21 July 2016
EMA/549473/2016
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Truberzi

International non-proprietary name: eluxadoline

Procedure No. EMEA/H/C/004098/0000



## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# List of abbreviations

ADR adverse drug reaction

AE adverse event

ALT alanine aminotransferase

AST aspartate aminotransferase

AUC area under the concentration-time curve

BID twice daily

BMI body mass index

BSS Bristol Stool Scale

CHMP Committee for Medicinal Products for Human Use

Cmax maximum observed plasma concentration

CNS central nervous system

CSR clinical study report

EMA European Medicines Agency

EU European Union

FDA US Food and Drug Administration

GERD gastroesophageal reflux disease

GI gastrointestinal

IBS irritable bowel syndrome

IBS-d diarrhea-predominant irritable bowel syndrome

IBS-m irritable bowel syndrome, where a mixture of constipation and diarrhea is predominant

IBS-QoL Irritable Bowel Syndrome Quality-of-Life

IR immediate release

ISE Integrated Summary of Efficacy

ISS integrated summary of safety

IVRS interactive voice response system

MAA marketing authorization application

MRI magnetic resonance imaging

NDA New Drug Application

NICE National Institute for Health and Care Excellence

δOR delta opioid receptor

μOR mu opioid receptor

PD pharmacodynamic

PK pharmacokinetic

SAE serious adverse event

SAP statistical analysis plan

SCE Summary of Clinical Efficacy, Module 2.7.3

SCS Summary of Clinical Safety, Module 2.7.4

SmPC Summary of Product Characteristics

SO sphincter of Oddi

SOC system organ class

SSRI selective serotonin reuptake inhibitor

TCA tricyclic antidepressant

ULN upper limit of normal

US United States

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Aptalis Pharma SAS submitted on 1 May 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Truberzi, through the centralised procedure under Article 3 (2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 September 2014.

The applicant applied for the following indication.

Truberzi is indicated in adults for the treatment of irritable bowel syndrome with diarrhoea (IBS-D).

**The legal basis for this application refers to:**

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that eluxadoline considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

***Information on Paediatric requirements***

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0021/2015 on the agreement of a paediatric investigation plan (PIP) and the granting of a product-specific waiver for the paediatric population from birth to less than 6 years.

At the time of submission of the application, the PIP P/0021/2015 was not yet completed as some measures were deferred.

***Information relating to orphan market exclusivity***

***Similarity***

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

**New active Substance status**

The applicant requested the active substance eluxadoline contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union

***Scientific Advice***

The applicant received Scientific Advice from the CHMP on 24th May 2012 (EMEA/H/SA/2319/1/2012/SME/III), 27th June 2013 (EMEA/H/SA/2319/1/FU/1/2013/SME/II) and 21st November 2013 (EMEA/H/SA/2319/1/FU/2/2013/SME/II). The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

***Licensing status***

Truberzi has been given a Marketing Authorisation in United States on 27th May 2015.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Harald Enzmann Co-Rapporteur: Greg Markey

- The application was received by the EMA on 1 May 2015.
- The procedure started on 28 May 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14th August 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 August 2015.
- PRAC assessment overview, adopted by PRAC on10 September 2015.
- During the meeting on 24 September 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 September 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22nd March 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28th April 2016.
- PRAC RMP Advice and assessment overview, adopted on 13 May 2016.
- During the CHMP meeting on 26 May 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20th June 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 28th April 2016.
- During the meeting on 21st July 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Truberzi.

# 2. Scientific discussion

## 2.1. Introduction

**Problem statement**

Irritable Bowel Syndrome (IBS) is a chronic, relapsing gastrointestinal problem characterised primarily by intestinal pain and/or discomfort and associated alterations of defecation and/or bowel habit. Associations with other symptoms are regularly present, such as abdominal distension, bloating, constipation, and/or diarrhoea.

The diagnosis and classification of IBS is based on the Rome III criteria, which is currently regarded the standard of diagnosis and classification. According to the Rome III criteria, IBS is diagnosed when the following is present: Recurrent abdominal pain or discomfort at least 2 days/month in the last 2 months associated with two or more of the following: 1. Improvement with defecation, 2. Onset associated with a change in frequency of stool 3. Onset associated with a change in form (appearance) of stool. The onset of the symptoms has to have occurred at least 6 months prior to diagnosis. IBS is sub-classified according to the predominant stool pattern. In "IBS with diarrhoea (IBS-d)" patients need to have "loose (mushy) or watery stools in ≥ 25% and hard or lumpy stool <25% of bowel movements.

The treatment of IBS is usually started with recommendations for a change in life-style (reduce stress), and dietary modifications, based on the evaluation of symptoms and history taking. Among patients diagnosed with IBS, a certain percentage of patients can indeed be identified to suffer from food allergies, and/or certain carbohydrate intolerances. Psychological therapies (cognitive behavioural therapy, hypnotherapy) have also shown to have some effect on the disease. The pharmacological treatment of IBS is usually symptomatic, and depends on the predominance of the symptoms. Treatment modalities include also antidepressants, and non-absorbable antibiotics. In 2012, linaclotide (Constella) has been approved for IBS with constipation IBS-c. However, no specific treatment is currently approved within the EU for IBS-d.



**About the product**

Truberzi (INN: eluxadoline; previously known as JNJ-27018966) is a locally acting, mixed mu opioid receptor (μOR) agonist/delta opioid receptor (δOR) antagonist with low oral bioavailability The claimed and approved indication is in adults for the

Treatment of irritable bowel syndrome (IBS) with diarrhoea (IBS-d).

The proposed posology was 200 mg daily (one 100 mg tablet twice daily). The proposed posology for post-cholecystectomy patients and those with tolerability problems was 150 mg (one 75 mg tablet twice daily).

The approved posology is 200 mg (one 100 mg tablet twice daily). For patients who are unable to tolerate the 100 mg dose, the dose can be lowered to 150 mg daily (one 75 mg tablet twice daily).

For patients 65 years of age or older a dose of 150 mg (one 75 mg tablet twice daily) could be considered.

The use in patients without gall bladder and in patients on treatment with potent inhibitors of OATP1B1 (e.g. Cyclosporin) has been contraindicated.

**Type of Application and aspects on development**

The MAA for eluxadoline is made under the Optional Scope of the Centralised Procedure (Regulation (EC) No 726/2004, Article 3(2) a) - new active substance. Eligibility for submission was confirmed by the CHMP on 2 September 2014. The MAA is submitted in accordance with Article 8(3) of Directive 2001/83/EC as amended.

The revised EMA "Guideline on the evaluation of medicinal products for the treatment of irritable bowel syndrome" (CPMP/EWP/785/97/Rev. 1) refers to two principal ways of evaluating efficacy of compounds in the disease (relating also to different courses of the disease): A continuous long-term use, and an intermittent use, consisting of repeated treatment cycles. The applicant has developed the substance eluxadoline for continuous long-term use, and designed their study programme accordingly.

The Phase 3 protocols were originally developed based upon discussions with the FDA and in parallel to finalization of the FDA guidance in May 2012 (FDA, 2012). However, the Phase 3 studies were also designed to support global registration of eluxadoline and therefore included additional considerations for the EMA, in particular the evaluation of efficacy over 26 weeks in both studies.

EMA scientific advice has been requested three times during the development: The main objective of the first advice requested in February 2012 was to obtain feedback on the overall acceptability of the clinical global development program proposed to support marketing authorization in the European Union. As a result of this initial scientific advice, the Applicant designed their Phase 3 program meeting both the FDA and EMA requirements, despite the lack of harmonized guidance at that time. As a further result of the advice, the applicant amended study 3001 by adding an additional 3 months of efficacy assessments to the treatment period of the original protocol, thus producing 2 nearly identical (up to the first 26 weeks) confirmatory Phase 3 trials having a minimum treatment duration of 26 weeks.

During the years 2012 to 2014, the EMA "Guideline on the evaluation of medicinal products for the treatment of irritable bowel syndrome" (CPMP/EWP/785/97/Rev. 1) has been revised. The requirements set out in the revised CHMP GDL are now similar to those of the FDA. The development programme is considered to be in line with the current recommendations of the CHMP IBS guideline and with the recommendations given in the repeated Scientific Advices. The primary endpoint was changed from a co-primary measure of global symptoms and abdominal pain to a composite endpoint of stool consistency and abdominal pain, already pre-specified as a secondary endpoint, in order to comply with the revised EU IBS guidelines.

Prior to completing enrolment into the studies, the applicant sought follow-up scientific advice in May 2012, as a result of a programming error that resulted in the interactive voice response system (IVRS) incorrectly allocating medication to subjects in both Phase 3 trials (see GCP issues). Based on CHMP advice, the Applicant did not implement any amendment to the protocol/SAPs as a consequence of the misallocations and evaluated the trials as prospectively planned.



## *2.2. Quality aspects*

### 2.2.1. Introduction

The finished product is presented as film-coated tablets containing 75 and 100 mg of eluxadoline as active substance.

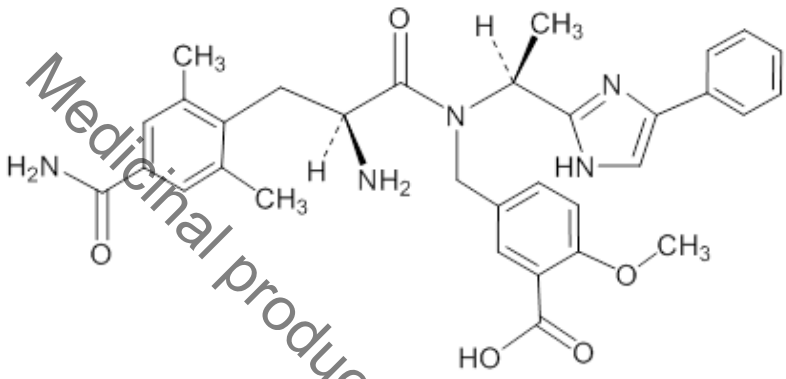
Other ingredients are: silicified microcrystalline cellulose (E460), colloidal anhydrous silica (E551), crospovidone type B (E1202), mannitol (E421), magnesium stearate (E570), poly vinyl alcohol (E1203),

titanium dioxide (E171), macrogol 3350 (E1521), talc (E553b), iron oxide yellow (E172), and iron oxide red (E172).

The product is available in PCTFE/PVC/Al-blister as described in section 6.5 of the SmPC.

## 2.2.2. Active Substance

The chemical names of eluxadoline are 5-[[[(2S)-2-amino-3-[4-(aminocarbonyl)-2,6-dimethylphenyl]-1-oxopropyl][(1S)-1-(4-phenyl-1Himidazol-2-yl)ethyl]amino]methyl]-2-methoxybenzoic acid and
5-({(4-carbamoyl-2,6-dimethyl-L-phenylalanyl)[(1S)-1-(4-phenyl-1H-imidazol-2-yl)ethyl]amino}methyl)-2-methoxybenzoic acid corresponding to the molecular formula $C_{32}H_{35}N_5O_5$ and has a relative molecular mass 569.65 g/mol and the following structure:





Structural elucidation was confirmed by elemental analysis, MS, IR, 1H-/13C-NMR and UV spectroscopy.

