspension in study EDI-1001 (SAD and MAD study)
- (b) (4) capsule in study EDI-1003 (mass balance study with 300 mg dose)
- Tablet (b) (4) in study EDI-1002 (food effect with 500 mg dose) and IBS-2001 (dose finding phase 2 study)
- To-be–marketed tablet in CPS-1005, CPS-1006, CPS-1007, CPS-1008, CPS-1009, CPS-1010, CPS-1011, CPS-1012, IBS-3001 and IBS-3002.

As most of the clinical pharmacology studies that has labeling implications were conducted with formulation that was used in pivotal phase III studies which is identical as the to-be-marketed formulation except for color of the film coat and embossed markings , no *in-vivo* bioequivalence or comparability studies were conducted to compare the PK or PD of various formulations.

Table 39: Comparison of Tablet Formulations

Ingredient	**Function**	**EDI-1002 and IBS-2001 100-mg tablet Formulation (mg/tab)**	**Phase 3 and to-be-marketed 100-mg tablet* # Amount (mg/tab)**
Eluxadoline	API	100	100
(b) (4)			(b) (4)
Silicified MCC (b) (4) (b) (4)			
Colloidal silica Mannitol Crospovidone (b) (4) (b) (4) Magnesium stearate (b) (4			
Opadry II (b) (4)			
Coated Tablet Weight		(b) (4)	824 mg
(b) (4)			

2.8.4 Was the proposed to-be-marketed formulation used in the pivotal clinical and bioavailability studies?

Yes

2.8.5 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The core tablet formulation for phase III and the to-be-marketed core formulation are identical. The only difference between the to-be-marketed formulation and phase 3 formulation is just the color of the film coat and embossed markings. According to the Biopharm reviewer from ONDQA, *in-vivo* BE study is not needed since these formulations only have a minor difference.

2.8.6 What is the effect of food on the bioavailability (BA) of the drug from the dosage form?

Administration of 100 mg eluxadoline with high-fat breakfast reduced the AUC and C_{max} by 60% and 50%, respectively compared to fasted state, while t_{max} remained comparable between the two treatments (1.5 hr vs. 2.0 hr). In the phase III efficacy and safety trials, patients were instructed to take the 100 mg eluxadoline twice daily (i.e, morning and evening) with food. The sponsor's proposed label recommends taking the tablet with food, and this recommendation reasonable since the phase III studies were conducted under fed condition.

Study CPS1009: The effect of food on 100 mg eluxadoline pharmacokinetic was evaluated in an open-label, randomized, single-dose, 2-period cross-over study in 28 healthy subjects. For both fed and fasted states, the subjects underwent an overnight fasting of at least 10 hours before the dosing. Under fasting condition, the subjects continued to fast 4 additional hours after the administration of a single dose 100 mg eluxadoline. Under fed condition, the subjects were given a single oral dose of 100 mg eluxadoline immediately after (defined as within 30 minutes after staring consumption of the meal) completing a standard high-fat breakfast. The standard high-fat breakfast contained approximately 800 to 1000 total calories, with 50% of calories being derived from fat content. An example of a standard high-fat breakfast was: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, and 8 ounces of whole milk. The content of the high-fat, high-caloric breakfast followed the recommendations given in the FDA guidance "Food Effect Bioavailability and Fed Bioequivalence Studies".

In this study, high fat, high-caloric breakfast reduced the AUC and C_{max} of eluxadoline by 60% and 50%, respectively, while it did not any significant effect on time to maximum concentration (t_{max}).

Figure 17: Mean (±SD) Plasma Concentrations of 100 mg Eluxadoline Versus Time under Fed and Fasted Condition in Healthy Subjects

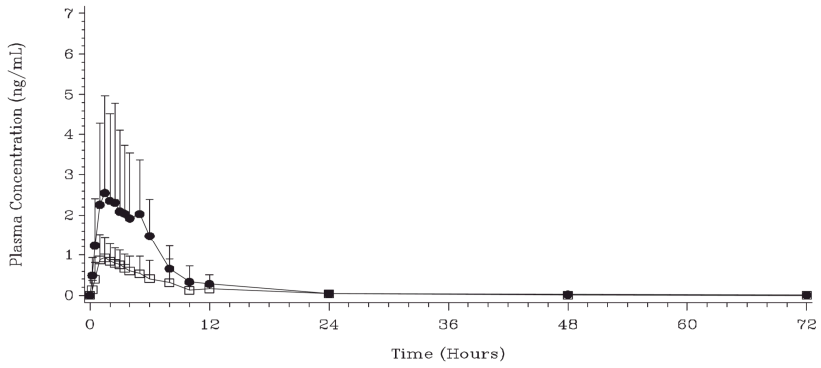


Table 40: Comparison of 100 mg Eluxadoline Mean PK Parameters (CV) between Fasted and Fed Healthy Subjects (n=28)

Parameters (unit)	Fasted	Fed
C_{max} (ng/mL)	3.15 (78.7)	1.36 (47.9)
$AUC_{0-\infty}$ (ng/mL·h)	19.91 (77.9)	6.92 (68.0)
AUC_{0-t} (ng•h/mL)	16.95 (83.1)	6.38 (72.3)
AUC_{0-24} (ng•h/mL)	18.55 (71.3)	6.74 (57.6)
Median T_{max} (h) [min, max]	2.00 (0.50, 6.00)	1.50 (1.00, 8.00)

Table 41: Statistical Comparison of Eluxadoline PK for Fed and Fasted States

Parameter (unit)	Treatment[a]	N	Geometric LS Means	Treatment Comparison	Ratio (%) of Geometric LS Means	90% CI of the Ratio
$AUC_{(0-t)}$ (ng•h/mL)	A	28	13.398	B/A	38.487	(33.23, 44.58)
	B	28	5.156			
$AUC_{(0-inf)}$ (ng•h/mL)	A	22	15.169	B/A	40.005	(32.65, 49.01)
	B	21	6.068			
$AUC_{(0-24)}$ (ng•h/mL)	A	24	14.766	B/A	39.178	(32.71, 46.93)
	B	25	5.785			
C_{max} (ng/mL)	A	28	2.501	B/A	49.399	(40.60, 60.11)
	B	28	1.235			

Abbreviations: CI, confidence interval; LS, least squares.
Note: An analysis of variance (ANOVA) was performed on the natural logarithms of the pharmacokinetic parameters with sequence, period, and treatment as fixed effects and subject within sequence as a random effect.
[a] Treatment A = Single 100 mg dose of eluxadoline under fasting conditions.
Treatment B = Single 100 mg dose of eluxadoline under fed conditions.