Eluxadoline is a crystalline, white to off-white hygroscopic powder, highly soluble in water (pH=7).

Eluxadoline exhibits stereoisomerism due to the presence of two chiral centres possessing S,S configuration. Enantiomeric purity is controlled routinely by chiral HPLC.

Polymorphism has been observed for the active substance. Polymorph screening studies determined that Form I is the only non-solvated, crystalline form of the active substance. Form I converts to the tri-hydrate at higher humidity. The hydrated form re-converts to Form I as it loses water. No other anhydrous form has been identified at any point during development.

***Manufacture, characterisation and process controls***

Eluxadoline is synthesized in three main steps using commercially available well-defined starting materials with acceptable specifications.

The initially submitted control strategy for the proposed starting materials for the synthesis of eluxadoline was considered insufficient to rigorously and consistently control the quality of these starting materials. A comprehensive review of origin and fate of all the potential impurities associated with the synthesis of starting material and the chiral purity of the active substance together with revised specifications has been presented during the evaluation. Overall the information and controls provided by the applicant reassured sufficiently the quality of the proposed starting materials. The provided information on synthesis process, scientific discussion, controls and representative batch analysis data provide assurance for consistent quality of the starting materials which do not have a negative impact to the quality of the active substance.

The manufacturing process consist of reductive amination, coupling reaction, ester saponification, deprotection followed by salt formation and purification.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified.

The most significant change made between the registration and validation batches during the manufacturing process development is the change from a tray dryer to a filter dryer upon commercial upscale. Drying conditions were optimised until acceptable results for particle size distribution was met. It has been demonstrated that the change did not have a significant impact on the quality of the product.

The active substance is packaged in double transparent low density polyethylene (LDPE) bags individually closed with zip ties, which comply with the EC directive 2002/72/EC and EC 10/2011 as amended, inside an aluminized pouch.



***Specification***

The active substance specification includes tests: description, identification (FTIR, HPLC), assay (HPLC), related substances (HPLC), residual solvents (GC), water content (Ph Eur), residue on ignition/sulphated ash (Ph Eur), heavy metals (Ph Eur), particle size (laser diffraction), steroisomeric purity (Chiral HPLC), microbiological enumeration tests (Ph Eur).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for used for the chiral purity, appearance, identity, and HPLC purity has been presented.

Batch analysis data (26 pilot and commercial scale batches) of the active substance were provided. The results are within the specifications and consistent from batch to batch.

***Stability***

Stability data on three pilot scale batches of active substance from the proposed manufacturer stored in the intended commercial package for 24 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. Test parameters were appearance, assay, related substances, water content, stereoisomeric purity, x-ray powder diffraction and microbial limits. With exception of microbial limits – tested at beginning, end and annually – tests are performed routinely according to stability program.

No significant trend was observed at long term and accelerated stability conditions, indicating that no chemical degradation or chiral conversion occur for eluxadoline. Water uptake has been observed during stability, in line with the hygroscopic nature of the material; however all results are in compliance with the specification. Moreover, PXRD results indicate no change in the solid form, confirming that the proposed

packaging system offers adequate protection from significant moisture ingress and consequent conversion into the trihydrate form.

Photostability testing following the ICH guideline Q1B Option 1 was performed on one batch with unpackaged samples and samples packaged in a container closure system that is representative of the commercial container. The studies confirmed that the commercial container provides appropriate protection from light.

Results on stress conditions (40 ºC / 75% RH, 50% RH and exposed to light) packed in the proposed commercial container were also provided on three batches. During stress studies, tests for appearance, assay, chromatographic purity and water content, stereoisomeric purity, particle size and crystallinity by XRD were performed. All tested parameters were within the specifications

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months without storage conditions in the proposed container.



## 2.2.3. Finished Medicinal Product

***Description of the product and Pharmaceutical development***

The finished product is an immediate release film-coated tablet intended for oral administration; two strengths have been developed, 75 mg and 100 mg. The 75 mg commercial finished product is a capsule shaped, pale-yellow to light tan coated tablet debossed with “FX75” on one side; the commercial 100mg finished product is a capsule shaped, pink-orange to peach coated tablet debossed with “FX100” on one side.

Eluxadoline is a locally acting, mixed mu opioid receptor (μOR) agonist/delta opioid receptor (δOR) antagonist with low oral bioavailability, with a proposed indication in adults for the treatment of irritable bowel syndrome (IBS) with diarrhoea (IBS-d). In order to maximise eluxadoline local action in the GI tract, the finished product development strategy has focuses on the delivery of a rapidly dissolving immediate release tablet.

The active substance is highly soluble with low permeability. Physical chemical properties with impact to pharmaceutical development were solubility, permeability, hygroscopicity, polymorphism and particle size. Eluxadoline is soluble at the highest proposed dose (100 mg) in 250 ml of solution from pH 1.2-7.5. The lowest measured solubility of eluxadoline was at least 3 mg/ml at approximately pH 4.5. The active substance is classified as highly soluble as per the Biopharmaceutical Classification System (BCS). Eluxadoline exists as a crystalline form. The thermodynamically stable anhydrous form (Form I) was used in the finished product.The common blend was compressed to specific tablet weights to deliver the intended strengths, including the commercial doses. The powder blend used for the proposed commercial tablet is the same formulation used in the Phase 3 clinical trials. To assist in differentiation, the to-be marketed tablets are debossed and have a coloured coating, light tan to pale yellow for the proposed 75-mg strength and pink-orange to peach for the proposed 100 mg strength.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The excipients of the tablet: silicified microcrystalline cellulose, colloidal silica, mannitol, crospovidone and magnesium stearate are common well-known excipients. Cellulose and mannitol are used as filler. Mannitol is not hygroscopic and

because it is a non-reducing sugar and eluxadoline contains a primary amine it will not undergo a Maillard reaction. Crospovidone is required for consistent rapid disintegration and magnesium stearate is used as a lubricant since the eluxadoline tablets are formed by a direct compression process. The proposed film coating is a non-functional film coating. The film coating includes colours which will help to differentiate the tablet strengths. They also provide a smooth outer coating to the tablets which helps to improve swallow ability for patient compliance. No incompatibility was observed with all these excipients after exposure to 40 °C/ 75% RH conditions in open and closed containers for four weeks. The compatibility of the components of the finished product is also confirmed with the long-term and accelerated stability studies.

The powder blend used for the proposed commercial tablet is the same formulation used in the Phase III clinical trials.

A dissolution method was developed in order to ensure that the release of eluxadoline is appropriately evaluated *in vitro*.

The proposed primary packaging for commercialization is a PCTFE/ PVC blister with heat-seal coated aluminium foil. The material complies with Ph Eur and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. During evaluation, the applicant withdrew its proposal of HDPE bottle as an additional primary packaging.



***Manufacture of the product and process controls***

The manufacturing process consists of 5 main steps: screening and blending (pre-lubrication), lubricant screening and blending (post-lubrication), compression, film coating of tablets and final packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

***Product specification***

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identification (UPLC, UV), assay (UPLC), related substances (UPLC), dissolution (HPLC), uniformity of dosage units (HPLC), microbial enumeration test (Ph Eur), specified microorganisms (Ph Eur).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The reference standard used for the testing of the finished product is the same as that used for the testing of the active substance and they are satisfactory.

Batch analysis results are provided for 3 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release.

***Stability of the product***

Stability data of 3 pilot scale batches per strength of finished product stored under long term conditions for 24 months at 25 ºC / 60% RH, for up 12 months under intermediate conditions at 30 °C / 65% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of the product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, water content, and assay by HPLC (later also by UPLC), impurity, any individual impurity and total impurities, chiral purity and microbial limits. The analytical procedures used are stability indicating.

All presented results are within the proposed specification. Physical and pharmaceutical attributes of the finished product did not change adversely. The assay of the tablets did not decrease over time at either the accelerated or long-term conditions.

In addition, 2 batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. It was concluded that the finished product was not sensitive to light.

In addition supporting stability data have been presented from batches used in Phase III clinical trials or during product development; these studies are on-going and data from one development batch has been presented for the 6 months' time point. All the data presented are within the acceptance criteria and no significant trend has been observed in any of the parameters tested.

Based on available stability data, the proposed shelf-life of 48 months and without any special storage conditions as stated in the SmPC (section 6.3) is acceptable.

***Adventitious agents***

No excipients derived from animal or human origin have been used.



## 2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

## 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

## 2.2.6. Recommendation(s) for future quality development

Not applicable

## 2.3. Non-clinical aspects

### 2.3.1. Introduction

The Applicant has provided a full non-clinical development program for the new chemical entity eluxadoline. The focus of the nonclinical program was to characterize eluxadoline's OR activity, the potential to cause the typical opioid-related adverse effects, including abuse and withdrawal potential, and to generally characterize the toxicity of eluxadoline. All studies were conducted in accordance with best scientific principles. Definitive studies were conducted according to Good Laboratory Practices (GLP).

### 2.3.2. Pharmacology

#### *Primary pharmacodynamic studies*



| Type of Study | Test System | Route (Vehicle/Formulation) | GLP Compliance | Testing Facility | Study No. |
|---|---|---|---|---|---|
| **Primary Pharmacodynamics** | | | | | |
| Mu and Delta Opioid Receptor Binding and Activity | Radioligand Binding [$^3$H] DPDPE and [$^3$H]DPDPE Rat Brain<br>Functional Assays NG108-15, CHO cells | In Vitro | No | J&JPRD | DD07373 |
| Kappa Opioid Receptor Binding | Binding Assay Guinea Pig Cerebellum | In Vitro | No | Cerep | DD07364 |
| Kappa Opioid Receptor Activity | Functional Assay Guinea Pig Proximal Colon | In Vitro | No | J&JPRD | DD07352 |
| Human Mu and Delta Opioid Receptor Binding | Radioligand Binding DAMGO, CHO [$^3$H] naltrindole, SK-N-BE(2) cells | In Vitro | No | J&JPRD | DD07371 |
| Delta Opioid Receptor Bioassay | Hamster Vas Deferens | In Vitro | No | Cerep | DD07363 |
| Mu-Delta Heteromers | Various | In Vitro and In Vivo | No | Mt. Sinai | Heterodimer |
| Mu and Delta Opioid Receptor Activity | Guinea Pig Ileum | Ex Vivo | No | J&JPRD | DD07354 |
| Effects on Upper GI Motility | Male CD-1 Mice | p.o. (0.5% hypromellose) i.v. (0.9% NaCl) | No | J&JPRD | DD07335 |
| Effects on Upper GI Motility | Male SD Rats | p.o. (0.5% hypromellose) | No | J&JPRD | DD07353 |
| Modulation of gastrointestinal function | Various | In Vitro, Ex Vivo and In Vivo | No | J&JPRD | Wade et al 201 |
| Effects on Stress-Induced Altered GI Motility and Defecation | Male CD-1 Mice | p.o. (0.5% hypromellose) | No | J&JPRD | DD07356 |
| Effects on Altered GI Motility in Post-Infamatory IBS Model | Male CD-1 Mice | p.o. (0.5% hypromellose) | No | J&JPRD | DD07351 |
| Effects on Visceral Hyperalgesia | Male SD Rats | p.o. (0.5% hypromellose) i.p. (0.9% NaCl) | No | J&JPRD | DD07378-amended |

CHO = Chinese Hamster Ovary Cells; DAMGO = [$^3$H] [D-Ala$^2$,N-Me-Phe$^4$,Gly$^5$-ol]-enkephalin; DPDPE = D-Penicillamine2-D-Penicillamine5 intraperitoneal; i.v. = intravenous; GI = gastrointestinal; NaCl = sodium chloride; p.o. = oral; SD = Sprague Dawley

The applicant has performed a comprehensive set of in vitro and in vivo pharmacology studies to characterise eluxadoline primary pharmacology, which confirmed that eluxadoline is a mixed μOR agonist/δOR antagonist with an EC50 of 0.96 nM and an IC50 of 95 nM for μOR and δOR respectively. The binding affinities (Ki) of eluxadoline for human μOR and δOR are 1.8 nM and 430 nM, respectively. Eluxadoline was shown to be only a weak κOR agonist (EC50 of 1.6 μM). The binding affinity (Ki) of eluxadoline for human κOR has not been determined; however, the Ki for guinea pig cerebellum κOR was shown to be 55 nM.

Eluxadoline has two stereogenic centres, and is the single diastereomer of the S,S configuration. The R,S-enantiomer of eluxadoline has been shown to be at least 60-fold less potent in a rat binding assay.

Eluxadoline possessed a differential profile than the pure μOR agonist loperamide in several in vitro assays with higher potency but lower overall efficacy. In a β-arrestin recruitment assay employing murine

μOR and δOR, signaling by eluxadoline was significantly blocked by an antibody specific to μOR/δOR heterodimers, whereas loperamide β-arrestin recruitment was unaffected.

In an ex-vivo study eluxadoline inhibited contractions of isolated guinea pig ileal preparations evoked by electrical field stimulation in a concentration-dependent and naloxone (μOR antagonist)-reversible manner.

Oral eluxadoline had local therapeutic effects on GI transit and faecal output in a number of animal models. Inhibition of GI transit time was shown in normal mice and rats (ED50 = 40 mg/kg and 25 mg/kg in mice and rats respectively). Eluxadoline prevented the increase in GI transit following restraint stress in mice, and also in mice with altered gastric motility as a result of post-inflammatory IBS (ED50= 45.7 mg/kg). When compared to loperamide (a pure μOR agonist), eluxadoline was less potent, but showed a wider therapeutic response dose range, and did not inhibit faecal output, as was observed at higher doses of loperamide. Eluxadoline was also shown to reverse the hyperalgesic response to colorectal stimuli in rats with acute colitis.

The role of eluxadoline antagonism at the δOR receptor was studied in WT mice and δOR-/- knock out mice in a castor oil-induced diarrhoea model comparing the effects of eluxadoline and loperamide. In WT mice, castor-oil caused severe diarrhoea, and treatment with eluxadoline or loperamide decreased the diarrhoea score. However, in δOR-/- mice, higher doses of eluxadoline were required to block diarrhoea. Further studies were conducted to evaluate the μOR/δOR heterodimers expressed in rat and mouse GI tissue. It is hypothesised that the δOR antagonist activity of eluxadoline at the μ-δOR heterodimer may reduce side effects of μOR agonists while maintaining the analgesic activity, thus eluxadoline may be less likely to cause constipation and tolerance with chronic therapy. However, as expression of μOR/δOR heterodimers has not been described in humans, the relevance of these data for the clinical effects of eluxadoline is unknown.



***Secondary pharmacodynamic studies***

| Type of Study | Test System | Route (Vehicle/Formulation) | GLP Compliance | Testing Facility | Study No. |
|---|---|---|---|---|---|
| **Secondary Pharmacodynamics** | | | | | |
| HTP Profile | 50 Receptor/Ion Channel Binding Screen | In Vitro | No | Cerep | DD07380 |
| Competitive Inhibition Binding | Histamine $H_2$, Muscarinic M1, Serotonin 5-$HT_6$, Somatostatin, Potassium Channel $SK^+_{Ca}{}^{2+}$ | In Vitro | No | Cerep | DD07362 |
| Human Muscarinic Acetylcholine Receptor Subtype 1 Activity | Human M1 receptor transfected in CHOK1 cells | In Vitro | No | J&JPRD | DD07355 |
| CB1, CB2, NMDA, N neuronal α4β2, N neuronal α7, N muscle-type receptor Binding | Receptor Binding Screen | In Vitro | No | Cerep | 100006176 |
| HTP Profile (M2 metabolite) | Receptor/Ion Channel Binding Screen | In Vitro | No | Cerep | DD07434 |
| Mu and Delta Opioid Receptor Binding and Activity (M2 metabolite) | Radioligand Binding [$^3$H]naltrindole, [$^3$H]DAMGO Functional Assays [$^{35}$S]GTPγS, NG108-15, CHO, rat brain | In Vitro | No | J&JPRD | DD07435 |
| Abdominal Sensitivity in Pancreatitis | Male SD Rat | In Vivo (0.5% hypomellose) | No | Bilsky Lab University of New England | Furiex-001 |

CHO = Chinese Hamster ovary cells; DMSO = dimethyl sulfoxide; HTP = high throughput; SD = Sprague Dawley

In a receptor/ion channel binding screen investigating 50 target structures eluxadoline (10 μM) inhibited the binding of control ligands ≥ 30 % for muscarinic M1 receptor (62 %), calcium-dependent potassium channel SK+Ca2+ (48 %), histamine H2 receptor (32 %), serotonin 5-HT6 and somatostatin receptor (31 %, each). However, no functional activity was shown. In addition, there was no significant binding to

an additional panel of receptors associated with abuse potential, including CB1, CB2, NMDA, N neuronal α4β2, N neuronal α7 and N muscle-type.

As opioids are known to cause spasm of the sphincter of oddi, a rat pancreatitis study was conducted to investigate the potential for eluxadoline to exacerbate the pain seen in that model. Eluxadoline (10 or 32 mg/kg bw PO) and morphine or loperamide (10 or 32 mg/kg bw PO, each), which were included in the study for reasons of comparison, did not increase abdominal sensitivity in this test system.

***Safety pharmacology programme***

Eluxadoline was not considered to be a hERG channel blocker when tested at concentrations up to 3 µM. At 10 µM, eluxadoline marginally reduced the effective refractory frequency in the isolated guinea pig right atrium, without affecting the rate and the force of contraction. No electrophysiological effects were found in the rabbit Purkinje fibre assay at concentrations up to 10 µM. The in vitro NOEL represents a plasma concentration of 5.7 µg/ml, which is >1000-fold the exposure at the 100 mg oral human dose (assuming a Cmax of 3 ng/mL).

Systemic administration of eluxadoline caused some cardiovascular changes in guinea pigs, dogs and cynomolgus monkeys. In guinea pigs, the mean arterial blood pressure and heart rate increased, with a concurrent decrease in the QT and QTc intervals. In conscious dogs, haemodynamic effects were observed after low intravenous doses of eluxadoline, which coincided with significant behavioural effects (including sedation), likely linked with µOR agonist pharmacology and which potentially confounded interpretation. Subsequent evaluation in anesthetised dogs showed no notable haemodynamic effects at cumulative intravenous doses up to 0.143 mg/kg. The in vivo NOEL (plasma level 373 ng/ml) in the anesthetised dog study represents an exposure margin of approximately 124, relative to the Cmax (2-3 ng/mL) in humans at the 100 mg therapeutic dose. Intravenous infusion of higher eluxadoline doses to anesthetised dogs showed a tendency for a decrease in arterial blood pressure and heart rate. In conscious telemetered cynomolgus monkeys, a notable decrease in arterial blood pressure was also found after subcutaneous administration of 5, 15 and 30 mg/kg eluxadoline, but these were not associated with an effect on heart rate, and slight QT changes were not statistically significant nor dose dependent.

Consistent with µOR agonist pharmacology, eluxadoline caused respiratory depression in rats following a single intravenous administration at all dose levels (up to 20 mg/kg), and several animals in the high dose group required rescuing by naloxone blockade shortly after dosing. Interestingly, subcutaneous administration of eluxadoline (up to 30 mg/kg) in rats caused increases in all the measured respiratory parameters (including respiratory rate) at all the dose-levels tested. A hypothesis for these divergent observations and a comment on the relevance of stimulatory or inhibitory effects of eluxadoline on respiration in humans was requested. In response the Applicant commented that the more recent study conducted via the IV route (1808-016, completed in 2012) should be considered as the more relevant study for assessment of respiratory effects of eluxadoline. The increases in respiratory parameters observed via the SC route (TOX-8158, completed in 2007) were not dose or exposure-related, and the Applicant questions the value of the SC route for assessing the opioid effects of eluxadoline. The Applicant has not provided any hypothesis for the divergent observations in the two studies. However, it can be accepted that the intravenous study is the more relevant study, as higher systemic exposure would have been achieved, and that any effects on respiration in humans are unlikely.

After the very high oral dose of 500 mg/kg bodyweight (bw) to rats no neurobehavioural effects were noted, in line with the low bioavailability of the molecule. Starting at 1000 mg/kg bw, decreased activity and miosis were observed. Both effects are consistent with eluxadoline opioid pharmacology. Antinociceptive effects of eluxadoline were demonstrated in mice using the hot plate test after

subcutaneous (SC, 10 mg/kg bw) and IV (ED50 1.5 ± 0.6 mg/kg bw), but not after oral administration of 1000 mg/kg bw, indicating a wide safety margin of eluxadoline via the oral route.

Abuse liability assessment was investigated in Rhesus monkeys using relatively few animals. In monkeys trained to discriminate between saline and morphine, the IV doses of 10 and 17.8 mg/kg bw (but not the dose of 3.2 mg/kg bw) of eluxadoline dose-dependently substituted for morphine (1.78 mg/kg bw IV). In Rhesus monkeys trained to self-administer heroin, 3.2 mg/kg bw IV of eluxadoline was determined as the lowest dose substituting for heroin (0.01 – 0.032 mg/kg bw/infusion).

The very high IV dose of 56 mg/kg produced in one part of the study just reduced response rates in a food presentation/shock termination stimulus test, whereas in a subsequent pharmacokinetic part of the study, at the same dose all 4 monkeys became unresponsive and exhibited apnoea. The Applicant was asked to comment on a possible explanation for this striking difference of effects observed in Rhesus monkeys after IV administration of the apparently same dose in this non-GLP compliant study. In response the Applicant suggests two reasonable facts as possible explanations for differences in tolerability towards eluxadoline seen in the study: the monkeys used in the study were no study-naïve animals but had instead had prior exposure to different substances (which had induced self-administration of these substances) which may have led to greater interindividual variability; due to a food reward in one part of the study a motivational influence may have contributed to a better tolerance towards eluxadoline. This explanation was considered acceptable by the CHMP.