EDI1002: The sponsor had also conducted another food effect study with 500 mg (5 x 100 mg tablets) eluxadoline in 18 healthy male only subjects. In this study, high fat meal had reduced the AUC by 25 % and C_{max} by 67%, delayed t_{max} by 2 hours. However, since this study used eluxadoline tablet with a formulation that is slightly different than the formulation used in phase III studies (b) (4) and dose strength used in this study 500 mg is much higher than the proposed dose 100 mg, this study was not reviewed in detail and will not have labeling implication.

2.9 Analytical Section

2.9.1 How are the active moieties identified and measured in the plasma/urine in the clinical pharmacology and biopharmaceutics studies?

Concentration of eluxadoline in human plasma and urine samples were identified and measured with validated HPLC-MS/MS

2.9.2 Which metabolites have been selected for analysis and why?

No metabolites were selected for analysis as no significant metabolites were detected in plasma in metabolic profiling studies.

2.9.3 For all moieties measured, is free, bound, or total measured?

Total drug concentration was measured.

2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?

The concentrations of eluxadoline in human plasma were determined using validated liquid chromatography mass spectrometry (HPLC/MS/MS) methods developed by (b) (4) in studies EDI-1003, CPS-1005, CPS-1006, CPS-1007, CPS-1008, CPS-1009, CPS-1010, CPS-1011, and IBS-2001 (method validation report LCMSC 529).

The concentrations of eluxadoline in human urine were determined using validated liquid chromatography mass spectrometry (HPLC/MS/MS) methods developed by (b) (4) in studies EDI-1003, CPS-1011 (method validation report LCMSC 529.2, project VGV2).).

The concentrations of eluxadoline in human plasma and urine in study EDI-1001 were determined using validated LC/MS/MS methods developed by (b) (4).

During the development of program, concentration of rosuvastatin, ethinyl estradiol and norethindrone were also determined in drug-drug interaction studies by HPLC/MS/MS methods developed by (b) (4) Corresponding assays were developed and validated with acceptable accuracy and precision. Please refer to individual reviews for further detail.

2.9.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used? What are the lower and upper limits of quantification (LLOQ/ULOQ)?

Plasma Eluxadoline: Calibration standard curve consisted of 8 levels ranged from 0.1 to 100 ng/mL in human plasma, with an LLOQ of 0.1 ng/mL, and was calculated using a linear (1/concentration squared weighted) least-squares regression algorithm.
Urine Eluxadoline: Calibration standard curve consisted of 8 levels ranged from 1.00 to 1000 ng/mL in human urine, with an LLOQ of 1.0 ng/mL, and was calculated using a linear (1/concentration squared weighted) least-squares regression algorithm.

2.9.6 What are the accuracy, precision and selectivity at these limits?

Matrix		Intra-assay	Inter-Assay
Plasma	Precision (CV%)	1.29% to 10.0%,	2.24% to 10.1%,
	Accuracy	5.34% to 4.44	-3.54% to 4.75%.
Urine	Precision (CV%)	1.00% to 4.28%,	3.955% to 4.99%,
	Accuracy	-3.14% to 1.93%.	-3.42% to 2.11%.

The ability to analyze samples with an insufficient volume for a full aliquot was validated by analyzing six replicate 3.00 ng/mL QCs in plasma sample and 30.0 ng/mL in urine samples as two-fold dilutions and the ability to dilute samples originally above the upper limit of the calibration range was validated by analyzing six replicate 200 ng/mL QCs in plasma samples and 2000 ng/mL QCs in urine sample as ten-fold dilutions. The both QCs in both plasma and urine had acceptable level of precision and accuracy (< 15%)

No apparent abnormalities associated with reinjection of sample extracts were observed. The bioanalytical methods were specific and selective. There was no significant matrix suppression effects indicated that could compromise the sensitivity or accuracy of the assay.

2.9.7 What is the sample stability under the conditions used in the study?

Eluxadoline in plasma and urine samples were stored at frozen at -20^{o}C until analysis and analyzed within the stability limit in all studies.

Matrix	Freeze-thaw	Room temperature	At 4°C	At -20°C	At -70°C
Plasma	5 cycles	24 hr	128 hours	350 Days	
Urine	5 cycles	24 hr	99 hours	152 Days	111 Days

2.9.8 What is the plan for the QC samples and for the reanalysis of the incurred samples?

QC samples at 5 different concentrations of eluxadoline were analyzed in both plasma and urine:
QC samples in human plasma were at 0.3, 0.8, 3.0, 12.0 and 75 ng/mL.
QC samples in human urine were at 3.0, 8.0, 30, 120 and 750 ng/mL.
At least 10% of the study samples were re-assayed as incurred sample repeats to demonstrate the reproducibility of quantification. The incurred sample repeats met the acceptance criteria of relative percent difference from the original and re-assay values from two-thirds of repeated samples being <20%.

3 Appendices

3.1 Pharmacogenomic Review

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS GROUP REVIEW

NDA/BLA Number	206940
Submission Date	06/26/2014
Applicant Name	Furiex Pharmaceuticals
Generic Name	Eluxadoline
Proposed Indication	Irritable Bowel Syndrome with Diarrhea (IBS-D).
Primary Reviewer	Jeffrey Kraft, PhD
Secondary Reviewer	Christian Grimstein, PhD

EXECUTIVE SUMMARY

The sponsor's assignment of transporter activity based on haplotype is accurate and acceptable. The post-hoc exposure data submitted by the sponsor seems to show a relationship between increasing exposures of eluxadoline and decreasing SLCO1B1 transporter function. In the reviewer's assessment, this relationship cannot be relied upon clinically as there is large inter-subject variability and the relationship does not seem consistent between dose groups.

1 Background

The current submission is for eluxadoline, a locally active, mixed mu opioid receptor (μOR) agonist and delta opioid receptor (δOR) antagonist, to be indicated in adults for the treatment of irritable bowel syndrome with diarrhea (IBS-D). In-vitro and drug-drug interaction studies have shown eluxadoline to be primarily transported by OATP1B1 (SLCO1B1). The sponsor has submitted summary data of exposure (AUC) and adverse events (AEs) by transporter function and dose. The purpose of this review is to determine if SLCO1B1 variation and its resulting effects on transporter function have a clinically relevant impact on eluxadoline exposure.