***Pharmacodynamic drug interactions***

Due to the low bioavailability of less than 3 % and eluxadolines local action in the gut, pharmacodynamic interactions are unlikely and the Applicant has not conducted non-clinical pharmacodynamics drug interaction studies. This was considered acceptable by the CHMP.

## 2.3.3. Pharmacokinetics

The pharmacokinetic properties of eluxadoline were studied in mice, rats, juvenile rats, dogs (beagle), monkeys (cynomolgus and rhesus monkeys) and rabbits after subcutaneous, intravenous, and oral administration. The oral ingestion is the intended route of administration in humans. To increase the systemic exposure a combination of oral and subcutaneous was used in several studies. Data for repeated administration of eluxadoline was obtained in toxicokinetic studies which accompanied the regular toxicity studies.

Bioanalytical methods have been adequately validated to determine the plasma, whole blood, urine and faeces concentrations of eluxadoline in non-clinical species (mouse, rat, rabbit and monkey).

Nevertheless a variety of studies was affected by incorrect analytical methods, which were identified by an internal review of the applicant and were excluded from further considerations. The affected 28-day cynomolgus monkey study has been superseded by longer toxicity studies, and the exposure data are therefore not considered critical. Similarly, the absence of exposure data in the cardiovascular safety pharmacology study is acceptable, considering the available supporting information relating to cardiovascular safety from other studies, including clinical studies. Therefore the removal of these data is considered to have no overall impact.

Absorption after a single oral dose of eluxadoline can be summarized to be moderate to rapid (Tmax 0.5 to 7.75 h) and with a low bioavailability (≤ 0.83 %) in mice, rats, dogs and monkeys. The low but variable

oral systemic exposure is due to limited absorption from the gastrointestinal tract and a significant first-pass effect.

In mice and rats absorption appears to be moderate to rapid after repeated application reaching maximum plasma concentrations between 0.5 to 8.0 hours lacking a clear dose proportional response although even time spans up to 24 hours are documented. The terminal half-life of eluxadoline was correspondingly variable and ranges from 3 to 39 hours. Exposure as given by the AUC or Cmax failed to show a clear linear dose response but an increase with increasing doses was visible. Eluxadoline accumulates after repeated dosing in rats. In humans the drug did not accumulate upon repeated dosing.

In monkeys the absorption appears to be moderate to slow in a 13-week oral/subcutaneous study [TOX08661] and highly variable in a 9-month oral study [1808-004]. Exposure increased with increasing doses, and higher exposure could be achieved by an accompanying subcutaneous administration of eluxadoline. Total body clearance of eluxadoline decreased as the dose increased [1808-012]. Accumulation was observed in 9-month oral toxicity study and there were no consistent gender differences. In humans the drug did not accumulate upon repeated dosing.

Data in pregnant animals obtained in rats and rabbits revealed similar results. Eluxadoline does not cross the blood/placental barrier in pregnant rats.

The absorption and first-pass clearance of eluxadoline was investigated in male rats by measuring plasma concentrations in the hepatic portal and jugular veins after a 10 mg/kg oral dose [DD07389]. Hepatic portal vein concentrations (Cmax = 72 ng/mL) were very low after oral administration indicating that absorption through the gastrointestinal wall was limited. The concentrations in jugular vein were below the limit of quantification in most samples indicating an extensive first-pass clearance of eluxadoline. Together, these data indicate that the poor systemic exposure achieved with eluxadoline after oral administration is caused by a poor absorption in combination with a significant firstpass effect. The applicant´s view that the pharmacodynamic effects of eluxadoline are mainly local is therefore considered reasonable.

Protein binding and distribution in blood cells was investigated in all relevant species including humans. Eluxadoline was moderately bound in plasma for all species including human and ranged from 68.5 % in the dog to 87.8 % in mice (FK6315). Negligible binding partitioning to red blood cells occurred.

Tissue distribution studies were performed in pigmented and non-pigmented rats and pregnant rats, and rabbits including secretion into breast milk. After an oral or SC administration of [14C]eluxadoline to rats, the highest exposure to total radioactivity (determined by AUC values) was observed in the tissues of the gastrointestinal (GI) tract and ranged from 16 to 525 µg eq.h/g. Further, total radioactivity was rapidly excreted primarily in feces (>90 %) but was also present in urine (<8 %). The greatest proportion of unchanged eluxadoline was found in the GI contents following oral dosing (FK5756). Similar results were obtained in a distribution study in mice. However, some animals showed a striking higher exposure in some tissues (e.g. brain). Placental transfer of eluxadoline administered via the subcutaneous route in pregnant rats was confirmed, but did not reach the fetal tissues. In lactating rats, eluxadoline was found to be excreted in milk, but occurred in a less than 1:1 ratio compared to systemic exposure.

A study in pigmented rats showed evenly that eluxadoline was poorly absorbed and distributed. In tissues where there were measureable concentrations, these most declined to below the LLOQ by 24 hours. Only pigmented tissues of the eye showed measureable concentrations out to 168 hours (FK6706). Therefore specific photo-toxicity studies have been performed as advised before filling (please refer to the respective toxicity section for further information).

Metabolic patterns were investigated in vitro in cryoconserved hepatocytes and in vivo in rat, dog, monkey, and human. The major metabolites and the main excretion routes were identified in each species.

Eluxadoline was not extensively metabolized in dog (11%) and human (3%) hepatocytes, but was moderately to extensively metabolized in hepatocytes from cynomolgus monkey (31%) and rat (76%) at 10 µM (FK5826). The major in vitro metabolic pathway in all non-rodent species and humans was direct glucuronidation of the methoxy-benzoic acid moiety to form the acyl glucuronide, M11. There were no metabolites identified in human hepatocytes that were not also found in rat, dog, and monkey hepatocytes. M11 was also the major metabolite identified in human intestinal microsomal incubations (FK5944). Following combination administration by the oral and SC routes, unchanged drug was the major drug-related component in the plasma of rats (99%) and cynomolgus monkeys (95-97%) as well as in urine (94-99%) and fecal samples (95-98%) of rats and monkeys (FK5858). All the in vitro metabolites identified in human hepatocytes and in clinical studies were also identified in rat, dog and monkey hepatocytes, confirming the validity of the chosen non-clinical species.

Eluxadoline is mainly excreted by faeces. Although some information is provided regarding biliary excretion of eluxadoline the database is limited.

Eluxadoline was assessed on a potential substrate or inhibitor of common drug transporters (OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, P-gp, BCRP, BSEP-, and MRP2) and its ability to induce or inhibit several CYP450 isoforms in vitro.

Eluxadoline showed no induction of CYP 1A2, 3A4, 2C9 and 2C19 in vitro in human hepatocytes or in vivo in rats. The initial in vitro induction experiment was, however, not performed to the recommendations in the EMA guideline on drug interactions (CPMP/EWP/560/95/rev corr 1*). The assessment was based on enzyme activity and CYP 2B6 was not studied. RNA levels were only measured from one donor and these showed a 2 fold increase for CYP 2C9. In a response the Applicant provided an in vitro study to evaluate eluxadoline (0.1 to 100 µM) effect on induction of CYP 2B6 in primary cultures of cryopreserved human hepatocytes (ELX-PH-03). The study revealed little or no effect on CYP 2B6 mRNA expression levels. Eluxadoline´s potential to induce CYP3A4 and CYP1A2 in vitro using human hepatocytes will be performed post authorisation and the applicant has committed to this.

The Applicant investigated as well eluxadoline´s potential for irreversible (so-called mechanism based) inhibition of hepatic CYP isoforms. Fifty micromolar of eluxadoline was found to inhibit testosterone and midazolam metabolism via CYP3A4 to 32% and 42%, respectively. The Applicant was asked to comment on a possible clinical relevance of CYP3A4 inhibition in gut epithelium, a site of possibly higher local eluxadoline concentration. As response an additional in vitro time dependent inhibition study with eluxadoline at up to 700 µM, (based on 100 mg dose and assuming 250 mL volume in the gut) in human liver microsomes (HLM) and human intestinal microsomes (HIM) was evaluated (ELX-PH-04). The results showed that eluxadoline is a metabolism-dependent inhibitor of CYP3A4/5. In NADPH-fortified HLM and HIM, an 8-fold (480 µM to 62 µM) and 14-fold (410 µM to 29 µM) shift in IC50 values, respectively, was observed with midazolam as substrate. With testosterone as substrate, the IC50 values shifted 3-fold (700 µM to 250 µM) and 15-fold (700 µM to 46 µM) in HLM and HIM, respectively. The study confirms eluxadolines potential for irreversible CYP 3A4 inhibition. In human liver microsomes, accurate KI and kinact values for inactivation of CYP3A4/5-mediated midazolam 1´-hydroxylation could not be determined due to insufficient inactivation of CYP3A4/5 within the range of eluxadoline concentrations (up to 700 µM) under the conditions studied. In human intestinal microsomes, kinact and KI values for inactivation of CYP3A4/5-mediated midazolam 1´-hydroxylation were determined to be 0.10 min-1 and 450 µM, respectively. An in vivo study to evaluate eluxadoline as a potential time dependent inhibitor with a pertinent substrate (midazolam) will be conducted post-approval as committed to by the applicant.

Eluxadoline was not transported by OAT1, OCT1, OCT2, OATP1B3, P-gp or BCRP. At the highest concentration tested (the Applicant claims that 400 ng/mL, is approximately 133-fold larger than the observed Cmax of the top therapeutic dose of 100 mg), eluxadoline was transported by OAT3, OATP1B1 and BSEP. MRP2 dependent vesicular accumulation of eluxadoline was observed at all three concentrations (4-400 ng/mL), indicating eluxadoline was a substrate of MRP2 under the experimental conditions. At a concentration of 400 ng/mL, eluxadoline did not significantly inhibit BCRP-, BSEP-, MRP2-, OCT1-, OCT2-, OAT1-, OAT3-, or OATP1B3- mediated transport of probe substrates. Compared to vehicle control, eluxadoline inhibited the transport of probe substrates of OATP1B1 and P-gp with respective inhibition of 32.6 % and 6.25 % (OPT-2012-063 and OPT-2012-064). An in vitro study was conducted to evaluate eluxadoline as a P-gp inhibitor using Caco-2 monolayer cells (ELX-PH-02). In the presence of eluxadoline (0.3 to 100 µM), the net flux of probe substrate digoxin across monolayer of Caco-2 cells was not reduced, indicating that eluxadoline is not an inhibitor of P-gp at the concentrations evaluated. Therefore inhibition of P-gp in the gut by eluxadoline appears to be unlikely.

## 2.3.4. Toxicology



The toxicity of eluxadoline was tested in mice and rats in single dose oral and intraperitoneal studies. Repeated oral toxicity was evaluated in mice, rat and monkeys. Subcutaneous injections were included to enhance the systemic exposure in rats and monkeys through the 3-month studies. Subcutaneous dose levels were limited because of local tissue irritation reactions. In rats and monkeys also 2 week intravenous studies were performed. A battery of genotoxicity studies, 2 -year carcinogenicity in mice and rats, reproductive toxicity studies, a juvenile study in rats, a local lymph node assay, a bovine corneal opacity-permeability assay and a neutral red uptake phototoxicity assay were performed.

An overview of the non-clinical toxicological studies is presented in the table below.

**Table 1 - Summary of the Toxicology Program for Eluxadoline**

| Summary of Toxicology Program for Eluxadoline | | |
|---|---|---|
| **Study type and duration** | **Route of administration** | **Species** |
| Single dose toxicity | Oral and IP | Mouse and rat |
| Repeat dose toxicity | | |
| 5 and 7 day | Oral, SC and Oral/SC | Rat and monkey |
| 1 month | Oral and Oral/SC | Mouse (Oral only), rat and monkey |
| 3 month | Oral and Oral/SC | Mouse (Oral only), rat and monkey |
| 6 month | Oral | Rat |
| 9 month | Oral | Monkey |
| 2 week | IV | Rat and monkey |
| Genotoxicity | | |
| AMES | In vitro | Bacteria |
| Lymphoma | In vitro | Mouse |
| Chromosome aberration | In vitro | Human |
| Micronucleus | IP | Rat |
| Carcinogenicity | | |
| 104 week | Oral | Mouse and rat |
| Reproductive toxicity | | |
| Fertility and early | Oral | Rat |

| Summary of Toxicology Program for Eluxadoline | | |
|---|---|---|
| **Study type and duration** | **Route of administration** | **Species** |
| embryonic development<br>Embryofetal development<br>Pre- and postnatal development | <br>Oral and SC<br><br>Oral | <br>Rat and rabbit<br><br>Rat |
| Juvenile Toxicity<br>1 month | <br>Oral | <br>Rat |
| Other<br>Murine lymph node<br>Bovine cornea<br>Phototoxicity | <br>Dermal<br>In vitro<br>In vitro | <br>Mouse<br>Bovine<br>Mouse |

Note: Oral/SC denotes studies done with concomitant oral and SC doses to increase systemic exposure



***Single dose toxicity***

Signs observed for the mice prior to death in the orally single dosed 1000 mg/kg groups were consistent with opioid pharmacology and therefore probably related to eluxadoline. Therefore 500 mg/kg was the maximum non-lethal dose of eluxadoline after a single dose administered orally or intraperitoneally in mice. Following a single oral administration, the maximum observed non-lethal dose in rats was 2000 mg/kg. After a single intraperitoneal dose of eluxadoline the observed maximum non-lethal dose was 62.5 mg/kg for males and 125 mg/kg for females.

***Repeat dose toxicity***

In the oral studies in rats (6 months) and monkeys (9 months) there were no adverse toxically signs up to the highest dose administered. The NOAEL for the rat was 2000 mg/kg/day. Based on administered dose, this represents a 100 fold margin relative to the anticipated human dose of 100 mg BID. Based on exposure (rat $AUC_{0\text{-last}}$ of approximately 260 ng·h/mL and human $AUC_{0\text{-}24h}$ of 22.8 ng·h/mL) the margin is greater than 10. The NOAEL for the monkey was 200 mg/kg/day. Based on an administered dose, this represents a 20-fold margin relative to the anticipated human recommended dose of 100 mg BID. Based on exposure (primate $AUC_{0\text{-last}}$ of approximately 300 ng·h/mL and human AUC0-24h of 22.8 ng·h/mL) the margin is approximately 13.

Eluxadoline was generally well tolerated when administered orally or by a combination of oral and subcutaneous administration to rats for 3 months at doses up to 1000 mg/kg or 200/5 mg/kg, respectively. Clinical signs were limited to the injections site after subcutaneous dosing. Evaluation of the injection site suggested the compound was an irritant in the subcutaneous tissue. Similar changes were seen at the injection site of the controls but with less distribution and severity. These changes are expected as a result of the route of administration of eluxadoline. Therefore the NOAEL level was determined to be 1000 mg/kg by oral administration and 200/5 mg/kg by oral and subcutaneous administration, respectively.

In the 28-day repeated oral/subcutaneous study in monkeys there were no effects from eluxadoline on mortality, body weights, physical, electrocardiographic or ophtalmoscopic examinations, organ weights macroscopic and microscopic observations. Not dose dependent, an increased incidence of emesis was seen with administration of eluxadoline. The NOAEL was established at 200/25 mg/kg/day.

Eluxadoline administered 13 weeks to cynomolgus monkeys oral via nasogastric intubation alone or by oral via nasogastric intubation and subcutaneous injection up to 200 mg/kg/d and 200/25 mg/kg, respectively, showed no adverse effects on mortality, food consumption, body weight, clinical pathology, macroscopic and microscopic pathology or organ weights and ECG parameters. At the injections site microscopic observation showed fibrosis, necrosis and infiltration of histiocytic cells most likely attributed to the vehicle and through repeated SC injection trauma. The NOAEL was considered to be 200 mg/kg/day and 200/25 mg/kg/day for the oral via nasogastric intubation alone or oral via nasogastric intubation and subcutaneous injection, respectively. Systemic levels with the SC boost as the $C_{max}$ and AUC0-24h values were greater than 12000 ng/ml and 15000 ng·h/ml, respectively. Based on administered dose, this represents a 4000- and 650-fold margin over the $C_{max}$ and AUC0-24h values at the human therapeutic dose of 100 mg BID.

Eluxadoline administered intravenously 7 days to cynomolgus monkeys at up to a dose of 40 mg/kg/day resulted in the rescue of animals at 30/40 mg/kg and death at 40 mg/kg (one animal). Body weight loss and inappetence was noted in a non-dose dependent manner at all dose levels, the loss in body weight was only considered to be adverse in males at 40/40 mg/kg. Decreased activity, unresponsiveness and decreased body temperature and/or respiration rates were adverse at ≥ 20 mg/kg. The NOAEL of eluxadoline when administered intravenously to monkeys for 7 day is 10 mg/kg/d.



Eluxadoline administered 2 weeks by IV injection to cynomolgus monkeys up to 20 mg/kg/d showed no effects on mortality, body weight, ophthalmological findings, haematology, coagulation, clinical chemistry, urinalysis parameters, macroscopic and microscopic pathology or organ weights. The incidence of tremors was considered test article related, but not adverse. Based on an administered dose, this represents a 170-fold to more than 1200-fold margin relative to the anticipated human recommended dose of 100 mg BID, based on exposure (primate $AUC_{0\text{-last}}$ of approximately 4000 ng·h/mL at the 5 mg/kg dose and 28000 ng·h/mL at the 20 mg/kg dose and human $AUC_{0\text{-}24h}$ of 22.8 ng·h/mL).

***Genotoxicity***

Eluxadoline was tested for genotoxicity in an ICH S2 compliant battery of tests with negative results. Eluxadoline precipitated at high concentrations (up to the guideline recommended limit of top dose) in the cell culture medium in in vitro tests, demonstrating saturation to the limit of solubility. Even at saturation eluxadoline exhibited only mild to moderate cytotoxicity (18 – 37 % reduction of mitotic index). Eluxadoline is therefore not considered to expose any biologically relevant genotoxic potential.

***Carcinogenicity***

Eluxadoline was tested for carcinogenic effects in two life time rodent bioassays. Dose selection was based on repeated dose studies in mice and rat. Top doses provided margins of exposure of >2 to >5 fold even to oral single doses of 2000 mg in humans (10 times the recommended daily treatment dose). Eluxadoline was non-toxic in mouse and rat compared to controls and did not provide evidence for any treatment related carcinogenic effects. All observations, non-neoplastic or neoplastic, were not significantly different to control animals. The only observations were those typical for ageing mice and rats of the strains used. In mice usual findings like hyperplasia in adrenal glands and usual types of lymphomas in various organs were equally observed in control and treated animals. In rats usual finding like minimal to mild chronic progressive nephropathy, bile duct hyperplasia in liver, alveolar histocytosis, mammary gland adenocarcinoma and lobular hyperplasia or benign pituitary gland adenomas or benign thyroid gland c-cell adenoma were equally observed in control and treated animals. Carcinogenicity studies did not show evidence for a tumorigenic potential of eluxadoline.

***Reproduction Toxicity***

In the fertility and embryo-foetal development study in rats, there were no adverse effects on reproductive parameters (estrous cyclicity, mating, fertility, and fecundity indices) at any dose. However, slightly lower body weight gains in male animals were noted in the 300 and 1000 mg/kg/day groups, there was no impact on mean body weight. Therefore the NOAEL for the reproductive parameters can be set at 1000 mg/kg/day.

Oral/subcutaneous developmental toxicity studies were performed in rats and rabbits. In rats 100 mg/kg/day of eluxadoline induced maternal toxic effects; therefore no NOAEL could be established for maternal toxicity. The findings observed in the dams were reduced body weight gain and food consumption, but did not occur during the post-treatment period. No other maternal toxicity occurred. Post implantation loss at the highest dose of 1000/5 mg/kg/day occurred, but presumably is a result of maternal toxicity and not a direct effect of eluxadoline. In the foetuses wavy ribs were seen. In foetuses the incidence of the skeletal variant wavy ribs are frequently observed, when maternal toxicity has been produced. These changes were considered to be an indication of a non-specific response to the observed maternal toxicity and not a direct effect of eluxadoline. Overall there was no effect on pregnancy parameters (corpora lutea, implantations, early and late resorptions, live foetuses, the extent or pre-implantation loss, mean foetal body weight or sex ratio). In rabbits 100 mg/kg/day of eluxadoline induced maternal toxic effects; therefore no NOAEL could be established for maternal toxicity. The findings observed in the dams were reduced body weight gain and food consumption. Due to maternal toxicity rib variations were seen in rabbits. The developmental NOAEL is considered to be higher than 300 mg/kg/day.

In the pre- and postnatal study in rats the NOAEL was set at the highest dose of 1000 mg/kg/d for maternal toxicity, maternal reproductive function and F1 reproductive function. Based on TK exposure data ($C_{max}$/AUC) from the oral 26 week toxicity study in rats (1808-007) at 1000 mg/kg/d the exposure margins are greater than 15 based on $C_{max}$ and 9.2 times based on AUC compared to the human exposure at 100 mg/bid the maximal clinical dose.

In the 4 week oral toxicity study in juvenile rats, there were no test article-related effects on mortality, body weight, and food consumption in females, clinical observations, haematology coagulation, clinical chemistry, urinalysis parameters, organ weight and macroscopic evaluation in either sex up to and inclusive of 1500 mg/kg/day. The slight decrease in food consumption in males in all treatment groups on day 4 had no impact on body weights and did not consists throughout the study. Therefore it was not considered to be adverse. The NOAEL was estimated to be 1500 mg/kg/day for male and female general toxicity. Thus the safety profile in juvenile animal's equivalent to a 6 year old human is comparable with that seen in adult animals.



***Toxicokinetic data***

Please refer to the above chapters on repeat-dose toxicity, reproductive toxicity and carcinogenicity.