2 Submission Contents Related to Genomics

2.1 Contents

The sponsor submitted summary level data for SLCO1B1 genotyping performed in a phase 2 dose-ranging study (27018966IBS2001) in order to investigate the effect of SLCO1B1 variation on the exposure of eluxadoline. Subject-level genotype data were included in an appendix to the study report within the current submission. No labeling claims related to SLCO1B1 genotype have been proposed.

Comment: DNA was collected on a voluntary basis during study enrollment allowing for additional pharmacogenetic analysis of SLCO1B1 when subsequent in vitro and clinical drug interaction studies indicated SLCO1B1 is the primary drug transporter involved in the hepatobiliary elimination of eluxadoline.

2.2 Methods

The pharmacogenetics dataset included 593 unique subjects genotyped for variants of SLCO1B1. Of the 593 subjects who were genotyped, 266 subjects (45%) also had sparse PK data and were utilized for the PopPK analyses. DNA samples were analyzed for two genetic variants in the SLCO1B1 gene (rs2306283 and rs4149056) via ABI Taqman assays. The sponsor was able to genotype for the *1A, *1B, *5, and *15 alleles of SLCO1B1 and classify each subject's functional transporter status based on haplotypes. Table 1 lists the haplotypes investigated and functional consequences of these haplotypes.

Table 1: Haplotypes Tested and Functional Activity for SLCO1B1

Haplotype	***rs2306283***	***rs4149056***	***Functional Transport Activity***
SLCO1B1*1A/*1A	A/A (WT)	T/T (WT)	Normal Transporter Function
SLCO1B1*1B/*1B	G/G (MUT)	T/T (WT)	Normal Transporter Function
SLCO1B1*1A/*1B	A/G (HET)	T/T (WT)	Normal Transporter Function
SLCO1B1*1A/*5	A/A (WT)	T/C (HET)	Intermediate Transporter Function
SLCO1B1*1A/*15	A/G (HET)	T/C (HET)	Intermediate Transporter Function
SLCO1B1*1B/*15	G/G (MUT)	T/C (HET)	Intermediate Transporter Function
SLCO1B1*5/*5	A/A (WT)	C/C (MUT)	Poor Transporter Function
SLCO1B1*5/*15	A/G (HET)	C/C (MUT)	Poor Transporter Function
SLCO1B1*15/*15	G/G (MUT)	C/C (MUT)	Poor Transporter Function

Comment: The sponsor genotyped the most frequent alleles to determine functional status for SLCO1B1 and the approach utilized by the sponsor for determining functional transport status is acceptable. Haplotypes and classification into functional transporter categories was verified by the reviewer to be accurate.

3 Key Questions and Summary of Findings

3.1 Does genetic variation in SLCO1B1 influence eluxadoline exposure?

There does appear to be a relationship between eluxadoline exposures and SLCO1B1 transporter function, although extrapolation is complicated by large inter-individual variation in AUC and relatively small numbers of subjects with poor transporter function.

To determine the impact of SLCO1B1 haplotype on PK, the Phase 2 data was summarized by SLCO1B1 haplotype and post-hoc AUC data (based on POP-PK analysis and sparse sampling) was provided for the subset of patients for whom PK and PGx data were both available (N=266). Post-hoc exposure by haplotype data from these analyses are shown in Table 2 below.

Comment: The sponsor's evaluation of the exposure summary statistics in Table 2 suggests a pattern of increasing total exposure with decreasing transporter function. However, based on the significant variability in AUC (coefficients of variation range from 50%-300%) and the relatively small numbers of subjects with poor transporter function, a robust relationship between haplotype function and total exposure was not seen.

Table 2: Post Hoc AUC (ng/mL*h) Results by SLCO1B1 Haplotype and Dose

Dose	*SLCO1B1 Function*	*N*	*Mean*	*Median*	*Std. Deviation*	*Min*	*Max*	*CV%*
5 mg	Normal	12	4.01	1.01	6.05	0.67	21.57	150.6
	Intermediate	9	1.87	1.68	0.98	0.77	4.06	52.5
	Poor	1	2.82	2.82	---	2.82	2.82	---
25 mg	Normal	64	6.07	2.45	18.22	0.95	144.65	300.1
	Intermediate	24	4.07	3.91	2.06	0.79	8.77	50.6
	Poor	1	9.10	9.10	---	9.10	9.10	---
100 mg	Normal	66	9.88	7.85	8.79	1.04	53.61	89.1
	Intermediate	19	16.36	8.80	24.87	2.97	110.76	152.0
	Poor	2	19.89	19.89	1.02	19.16	20.62	5.2
200 mg	Normal	50	22.09	14.31	28.44	3.67	157.92	128.7
	Intermediate	17	23.95	16.55	19.68	5.78	65.65	82.2
	Poor	1	33.28	33.28	---	33.28	33.28	---

Source: IBS-2001 Study Report 8, Page 2, Table 1

To determine the impact of SLCO1B1 haplotypes on safety, the sponsor reviewed the distribution of adverse events between patients with normal, intermediate, and poor transport function. The sponsor indicates that there were insufficient numbers of patients with poor transport function (N=18) to make meaningful conclusions and that there did not appear to be any differences across treatments or variants.

Comment: The reviewer agrees with the sponsor's findings that there does not appear to be any relationship between AE's and transporter function as presented by the sponsor.

4 Summary and Conclusions

The in vitro and clinical drug interaction studies indicated that eluxadoline is primarily transported by SLCO1B1. Analyses by the sponsor seem to support that there is a relationship between increasing exposure to eluxadoline and decreasing transporter function. However, extrapolation of this relationship and its clinical significance is complicated by very low numbers of poor transporters (N=5) with exposure data, very large inter-subject variability (CV greater than 50%), and inconsistencies in the relationship between dose groups.

5 Recommendation

None.

5.1 Post marketing studies

None.

5.2 Labeling

None.

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

/s/

DILARA JAPPAR
03/27/2015

JEFFREY B KRAFT
03/27/2015

CHRISTIAN GRIMSTEIN
03/27/2015

SUE CHIH H LEE
03/27/2015

EDWARD D BASHAW
03/30/2015

BIOPHARMACEUTICS REVIEW Office of New Drug Product		
NDA:	206-940	Reviewer: Assadollah Noory, Ph.D.
Submission Date:	June 26, 2014; Feb. 09, 2015	
Division:	DGIEP	Acting Biopharmaceutics Lead: Tien-Mien Chen, Ph.D.
Applicant:	Furiex Pharmaceuticals	Acting Division Director: Paul Seo, Ph.D.
Trade Name:	(b) (4)	
Generic Name:	Eluxadoline	
Indication:	Treatment of diarrhea and abdominal pain in men and women with diarrhea predominant irritable bowel syndrome (IBS-d)	
Formulation/strengths:	Tablets, 75 and 100 mg	
Route of Administration:	Oral	

Summary:
Under the provisions of 505(b)(1), Furiex Pharmaceuticals submitted NDA 206-940 seeking approval for their eluxadoline 100 mg tablet, for the treatment of diarrhea and abdominal pain in men and women with diarrhea predominant irritable bowel syndrome (IBS-d). In support of the approval of this product, the sponsor submitted dissolution method development report and dissolution profile data as part of the biopharmaceutics requirement characterizing the *in vitro* release profile of their product.

A lower strength of 75 mg tablet strength was also tested in the clinical trials and the dissolution profile data on the 75 mg tablet strength were also included in the submission. Per Medical Division's request, the dissolution profile data on the 75 mg tablet strength are reviewed here. However, the OCP (Office of Clinical Pharmacology) reported that no pharmacokinetic study was available for the 75 mg tablet strength. A biowaiver for the 75 mg tablet is therefore, needed.

The 75 and 100 mg tablet strengths (b) (4) Both 75 and 100 mg tablet strengths dissolved (b) (4) % at 10 min timepoint, therefore, a waiver of a bioequivalence study for the 75 mg tablet is granted based on the formulation similarity and dissolution profile smilarity.

The dissolution method is reviewed and found acceptable. The proposed dissolution acceptance criterion of Q= (b) (4) % at 20 min was not supported by dissolution data submitted. The Agency recommended Q= (b) (4) % at 10 min for this drug product in a communication to the Sponsor.
On Feb, 09, 2015, as a Phase 4 commitment, the Sponsor has committed to performing additional dissolution test using the next 30 manufactured batches to establish a revised dissolution specification for their product. In the meantime, the current proposed dissolution specification is to be considered as an interim specification for the batch release and quality control.

The Sponsor's commitment is also reviewed and acceptable. The final acceptance criterion will be determined by the Agency upon reviewing the additional dissolution information.

Recommendation:

ONDP-Biopharmaceutics completed the review of the Biopharmaceutics portion of this NDA. The Division of Biopharmaceutics recommends approval of NDA 206940 with a Phase 4 commitment. The Sponsor's proposed dissolution acceptance criterion of Q= (b) (4)% at 20 min is accepted as the interim product release and quality control criterion.

The following comments should be conveyed to the Sponsor.
COMMMENTS: (Need to be sent to the Sponsor)

1. Phase 4 Commitment:

On Feb. 09, 2015, you committed as follows:

To re-evaluate the dissolution acceptance criterion after dissolution data from at least 30 lots of commercial drug products are available, or a maximum period of 1 year post-launch. Additionally a 15 minute time-point will be added to the dissolution test at time of product release and in the stability protocol where profiles will be followed at 10, 15, 20 and 30 minutes. The final evaluation will include an assessment of whether the dissolution criterion of Q= (b) (4)% can be applied at 10-minutes or 15-minutes, instead of the 20-minute interval.

Your commitment is reviewed and found acceptable.

2. Therefore, the interim dissolution method and specification criteria for batch release and quality control of (b) (4) are shown in the table below.

Table 1: Interim Dissolution Methodology and Specification

Apparatus	USP Apparatus I, Basket Method
Rotation Speed	100 rpm
Medium	900 mL of 0.05M Phosphate Buffer pH 4.5
Temperature	37°C ±0.5°C
Sampling Time	20 minutes
Dissolution Specification	Q = NLT (b) (4)%

Assadollah Noory, Ph.D. 02/10/2015
Reviewer
Division of Biopharmaceutics
Office of New Drug Product

Tien-Mien Chen, Ph.D. 02/10/2015
Acting Biopharmaceutics Lead:
Division of Biopharmaceutics
Office of New Drug Product

BACKGROUND

Eluxadoline is a locally acting immediate release tablet developed for irritable bowel syndrome (IBS-d). Eluxadoline has been classified as a Biopharmaceutics Class 3 (BCS 3) drug with rapid dissolution.

FORMULATION COMPOSITION

The following table shows the formulation composition of the to-be-marketed formulations (75 mg and 100 mg). The 75 and 100 mg tablet strengths are compositionally the same and dosage-strength proportional in terms of active and inactive ingredients.

Formulation Composition

Ingredient	Function	75 mg Tablet Amount (mg/tab)	100 mg Tablet Amount (mg/tab)	% w/w
eluxadoline drug substance (Company Specification)	Active substance	75	100	(b) (4)
Silicified MCC (b) (4) NF	(b) (4)			(b) (4)
Colloidal silica, NF, Ph Eur, JP				
Mannitol, USP, Ph Eur				
Crospovidone (b) (4) NF, Ph Eur				
Magnesium stearate, NF, Ph Eur, JP				
(b) (4)				
Opadry II (b) (4) (Company Specification)				
(b) (4)				
Coated Tablet Weight		**618 mg**	**824 mg**	------

JP = Japanese Pharmacopeia; MCC = microcrystalline cellulose; NF = National Formulary; Ph Eur = European Pharmacopeia; USP = United States Pharmacopeia

(b) (4)

Dissolution of the Products: (100 and 75 mg Tablets)

The proposed dissolution method (USP apparatus 1 at 100 rpm with 0.05M phosphate buffer at pH 4.5) was employed for the dissolution profiles of the to-be-marketed products (n=12 tablets/lot). The dissolution profile for the 100 mg commercial formulation is shown in the following table and figure.

2 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Dissolution Methodology Development:

(b) (4) the basket method was selected with a rotation speed of 100 rpm.