***Local Tolerance***

A local lymph node assay was performed to evaluate the skin sensitization potential of eluxadoline by measuring the ability of eluxadoline to induce proliferation of lymphocytes from the auricular lymph nodes of topically-treated CBA/J mice. Doses were 10, 25, and 50 % (w/w) of eluxadoline in N,N-dimethylformamide. The mean stimulation indexes were 1.0, 1.3 and 1.2, respectively. Therefore eluxadoline was not a contact sensitizer under the study conditions.

The ocular irritation potential of eluxadoline was assessed in a vitro bovine corneal opacity-permeability (BCOP) assay. Eluxadoline was tested as a 20% suspension and induced no increase in corneal opacity and no relevant increase in permeability. Eluxadoline was classified as a non eye irritant.

***Other toxicity studies***

A neutral red uptake phototoxicity assay was performed with eluxadoline in Balb/c3T3 mouse fibroblasts, because eluxadoline showed a slight absorption at 280 nm. Eluxadoline did not demonstrate cytotoxicity or phototoxicity in the assay. Although eluxadoline apparently accumulates in the pigmented parts of eyeball and uveal tract, eluxadoline likely does not seem to exhibit a risk for phototoxic effects within the eye due to accumulation.

## 2.3.5. Ecotoxicity / environmental risk assessment

**Summary of main study results**



| **Substance (INN / Invented Name): Eluxadolin** | | | | | |
|---|---|---|---|---|---|
| **CAS-number (if available):** 864821-90-9 | | | | | |
| ***PBT screening*** | | Result | | | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | OECD107 | -0.8 (pH 4)<br>-0.5 (pH 7)<br>-1.4 (pH 9) | | | Potential PBT N |
| ***PBT-assessment*** | | | | | |
| **Parameter** | **Result relevant for conclusion** | | | | **Conclusion** |
| Bioaccumulation | log $K_{ow}$ | <1 at pH 4,7 and 9 | | | not B |
| **PBT-statement :** | The compound is not considered as PBT nor vPvB | | | | |
| ***Phase I*** | | | | | |
| ***Calculation*** | **Value** | **Unit** | | | **Conclusion** |
| PEC $_{surfacewater}$ , default or refined (e.g. prevalence, literature) | 1 | µg/L | | | > 0.01 threshold Y |
| Other concerns (e.g. chemical class) | | | | | N |
| ***Phase II Physical-chemical properties and fate*** | | | | | |
| **Study type** | **Test protocol** | **Results** | | | **Remarks** |
| Adsorption-Desorption | OECD 106 | $K_{oc}$ = | | | Pending |
| Aerobic and Anaerobic Transformation in Aquatic Sediment systems | OECD 308 | $DT_{50, water}$ =<br>$DT_{50, sediment}$ =<br>$DT_{50, whole system}$ =<br>% shifting to sediment = | | | Pending |
| ***Phase IIa Effect studies*** | | | | | |
| **Study type** | **Test protocol** | **Endpoint** | **value** | **Unit** | **Remarks** |
| Algae, Growth Inhibition Test/*Species* | OECD 201 | NOEC | 100 | mg/L | *Pseudokirchneriella subcapitata* |
| *Daphnia* sp. Reproduction Test | OECD 211 | NOEC | 100 | mg/L | *Daphnia magna* |
| Fish, Early Life Stage Toxicity Test/*Species* | OECD 210 | NOEC | | µg/L | Pending |
| Activated Sludge, Respiration Inhibition Test | OECD 209 | EC | | µg/L | Not acceptable |

The Applicant provided 4 study reports on Phase Tier A environmental risk assessment.

The studies on the partition coefficient by shake flask method (OECD 107), on algal growth inhibition (OECD 201) and on Daphnia magna reproduction (OECD 211) are considered acceptable for the environmental risk assessment.

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of Eluxadoline to the environment.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for further investigation:

To submit all the relevant Phase II Tier A & Tier B study reports including an updated ERA after completion. Beside a water-sediment study and an adsorption/desorption study, the applicant should provide a new respiration inhibition study according to OECD 209 under consideration of the above mentioned points for improvement. The test substance should be added directly into the test vessels or an analytical estimation of the real test concentration in the test vessels should be performed.

## 2.3.6. Discussion on non-clinical aspects



Eluxadoline was shown to act as an agonist at the μ opioid receptor and as an antagonist at the δ opioid receptor. The binding affinities (Ki) of eluxadoline for human μOR and δOR were 1.8 nM and 430 nM, respectively. Pharmacodynamic action was demonstrated in several models of stress induced or post GI inflammation-altered GI function in animals showing normalizing GI transit and defecation.

Pharmacokinetic studies showed that eluxadoline has a very low oral bioavailability, supporting the claimed local activity of eluxadoline in the gut. In vitro studies demonstrated that eluxadoline was stable in human hepatocytes, liver and intestinal microsomes, and that the only minor and inactive metabolite of eluxadoline detected was the acyl glucuronide metabolite (M11) formed through glucuronidation of the methoxybenzoic acid moiety. However it is considered that further work is required to investigate possible reactive metabolites e.g. reactive metabolite assays in human liver, and if possible also gut, microsomes to provide more information on the mechanism and the applicant is recommended to investigate the potential for reactive metabolites in human and gut liver microsomes.

In rat, eluxadoline was excreted into milk in an approximately dose proportional manner with maximal concentrations less than plasma concentrations. As it is unknown whether eluxadoline is excreted in human milk and a risk to the newborns/infants cannot be excluded a decision must therfore be made whether to discontinue breast-feeding or to discontinue/abstain from Truberzi therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman as outlined in 4.6 of the SmPC. Some animals showed an atypical increase of eluxadoline concentrations in different tissues and in milk however eluxadoline was safe and well tolerated following a single 1000 mg dose (10-fold higher than the therapeutic dose) in humans and the drug did not accumulate upon repeated dosing.

Results of safety pharmacology studies are in line with eluxadoline´s action via opioid receptors. When the product was administered orally to animals at effective doses there were no detectable central nervous system (CNS)-mediated effects.

Eluxadoline was not considered to be a hERG channel blocker when tested at concentrations up to 3 μM. Minor effects on QTc in guinea pigs are not thought to be related to eluxadoline administration, supported by the absence of electrophysiological effects in in vitro studies. In addition, long term administration of oral eluxadoline to cynomolgus monkeys at dose levels up to 200 mg/kg was not associated with changes in qualitative or quantitative ECG parameters. In humans, no effects on cardiac repolarisation were seen following a definitive oral QTc study at oral doses of 100 mg and 1000 mg.

The in vitro studies in human intestinal microsomes demonstrating eluxadoline to be a metabolism-dependent inhibitor of CYP3A4/5 were not substantiated by an in vivo DDI study as per EMA guideline CPMP/EWP/560/95/Rev. 1 Corr. 2**. An in vivo DDI study to evaluate eluxadoline as a potential time dependent inhibitor of Cyp3A using midazolam as pertinent substrate of Cyp3A4 will be carried out as a Post Authorisation Measure. Also Eluxadoline´s potential to induce CYP3A4 and CYP1A2 in vitro using human hepatocytes was not investigated by the applicant and will be performed post authorisation.

As a result of the abuse liability studies in Rhesus monkeys, eluxadoline could have opioid-like abuse liability if parenteral administration of sufficiently high doses could achieve exposures in the range of the lowest dose producing a liability signal in monkeys. The Applicant calculated that in humans either 1023 g PO, or ~31 g intranasal (IN) or 318 mg IV would be needed to reach such exposures (Cmax). The predicted PO and IN doses are considered not practical for abusive purpose. It is concluded that the non-clinical data clearly suggest that eluxadoline has no abuse or dependence liability if used as directed by the oral route of administration. The applicant has conducted two abuse liability studies and this potential risk is addressed further in the clinical part of this assessment report. As outlined in the SmPC based on the physical-chemical and biopharmaceutical properties (very low oral bioavailability), Eluxaduline is expected to have minimal abuse or dependence liability.

The principal findings in the toxicity studies could be generally attributed to the pharmacological effects of eluxadoline and occurred only after either SC-boost or when administered intravenously. The results from the toxicity studies showed no evidence for genotoxicity, carcinogenic potential and toxicity to reproduction and development.

The available data on environmental risk assessment do not allow concluding definitively on the potential risk of Eluxadoline to the environment. This issue will be addressed after completion of all the relevant study reports and submission an updated ERA post authorisation.



### 2.3.7. Conclusion on the non-clinical aspects

There are no non-clinical objections to the granting of a marketing authorisation to eluxadoline. To give further insight into potential drug-drug interactions an in vivo DDI study to evaluate eluxadoline as a potential time dependent inhibitor of Cyp3A using midazolam as pertinent substrate of Cyp3A4 will be carried out as a Post Authorisation Measure. Also Eluxadoline´s potential to induce CYP3A4 and CYP1A2 in vitro using human hepatocytes was not investigated by the applicant and will be performed post authorisation as described in the RMP.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

The applicant presents 13 clinical studies in support of the MAA.

The clinical pharmacokinetic (PK) profile of eluxadoline has been evaluated in 11 studies in which the plasma concentrations of drug were measured following administration to healthy subjects and to patients with IBS-d. These include 10 Phase 1 studies in healthy and hepatic impaired subjects, and one dose ranging Phase 2 study in which pharmacokinetic data in IBS-d patients was collected using a sparse sampling approach (Population PK). 3 of these 10 studies primarily investigated off-target pharmacodynamics (QT prolongation and abuse liability).

In support of the clinical efficacy and safety, 3 studies are presented, IBS-2001 is the phase 2 dose-finding and preliminary efficacy and safety study mentioned above, and 2 phase 3 efficacy and safety study, with both having a 6 months study period for the proof of efficacy, and one of them having an extended placebo-controlled safety extension of up to 1 year.

***GCP***

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

**Table 2 - Overview of Clinical Pharmacokinetics and Pharmacodynamic Studies for eluxadoline:**

| Type of Study | Study Identifier | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Total N° of Subjects enrolled | Healthy Subjects or Diagnosis of Patients | Duration of Treatment |
|---|---|---|---|---|---|---|---|
| **Phase 1 studies** | | | | | | | |
| BA | 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 | Single dose |
| BA | 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 | Single dose |
| SAD/ MAD | 27018966 EDI1001 (EDI-1001) | 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 |
| | | | | 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) | Mass balance | Open label, single dose | Capsule containing 100 µCi [$^{14}$C]-eluxadoline; 300 mg single dose; PO | 8 | Healthy men | Single dose |
| PK in special population | 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 | Single dose |
| DDI | 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 | 53 | Healthy women | 7 days |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| DDI | 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 | Single dose |
| PD QTc | 27018966 CPS1008 (CPS-1008) | QTc | Randomized, evaluator blinded, single dose, 4 period, crossover<br>Placebo and positive control (moxifloxacin) | Eluxadoline tablet; 100 and 1000 mg single dose; PO | 64 | Healthy men and women | Single dose |
| PD | 27018966 CPS1006 (CPS-1006) | Oral abuse potential | Randomized, double blind, 6 period, crossover<br>Placebo and active control (oxycodone) | Eluxadoline tablets; 100, 300, and 1000 mg single dose; PO<br>Oxycodone IR tablets; 30 and 60 mg single dose; PO | 40 | Nondependent recreational opioid users, otherwise healthy men and women | Single dose |
| PD | 27018966 CPS1010 (CPS-1010) | Intranasal abuse potential | Randomized, double blind, 6 period, crossover<br>Placebo and active control (oxycodone) | Eluxadoline tablets (crushed); 100 and 200 mg single dose; intranasal<br>Oxycodone IR tablets (crushed); 15 and 30 mg single dose; intranasal | 36 | Nondependent recreational opioid users, otherwise healthy men and women | Single dose |

**Table 3 - Description of efficacy and safety studies:**

| Study ID/ year of conduct | Design | Study Posology | Study Objective | Subjs by arm entered / compl. | Duration | Gender M/F Median Age | Diagnosis Incl. criteria | Primary Endpoint |
|---|---|---|---|---|---|---|---|---|
| IBS-2001<br><br>4/ 2010 – 07/ 2011 | Randomized, double-blind, parallel Placebo control | Eluxadoline: 5 mg PO BID<br>25 mg PO BID<br>100 mg PO BID<br>200 mg PO BID<br>Placebo | Efficacy, safety, and PK | 111/50<br>174/131<br>176/123<br>174/103<br>172/118 | 12 weeks + 2-week post-treatment follow-up | 246/561<br>46 yrs<br>(18-65) | IBS-d<br>1 wk prior to random:<br>-average daily abdominal pain scores ≥ 3.0<br>-average BSS ≥ 5.5<br>-diary compliance | Study composite response over Weeks 1 -12 (post hoc) |
| IBS 3001<br><br>5/ 2012 - 07/ 2014 | Randomized, double-blind, parallel Placebo control | Eluxadoline: 75 mg PO BID<br>100 mg PO BID<br>Placebo | Efficacy, safety, and long-term safety | 429/257<br>426/257<br>427/269 | 52 weeks + 2-week post-treatment follow-up<br><br>(efficacy evaluations for 6 months) | 444/838<br>45 yrs<br>(18-80) | IBS-d<br>1 wk prior to random:<br>-average daily worst abdominal pain > 3.0<br>-average BSS score ≥ 5.5 & ≥ 5 days with a BSS score ≥ 5<br>-IBS-d global symptom score ≥ 2<br>-diary compliance | Proportion of composite responders for Weeks 1 12 (FDA) and Weeks 1 26 (EMA) |
| IBS 3002<br><br>5/ 2012 - 01/ 2014 | Randomized, double-blind, parallel Placebo control | Eluxadoline: 75 mg PO BID<br>100 mg PO BID<br>Placebo | Efficacy and Safety | 381/250<br>383/264<br>382/273 | 26 weeks + 4-weeks single-blinded withdrawal | 378/768<br>45.5 yrs<br>(18-77) | IBS-d<br>1 wk prior to random:<br>-average daily worst abdominal pain > 3.0<br>-average BSS score ≥ 5.5 & ≥ 5 days with a BSS score ≥ 5<br>-IBS-d global symptom score ≥ 2<br>-diary compliance | Proportion of composite responders for Weeks 1 12 (FDA) and Weeks 1 26 (EMA) |



## 2.4.2. Pharmacokinetics

***Absorption***

Aqueous solubility across the pertinent pH range is complete and rapid and eluxadoline tablets were developed as a rapidly dissolving (immediate release) solid tablet dosage form reaching more than 85% dissolution in less than 15 minutes.

A formal absolute bioavailability study in humans has not been performed and an IV formulation was not developed for use in humans. Allometric PK scaling from animal data was used to estimate the human IV/systemic clearance and resulted in $F_{oral}$ of 1.02% to 1.34% depending on the method used. The available pharmacokinetic data confirm that exposure of eluxadoline is low, regardless of formulation used.

The absorption of eluxadoline is rapid with a median Tmax observed between 1.5 and 3 hours, in different studies.

Two open-label crossover studies evaluated the effect of a high fat meal on the PK profile of a single oral dose of eluxadoline in healthy adult subjects (500mg in Study EDI-1002 and 100mg in CPS-1009). The administration of eluxadoline with a high fat meal significantly decreased both $C_{max}$ (50%) and AUC (60%) without any effect on $T_{max}$. Upon administration of multiple oral doses twice daily, there was no accumulation of drug. These studies demonstrate that both eluxadoline peak and total exposures are reduced in the presence of food to a similar degree, indicating that food affects both rate and extent of absorption. Consequently, it is recommended that eluxadoline be taken with food to reduce systemic exposure, as reflected in the PI.

***Distribution***

Eluxadoline is moderately (81%) bound to human plasma proteins and, in pre-clinical species, the volume of distribution is low. In a population pharmacokinetic analysis, the estimated apparent volume of distribution of eluxadoline was 27100 L. It is suggested that eluxadoline is transported by OAT3, OATP1B1 and BSEP at the highest concentration studied and by MRP2 at all concentrations.

After Tmax, plasma concentrations showed a biphasic decline with a rapid initial alpha phase, followed by a more gradual terminal beta-phase which may reflect enterohepatic recycling of eluxadoline.

The variability of eluxadoline pharmacokinetic parameters was high (up to 98%). Low oral bioavailability (estimated Foral ~1.02% to 1.3% for oral suspension formulation) is suggested a major source of between-subject variability in eluxadoline exposures. The poor oral BA is suggested to be primarily due to poor GI permeability, but also to moderate hepatic first-pass extraction.

***Elimination***

According to the mass balance ADME study of 14C-labeled eluxadoline (EDI-1003), faecal excretion is the primary route of elimination for eluxadoline, while renal excretion is minor. Following a single oral dose of 300 mg [14C] eluxadoline in healthy male subjects, on average 0.12% of the administered total radioactivity was recovered in urine in 192 hours and the majority of 82.2% was recovered in faeces in 336 hours. In study EDI-1001 (MAD), the very low percentage of dose (<0.14%) recovered as unchanged drug in the urine supports limited renal excretion and/or poor oral bioavailability.

Metabolism of eluxadoline is not clearly established. There is evidence that glucuronidation can occur to form an acyl glucuronide metabolite of eluxadoline (M11). M11 was the only metabolite detected in urine in study FK6533 and accounted for less than 0.1% of the total dose of eluxadoline. No circulating metabolites have been identified in human plasma. Based on in-vitro and animal data, elimination occurs mainly as unchanged drug with some metabolism by CYP1A2 and CYP2D6 as well as UGT1A3 and UGT2B7.

S,S-eluxadoline is not bio-transformed into S,R-eluxadoline at quantifiable levels. Following supratherapeutic dosing with 1000 mg of eluxadoline, systemic exposure to S,R-eluxadoline was less than 1% of the systemic exposure to S,S-eluxadoline in the few individuals that had quantifiable concentrations.

The in vitro assays indicated that eluxadoline has a low potential for drug-drug interactions (DDIs) based on CYP reversible inhibition or induction at clinically relevant systemic concentrations. However, eluxadoline has some potential for the mechanism based inactivation of CYP3A4. A new in-vitro study conducted during the assessment and the estimation of the ratio of predicted clearance of enzyme in the absence and the presence of the inhibitor was calculated according to the Guideline on the Investigation of Drug interactions (CPMP/EWP/560/95/Rev.1 Corr 2) and revealed a need for the conduct of a further

in-vivo study, which will be conducted post-approval and should be submitted as a Post Authorisation Measure as reflected in the RMP.

In vitro assays further suggest that eluxadoline is a substrate for OAT3, OATP1B1, BSEP and MRP2, but not for OAT1, OCT1, OCT2, OATP1B3, P-gp and BCRP (Study OPT-2013-064).However, based on in vitro assays, clinically meaningful interaction via inhibition of OCT1, OCT2, OAT1, OAT3, OATP1B3, BSEP and MRP2 by eluxadoline is unlikely.

Eluxadoline demonstrated some inhibition potential for OATP1B1 and P-gp. Regarding P-gp, an in vitro study using a concentration range complying with EMA guideline CPMP/EWP/560/95/Rev. 1 Corr. 2**, however, did not confirm the inhibitory potential previously observed at lower concentration.

***Dose proportionality and time dependencies***

Eluxadoline appears to be essentially dose proportional for Cmax and AUC0-24 over the range of 30- 300 mg. Eluxadoline does not accumulate on multiple dosing. There is some evidence of a decrease in Cmax on Day 7 which is attributed to variability and inconsistency in fed status.



***Special populations***

**Impaired renal function**

Eluxadoline has not been specifically studied in patients who have renal impairment. Given the low oral bioavailability (estimated Foral 1.3% for the suspension formulation) of eluxadoline and limited renal elimination, renal impairment is not expected to affect clearance of eluxadoline in a clinically significant manner. Severe renal failure is expected to increase systemic exposure of eluxadoline by no more than 25-30%. Adequate statements have been included in the PI.

**Impaired hepatic function**

The influence of hepatic impairment on the pharmacokinetics of eluxadoline was investigated in study (CPS-1005), an open-label, single-dose, parallel-group, multicentre study. Following a single oral 100–mg dose to-be marketed formulation in subjects with varying degrees of liver impairment and healthy subjects, mean eluxadoline plasma exposure was 6-fold, 4-fold, and 16-fold higher in mild, moderate, and severe hepatically impaired subjects (Child Pugh Class A, B, C), respectively, compared to the subjects with normal liver function. The apparent clearance of eluxadoline is markedly reduced and half-life is increased in hepatic-impaired patients. The hepatic impairment study CPS-1005 supports hepatic elimination as the key route of elimination for eluxadoline. Hepatic impairment is a contraindication as outlined in the SmPC.

**Gender, Race, BMI, Age**

Prospective clinical studies regarding differences in age, weight (body mass index (BMI)), ethnicity, In the pooled analysis of PK data for healthy volunteers across Phase 1 studies using the 100 mg single oral dose, the observed variability of the PK parameters was large for all analysed intrinsic factors (i.e. gender, race, weight and age) and the data range substantially overlapped. Hence, no significant differences in the PK parameters among any of the intrinsic factors (age, BMI, gender, etc.) were observable. Based on this, and the fact that the clinical documentation for the age group of patients above 65 years of age was considered sufficient, the complete lack in the documentation of PK for patients older than 65 years of age was considered acceptable. PK was not measured in patients with IBS-d using full pharmacokinetic sampling. In the Population PK/PD analysis including patients with IBS-d from Phase 2 study IBS-2001, demographic covariates were not detected as significant components explaining the variability of PK

parameters of eluxadoline. However maximum age of included patients was 65, hence PK in older subjects was potentially not fully addressed in this study (see above). From the data, PK in the target population does not appear to be any different from that in healthy volunteers.

High between-individual variability was observed for all the model parameters. Consequently, individual subjects /patients are expected to experience much higher rate and extent of exposures as compared to the described means. The potential for increased plasma levels due to OATP1B1 genetic variability and due to any other cause of is addressed in section 4.4 of the SmPC with a recommendation to monitor for impaired mental or physical abilities.