Media Selection: A dissolution volume of 900 mL was selected (b) (4) . Three dissolution media covering pH (b) (4) 4.5, and (b) (4) were studied. The following table and figure show the results of the 100 mg eluxadoline tablets in hydrochloric acid pH (b) (4)

(b) (4)

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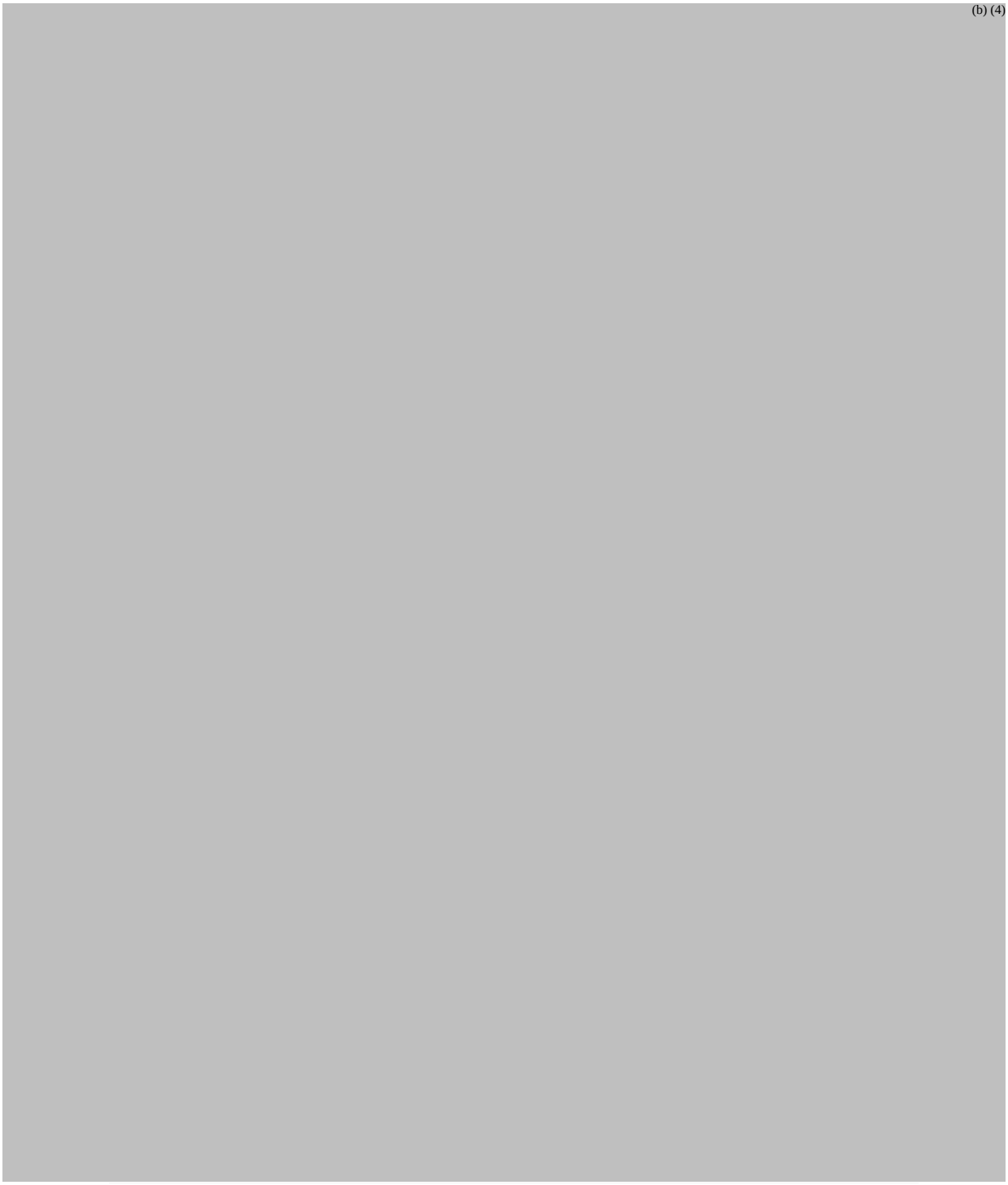
The following table and figure show the results for the 100 mg eluxadoline tablets in phosphate buffer pH (b) (4)

(b) (4)



Based on the dissolution profiles, phosphate buffer pH 4.5 was selected as the dissolution medium.

Discriminating Capability Tests: To demonstrate the discriminating capability of the dissolution method, the formulation was modified and dissolution tests were performed on formulations with and without disintegrant. The table below shows the formulation ph02-054 which does not contain disintegrant with slow dissolution profile relative to the formulations that contain disintegrant (ph02-055 and ph02-056); the profiles are shown in the figure below.

Product Ingredient	mg/tablet ph02-054	mg/tablet ph02-055	mg/tablet ph02-056
Eluxadoline	100	100	100
Silicified Microcrystalline Cellulose (b) (4)	(b) (4)		
Colloidal silicon dioxide			
Crospolyvidone (b) (4)			
(b) (4)			
Magnesium stearate			
Total			

(b) (4)

Proposed Dissolution Specification: The Sponsor is proposing acceptance criterion Q of (b) (4)% at 20 minutes. Their justification is that (b) (4) As a result of the analysis of these data and as recommended in the Agency's preliminary response at the CMC pre-NDA meeting (Date), a tighter acceptance criterion was selected (Q = (b) (4)% at 20 minute).

Biowaiver:
A waiver request of a bioequivalence study for the 75 mg tablet is granted based on the formulation similarity and dissolution profile smilarity.

Reviewer's Comment:
The dissolution methodology adapted by the Sponsor for the batch release and quality control of (b) (4) *is acceptable; however, the proposed acceptance criterion (Q=* (b) (4) *% at 20 min)) should be changed to Q of* (b) (4) *% at 10 minutes.*

Commitment by the Sponsor:
In a communication dated February 9, 2015 the Sponsor responded to the Agency's information request and committed to performing additional dissolution studies to investigate a most suitable dissolution specification for the product release and quality control using the first 30 lots of manufactured product. Quoting the Sponsor from their communication is shown below:

> "The sponsor commits to re-evaluate the dissolution acceptance criterion after dissolution data from at least 30 lots of commercial drug product are available, or a maximum period of 1 year post-launch. Additionally a 15 minute time-point will be added to the dissolution test at time of product release and in the stability protocol where profiles will be followed at 10, 15, 20 and 30 minutes. The final evaluation will include an assessment of whether the dissolution criterion of Q= (b) (4) % can be applied at 10-minutes or 15-minutes, instead of the 20-minute interval."

Based on this commitment the current proposed specification by the Sponsor is acceptable as the interim product release and quality control criterion.

Reviewer's Overall Comment:
The Sponsor's commitment was also reviewed and acceptable. The final acceptance criterion will be determined by the Agency upon reviewing the additional dissolution information.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**206940**	**Brand Name**	**(b) (4)**
OCP Division (I, II, III, IV, V)	**OCP 3**	**Generic Name**	**Eluxadoline**
Medical Division	**DGIEP**	**Drug Class**	**mixed mu opioid receptor (μOR) agonist and delta opioid receptor (δOR) antagonist**
OCP Reviewer	**Dilara Jappar**	**Indication(s)**	**treatment of pain and diarrhea associated with diarrhea-predominant Irritable Bowel Syndrome (IBS-d).**
OCP Team Leader	**Sue Chih Lee**	**Dosage Form**	**Immediate Release Tablet**
Pharmacometrics Reviewer		**Dosing Regimen**	**100 mg twice daily**
Date of Submission	**06/26/2014**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review		**Sponsor**	**Furiex Pharmaceuticals,**
Medical Division Due Date		**Priority Classification**	**Priority review, , 505(b)(1) (NME)**
PDUFA Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**7**		**Submitted on 08/12/14 after an IR request date 08/8/14**
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		**14C-labeled**
Isozyme characterization:				**No significant metabolite identified**
Blood/plasma ratio:				
Plasma protein binding:	**X**	**1**		
Pharmacokinetics (e.g., Phase I) -	**X**			
Healthy Volunteers-				
single dose:	**X**			
multiple dose:	**X**	**1**		**SAD and MAD**
Patients-				
single dose:				
multiple dose:	**X**			**Population PK analysis**
Dose proportionality -				
fasting / non-fasting single dose:	**X**			**SAD with oral suspension**
fasting / non-fasting multiple dose:	**X**			**MAD with oral suspension**
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**1**		**study with cyclosporine and probenecid**
In-vivo effects of primary drug:	**X**	**2**		**Stud with Rosovastatin and oral contraceptives**
In-vitro:	**X**	**8**		**CYP and transporters studies**
Subpopulation studies -				
ethnicity:	**X**			**Pop PK**

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

gender:	**X**			**Pop PK**
pediatrics:				
geriatrics:				
renal impairment:				**Renal impairment study will be conducted as post-approval study which was agreed at pre-NDA meeting**
hepatic impairment:	**X**	**1**		
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**4**		**1 TQT study 2 PK/PD analysis in phase I drug abuse studies 1 PK/PD analysis with Phase 2, dose ranging study**
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	**X**	**1**		**Pooled analysis from phase 1 studies**
Data sparse:	**X**	**1**		**phase 2 dose ranging study**
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**2**		**1 study with 500 mg tablet 1 study with 100 mg**
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies	**X**	**1**		**OATP1B1 genotyping in subset population in phase 2 dose ranging study**
Chronopharmacokinetics				
Pediatric development plan	**X**			
Literature References				
Total Number of Studies				
		31		

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements

No	Content Parameter	Yes	No	N/A	Comment
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		X		The core tablet formulation for Phase 3 and the TBM core formulation are identical. The TBM formulation differs in the color of the film coat and having embossed markings.

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

					According to Biopharm reviewer, no BE study is needed.
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	X			
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	X			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			X	This is an NME
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	X			Submitted on 08/12/14 after an IR request date 08/8/14
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	X			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	X			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	X			
Complete Application					
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	X			

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

The following Information Request was sent to the sponsor on 08/08/2014. The responses to Items 1 and 2 were received on 08/12/2014.

Please provide response to items 1-2 within 2 business days and items 3-7 within 10 business days.

1. Please submit the full bioanalytical assay validation reports for all bioanalytical methods utilized in this application. If you already have done so, please assist us locating them. Please refer to the following guidance for more information.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf

We note that you have submitted a validation report for measuring plasma eluxadoline concentration via HPLC-MS/MS by (b) (4) in in population PK /PD report, Amendment 1 (dated 02/03/2012) as an attachment 11(dated June 2010). However, in this validation report, stability of eluxadoline at (b) (4) °C and (b) (4) °C were only established for (b) (4) days. Please provide the long term sample storage stability that cover the duration of time from samples collection to sample analysis.

List of identified bioanalytical method used in the clinical pharmacology studies:

1) Plasma eluxadoline concentration via HPLC-MS/MS by (b) (4)
2) Urine eluxadoline concentration via HPLC-MS/MS by (b) (4)
3) Plasma rosuvatatin concentration by HPLC-MS/MS by (b) (4)
4) Plasma ethinyl estradiol concentration by HPLC-MS/MS by (b) (4)
5) Plasma norethindrone concentration by HPLC-MS/MS by (b) (4)
6) Plasma eluxadoline concentration with LC-MS/MS by (b) (4)
7) Urine eluxadoline concentration with LC-MS/MS by (b) (4)

2. Please clarify if you have addressed the potential for drug interactions with gastric acid reducing agents as agreed at the Pre-NDA meeting**?**

3. We could not locate the POPPK and PK/PD datasets for NDA 206940 (study IBS-2001). Please submit all the datasets, program codes, definition files associated with poppk and pk/pd reports. If you have already submitted, please point us to the exact location in the EDR. For general expectations for submitting pharmacometric data and models, please refer to http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

4. For study EDI-1001, please include the corresponding dose for both concentration time profile dataset and PK parameter dataset.

5. Provide supporting evidence that eluxadoline is eliminated primarily by biliary route.

6. Based on in vitro studies, eluxadoline is substrate for BSEP transporter. Please clarify if you have evaluated the in vivo potential interaction of eluxadoline with BSEP transport.

7. In order to facilitate our analysis, please put each PK parameters in different columns in PK parameter dataset in all clinical pharmacology studies. In addition, the PK parameter dataset should also include subject ID, treatment, period, and sequence in different columns.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Clinical Pharmacology Filing Memo:

This is an original 505(b)(1) submission for a NME eluxadoline for the treatment of abdominal pain and diarrhea in adult patients with diarrhea predominant irritable bowel syndrome (IBS-d). Eluxadoline is a mixed mu opioid receptor (μOR) agonist/delta opioid receptor (δOR) antagonist. The proposed formulation is immediate release tablet for oral administration and the proposed dose is 100 mg taken twice orally with food. The proposed trade name is (b) (4)

This submission contain total of 11 phase 1 studies in normal healthy subject, one phase 2 dose-ranging study, and two confirmatory Phase 3 studies in patients with IBS-d. In addition, it 9 in-vitro studies and draft label with clinical pharmacology section were submitted.

In the clinical pharmacology studies, the sponsor had used 7 different bioanalytical methods. However, the validation reports for these 7 different bioanalytical methods could not be located in the original submission dated 06/27/2014. An IR requesting this information was sent to sponsor on 08/08/2014.

List of Clinical Pharmacology studies:

- 11 Phase 1 PK studies
  - 1 Single dose an multiple ascending dose PK
  - 1 Mass balance study
  - 2 Food Effect study
  - 1 Hepatic Impairment study
  - 3 DDI studies
  - 1 TQT study
  - 2 PK/PD analysis in 2 drug abuse (PD) studies
- 1 Pooled PK analysis for covariates from phase 1 data
- 1 Phase 2, dose ranging study
  - 1 Population PK analysis
  - 1 PK/PD analysis
  - 1 OATP1B1 genotype-PK and safety analysis
- 2 Phase III studies with limited PK data (not adequate for E-R analysis)
- 9 In-vitro studies
- 7 Bioanalytical validation reports

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

5.2 Tabular Listing of all Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects[a]	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	27018966 EDI1002 (EDI-1002)	Module 5.3.1.1	Food effect	Open label, single dose, crossover	Eluxadoline tablet; 500 mg single dose in fasted and fed state; PO	18	Healthy men	Single dose	Complete; Synoptic CSR
BA	27018966 CPS1009 (CPS-1009)	Module 5.3.1.1	Food effect	Open label, single dose, crossover	Eluxadoline tablet; 100 mg single dose in fasted and fed state; PO	28	Healthy men and women	Single dose	Complete; Full CSR
SAD/ MAD	27018966 EDI1001 (EDI-1001)	Module 5.3.3.1	Initial tolerability	Randomized, double blind, 2 part, SAD, MAD Placebo control	Eluxadoline oral suspension; 30, 100, 300, 1000, 1500, or 2000 mg single dose; PO	18	Healthy men	Single dose	Complete; Synoptic CSR CSR Addendum
					Eluxadoline oral suspension; 1000 mg single dose; PO	8	Healthy women	Single dose	
					Eluxadoline oral suspension; 100 mg QD; 150, 230, 300, or 500 mg BID; PO	40	Healthy men	7 days	
					Eluxadoline oral suspension; 150 mg BID; PO	8	Healthy women	7 days	
Mass balance	27018966 EDI1003 (EDI-1003)	Module 5.3.3.1	Mass balance	Open label, single dose	Capsule containing 100 µCi [^{14}C]-eluxadoline; 300 mg single dose; PO	8	Healthy men	Single dose	Complete; Full CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects[a]	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK	27018966 CPS1005 (CPS-1005)	Module 5.3.3.3	Hepatic impairment	Open label, single dose, parallel group	Eluxadoline tablet; 100 mg single dose; PO	30	Hepatic impaired men and women (mild, moderate, and severe) and matched, healthy men and women	Single dose	Complete; Full CSR
DDI	27018966 CPS1007 (CPS-1007)	Module 5.3.3.4	Drug interaction with an oral contraceptive (Brevicon)	Open label, multiple dose, 3 period, single sequence	Eluxadoline tablet; 100 mg BID with and without steady-state Brevicon; PO	53	Healthy women	7 days	Complete; Full CSR
DDI	27018966 CPS1011 (CPS-1011)	Module 5.3.3.4	Drug interaction with cyclosporine or probenecid	Open label, single dose, 3 period, crossover	Eluxadoline tablet; 100 mg single dose alone and with cyclosporine (600 mg) or with probenecid (500 mg); PO	30	Healthy men and women	Single dose	Complete; Full CSR
DDI	27018966 CPS1012 (CPS-1012)	Module 5.3.3.4	Drug interaction with rosuvastatin	Open label, multiple dose, 2 period, crossover	Eluxadoline tablet; Rosuvastatin (20 mg) single dose alone and with 100 mg BID eluxadoline; PO	28	Healthy men and women	3 days	Complete; Full CSR
QTc	27018966 CPS1008 (CPS-1008)	Module 5.3.4.1	QTc	Randomized, evaluator blinded, single dose, 4 period, crossover Placebo and positive control (moxifloxacin)	Eluxadoline tablet; 100 and 1000 mg single dose; PO	64	Healthy men and women	Single dose	Complete; Full CSR

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects[a]	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PD	27018966 CPS1006 (CPS-1006)	Module 5.3.4.1	Oral abuse potential	Randomized, double blind, 6 period, crossover Placebo and active control (oxycodone)	Eluxadoline tablets; 100, 300, and 1000 mg single dose; PO Oxycodone IR tablets; 30 and 60 mg single dose; PO	40	Nondependent recreational opioid users, otherwise healthy men and women	Single dose	Complete; Full CSR
PD	27018966 CPS1010 (CPS-1010)	Module 5.3.4.1	Intranasal abuse potential	Randomized, double blind, 6 period, crossover Placebo and active control (oxycodone)	Eluxadoline tablets (crushed); 100 and 200 mg single dose; intranasal Oxycodone IR tablets (crushed); 15 and 30 mg single dose; intranasal	36	Nondependent recreational opioid users, otherwise healthy men and women	Single dose	Complete; Full CSR
Efficacy	27018966 IBS2001 (IBS-2001)	Module 5.3.5.1	Dose ranging, efficacy, safety, and population PK	Randomized, double blind, parallel group, dose ranging Placebo control	Eluxadoline tablets; 5, 25, 100, or 200 mg BID; PO	807	Men and women with IBS-d 1 wk prior to random: • average daily pain scores ≥3.0 • average BSS ≥5.5 • diary compliance	12 weeks	Complete; Full CSR CSR Errata PK/PD Addendum Haplotype Analysis
Efficacy	27018966 IBS3001 (IBS-3001)	Module 5.3.5.1	Efficacy, safety, and long-term safety	Randomized, double blind, parallel group Placebo control	Eluxadoline tablets; 75 or 100 mg BID; PO	1282	Men and women with IBS-d; 1 wk prior to random: • average daily worst abdominal pain >3.0 • average BSS score ≥5.5 & ≥5 days with a BSS score ≥5 • IBS-d global ≥2 • diary compliance	52 weeks	Ongoing (long-term safety only); Full CSR
Efficacy	27018966 IBS3002 (IBS-3002)	Module 5.3.5.1	Efficacy and safety	Randomized, double blind, parallel group Placebo control	Eluxadoline tablets; 75 or 100 mg BID; PO	1146	Men and women with IBS-d; 1 wk prior to random: • average daily worst abdominal pain >3.0 • average BSS score ≥5.5 & ≥5 days with a BSS score ≥5 • IBS-d global ≥2 • diary compliance	26 weeks	Complete; Full CSR

Abbreviations: BA = bioavailability; BID = twice daily; CSR = clinical study report; DDI = drug-drug interaction; IR = immediate release; MAD = multiple ascending dose; PD = pharmacodynamic; PK = pharmacokinetic; PO = oral; SAD = single ascending dose; wk = week.

[a] Total number of subjects enrolled.

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Table 8 In Vitro/Ex Vivo Human Biomaterial Pharmacology Studies

Study #/Title	Objective	Results
DD07373 Primary *In Vitro* Pharmacology of JNJ-27018966: Delta and Mu Opioid Receptor Binding and Function	The affinities of JNJ-27018966 for the delta opioid receptor (DOR) and mu opioid receptor (MOR) were evaluated in competition radioligand binding assays of rat brain membranes using [3H]DPDPE and [^{3}H]DAMGO as radioligands for DOR and MOR , respectively. The compound also was evaluated in DOR and MOR functional assays measuring agonist stimulated [^{35}S]GTPγS binding, respectively, in membranes from NG108-15 cells1 or in Chinese hamster ovary (CHO) cells transfected with MOR.	Radioligand binding assays in rat brain membranes confirmed that eluxadoline has relatively high affinity for human δOR and μOR (Ki values of 4.3 nM and 0.59 nM, respectively). The activity of eluxadoline was evaluated in μOR and δOR functional assays of agonist-stimulated [^{35}S]GTPγS binding using membranes from CHO cells transfected with human μOR. In these assays, eluxadoline behaved as a μOR agonist based on stimulation [^{35}S]GTPγS binding (EC_{50} = 0.96 nM; relative intrinsic efficacy (α) = 0.86). Eluxadoline did not stimulate [^{35}S]GTPγS binding up to 10 μM in mouse/rat hybridoma NG108-15 cell membranes expressing δOR and it completely inhibited the [^{35}S]GTPγS binding stimulated by the selective δOR agonist SNC 80 (1 μM) at 10 μM (DD07373) (DD07371) (DD07363), demonstrating eluxadoline is a δOR antagonist and does not have agonistic activity at the δOR.
FK5826 *In vitro* Metabolism of JNJ-27018966 in Cryopreserved Rat, Dog, Monkey and Human Hepatocytes	To identify and estimate the *in vitro* metabolites of the JNJ-27018966 produced by cryopreserved hepatocytes of rat, dog, monkey and human, followed by comparison of metabolic profiles across the species to ensure all *in vitro* metabolites of human are covered by the toxicological species	Slow metabolic clearance was observed in all species. All the metabolites generated by the human hepatocytes were also produced by rat, dog and monkey hepatocytes. The major metabolic pathway of JNJ-27018966 in all non-rodent species and human is direct glucuronidation of the methoxy-benzoic acid moiety to form acyl glucuronides and the methoxy-benzoic acid moiety is the major metabolic soft-spot in these species.
FK5944 The In Vitro Stability Studies of Acyl Glucuronide of JNJ-27018966	To determine the configuration and chemical degradation half-life ($t_{1/2}$) of the major acyl glucuronide of JNJ-27018966. Another objective is to investigate the in vitro metabolism of JNJ-27018966 by human intestinal microsomes.	The only metabolite in humans is the acyl glucuronide metabolite (M11) formed through glucuronidation of the methoxybenzoic acid moiety
FK6533 *In vivo* Metabolism of JNJ-27018966 in Humans	To identify and estimate the *in vivo* metabolites of JNJ-27018966 following oral administration of 1000 mg dose to healthy male subjects enrolled in a single ascending dose study to assess safety and tolerability of JNJ-27018966.	At the 1000-mg dose, no circulating metabolites were detected in plasma, while 6% and 22% of total drug-derived materials in pooled 0- to 8-hour and 8- to 24-hour urine samples, respectively, were the M11 metabolite; less than 0.1% of the total oral dose given was recovered in urine.
FK6315 The Binding of JNJ-27018966 to the Proteins of Mouse, Rat, Rabbit, Dog, Monkey and Human Plasma	To evaluate the binding of JNJ-27018966 to the proteins of rat, dog, mouse, monkey and human plasma over an observed and theoretical concentration range in the above species	Eluxadoline was moderately bound in plasma for all species (81% in human pooled plasma samples).
FK5731 A Study of the Potential Effects of JNJ-27018966 in the Induction of CYP1A2, CYP2C9, CYP2C19, and CYP3A4 in Cryo-Preserved Human Hepatocytes	To evaluate potential for JNJ-27018966 to induce cytochrome P450-isoforms in human hepatocytes	Eluxadoline did not induce CYP enzymes in vitro at concentrations up to 10 μM (5696 ng/mL)
FK5873 An In Vitro Investigation of the Potential of JNJ-27018966 to Inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 in Human Liver Microsomes	To evaluate the reversible and mechanism-based inhibitory potentials of JNJ-27018966 on the major cytochrome P450 (CYP450) isoforms in pooled, mixed gender, human liver microsomes.	Eluxadoline did not significantly inhibit/inactivate CYP enzymes in vitro at concentrations up to 100 μM (57 μg/mL) except for CYP2E1 which was slightly inhibited (EC_{50}≈ 20 μM (11 μg/mL).
OPT-2012-063 Assessment of JNJ-27018966 as a potential inhibitor of human Pgp, BCRP, BSEP, MRP2, OAT1, OAT3, OCT1, OCT2, OATP1B1 and OATP1B3-mediated transport.	To determine whether or not JNJ-27018966 inhibit the transport of substrate by P-gp, BCRP, BSEP, MRP2, OAT1, OAT3, OCT1, OCT2, OATP1B1 or OATP1B3.	Eluxadoline (0.70 uM, 400 ng/mL) did not inhibit any drug transporters tested with exception of OATP1B1 and P-gp, with respective inhibition of 32.6% and 6.3%
OPT-2012-064 Assessment of JNJ-27018966 as a potential substrate of human P-gp, BCRP, BSEP, MRP2, OAT1, OAT3, OCT1, OCT2, OATP1B1 and OATP1B3-mediated transport	To determine whether JNJ-27018966 is transported by P-gp, BCRP, BSEP, MRP2, OAT1, OAT3, OCT1, OCT2, OATP1B1 or OATP1B3.	Eluxadoline was transported by OAT3, OATP1B1 and BSEP (at 0.70 uM, 400 ng/mL, i.e., 133-times the C_{max} of the 100 mg therapeutic dose) and MRP2 at all tested concentrations (4 to 400 ng/mL)

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/s/

DILARA JAPPAR
08/14/2014

SUE CHIH H LEE
08/15/2014