***Pharmacokinetic interaction studies***

In vitro and clinical drug-drug interaction studies indicated OATP1B1 is the primary drug transporter involved in the hepatobiliary elimination of eluxadoline. Data on the impact of OATP1B1 haplotype on the PK (based on POP-PK analysis and sparse sampling) indicate a consistent pattern of increasing total exposure with decreasing transporter function, the clinical relevance of which is, however, difficult to assess, due to the low numbers of patients with poor OATP1B1 function and the overall high variability. Co-administration of eluxadoline with Cyclosporine A (CSA) confirms the primary involvement of OATB1B1 in the elimination of eluxadoline. A 4- to 6-fold elevation of rate and extent of exposure was seen in this DDI study. The magnitude of the influence of this effect is similar to the one seen in patients with hepatic impairment, and therefore a contraindication (as for hepatically impaired patients) is included in the SmPC.

Whether SLCO1B1 polymorphism additionally affects the extent of interaction between OATP1B1 inhibitors (e.g. CSA) and eluxadoline or the in vivo handling of glucuronic acid conjugates of eluxadoline was not investigated.

Following a single oral 100–mg dose to-be marketed formulation in subjects with varying degrees of liver impairment and healthy subjects, mean eluxadoline plasma exposure was 6-fold, 4-fold, and 16-fold higher in mild, moderate, and severe hepatically impaired subjects (Child Pugh Class A, B, C), respectively, compared to the subjects with normal liver function. Consequently, the substance is proposed to be contraindicated in all patients with any grade of liver impairment based on the observed increase in adverse events with higher doses (both for HVs and patients and mainly due to CNS-related and gastrointestinal events). Similar considerations do apply for the patients taking OATP1B1 inhibitors (see above).

Further interaction studies with Probenicid and oral contraceptives only indicated minor or no changes in PK. The results with regard to probenecid indicate a minor role of the efflux transporter MRP2 in (hepatic and renal) elimination of eluxadoline as well as in the intestinal absorption of eluxadoline. Hence, co-administration with any MRP2 inhibitor is not thought to require dose adjustment of eluxadoline.

An interaction study with the OATP1B1 substrate rosuvastatin indicated only minor differences in the PK profile of rosuvastatin and the comparison of adverse event frequencies in patients taking concomitant OATP1B1 substrates did not reveal relevant differences compared to those patients not taking these medicines. Nevertheless, a warning has been implemented in cases when high doses of these compounds are already given to patients (e.g. statins and sartans).

## 2.4.3. Pharmacodynamics

No PD biomarkers for eluxadoline have been identified. The PD effect was assessed by improvement in stool frequency and consistency. However, no clear dose- response relationship was identified in the Phase 1 dose-escalation study (EDI-1001) with similar decreases in stool frequency and consistency observed with the 150mg BID and 500mg BID doses for 7 days. The therapeutic potential with regard to the influence on abdominal pain has not been evaluated.

Three PD studies have been performed to investigate potential "off-target" effects.

These included a study to demonstrate CV safety (study CPS-1008 as a t-QT study), and two abuse liability studies (CPS-1006 for the oral abuse potential, and CPS-1010 for the intranasal abuse potential).

The primary pharmacodynamics have been elucidated by in vitro radioligand binding studies and functional assays which demonstrated that eluxadoline is a mu opioid receptor (μOR) agonist and delta opioid receptor (δOR) antagonist as well as by animal models of stress-induced or post-GI inflammation-altered GI function which proved the ability of eluxadoline to normalize GI transit and defecation and to reverse hyperalgesic responses.



***Mechanism of action***

Eluxadoline is a locally acting, mixed mu opioid receptor (μOR) agonist and delta opioid receptor (δOR) antagonist. Eluxadoline is also an agonist at the kappa opioid receptor (κOR). The binding affinities (Ki) of eluxadoline for human μOR and δOR are 1.8 nM and 430 nM, respectively. The binding affinity (Ki) of eluxadoline for human κOR has not been determined; however, the Ki for guinea pig cerebellum κOR is 55 nM. In animals, eluxadoline interacts with opioid receptors in the gut. Eluxadoline has demonstrated efficacy in normalizing GI transit and defecation in several models of stress induced or post GI inflammation-altered GI function in animals. Eluxadoline has very low oral bioavailability and exerts no detectable central nervous system (CNS)-mediated effects when administered orally to animals at effective doses. Eluxadoline also reverses hyperalgesic responses in an animal model of acute colitis-induced visceral pain.

***Primary and Secondary pharmacology***

***Primary pharmacology***

Eluxadoline has GI-transit inhibiting activity consistent with a μOR agonist. No PD biomarkers for eluxadoline have been identified. The PD effect is assessed by improvement in abdominal pain and stool consistency. No clear dose- response relationship was identified in the Phase 1 dose-escalation study (EDI-1001) with similar decreases in stool frequency and consistency observed with the 150mg BID and 500mg BID doses for 7 days. The maximum tolerated dose of eluxadoline after single dose administration was determined to be 1500mg in men due to higher incidence of AEs at 2000mg, which were predominantly GI in nature (nausea, abdominal pain and constipation).

IBS-d patients were postulated to be more sensitive to all drugs compared to healthy volunteers. Therefore, the applicant elected to assess 4 doses of eluxadoline in the Phase 2 study (5mg, 25mg, 100mg and 200mg all BID); the maximum dose of 200mg BID was in the lower-mid range of the multiple ascending dose study.

***Secondary pharmacology***

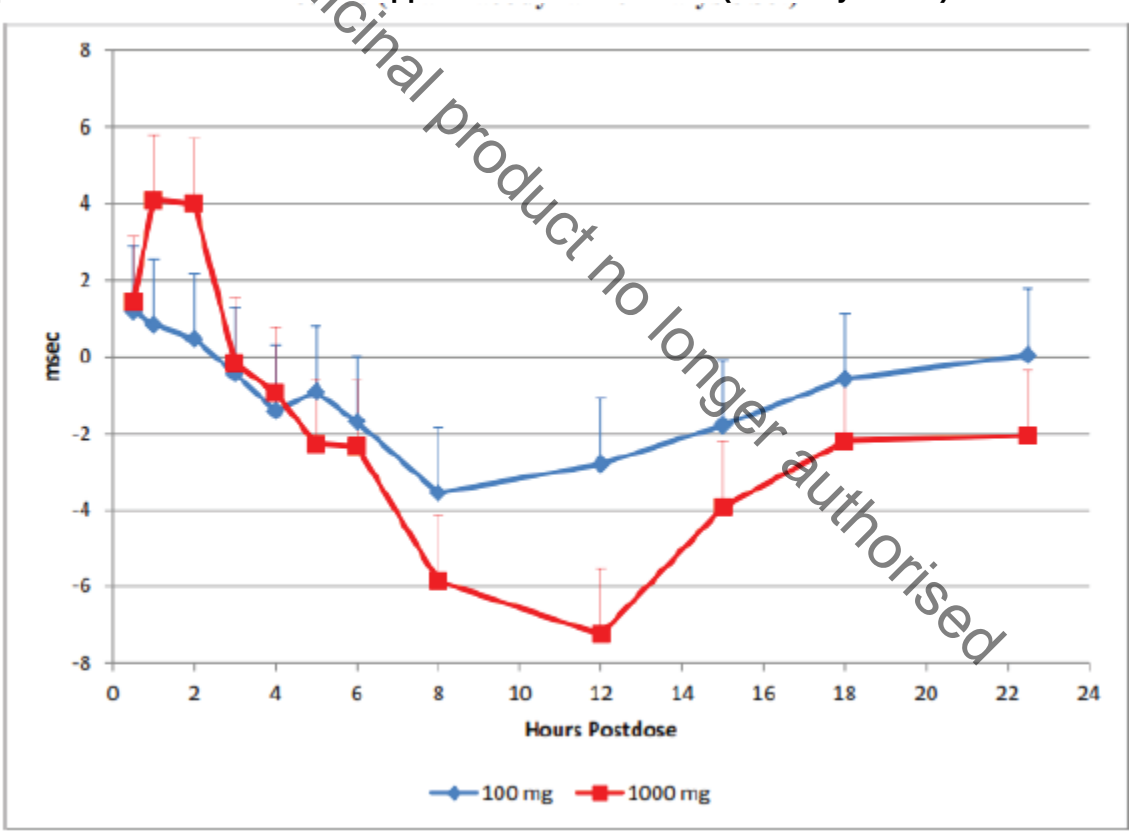
The most frequent AEs in the phase 1 dose-escalation study were nervous system disorders, particularly dizziness, postural dizziness and headache, which did not appear to be dose related. The incidence of orthostatic hypotension prompted the applicant to conduct ambulatory blood pressure monitoring in a subset of patients in the Phase 2 trial. Overall, mean ambulatory blood pressure results were similar between treatment groups and the mean values observed at Week 2 were similar to those observed at Baseline. Assessment of sitting and standing blood pressure revealed no consistent pattern and the incidence of asymptomatic orthostatic hypotension was comparable across treatment groups.

*Through QT Study*

Study CPS-1008 was a 4-period crossover study evaluating the effect of single oral therapeutic and supratherapeutic doses of eluxadoline (100 and 1000 mg) on cardiac repolarization in healthy subjects. A positive control (400 mg moxifloxacin) was used to validate assay sensitivity and a placebo arm was also included. The study was conducted in 60 healthy volunteers. The following graphical display shows the main results of the study:



**Figure 1 - Mean eluxadoline time-matched QTcI differences from placebo in change from pre-dose baseline and 95% upper confidence bounds (PD analysis set):**




Assay sensitivity could be demonstrated by showing that moxifloxacin exceeded the pre-defined lower 1-sided 95% CIs on the mean differences (up to 10.25 ms). Contrary to this, the supratherapeutic dose of eluxadoline showed only marginal increases (with “borderline” results at two time-points), and the therapeutic dose did not exceed the pre-defined safety threshold at any time-point. Categorical analyses were unremrakable.

***Abuse Liability Studies***

Studies CPS-1006 and CPS 1010 investigated the oral and intranasal abuse potential of the compound by standard evaluations with regard to the determination of the abuse potential. Both studies were blinded, randomised, placebo and active-controlled cross-over studies conducted in subjects with a history of opioid (ab-)use without being addicted. The study for the oral use investigated the doses of 100, 300, and 1000 mg eluxadoline, and the intranasal study investigated the doses of 100 and 200 mg exluxadoline. Active control consisted of 30 and 60 mg IR oxycodone orally 15 and 30 mg IR oxycodone intranasally. Both studies included a "qualification procedure" in order to evaluate suitability of the subjects included and "assay sensitivty" of administering oxycodone.

The following endpoints were evaluated in these studies:

- Evaluation of "Drug Liking" via VAS ("good" effects and "bad" effects). This was done with the Overall Drug Liking VAS, Good Effects VAS, High VAS, Bad Effects VAS, Any Effects VAS, Alerness/Drowsiness VAS, Take Drug Again VAS, and the Drug Similarity VAS).
- The Addiction Research Center of the US Public Health Service Inventory (ARCI short version, a 5-item instrument for the assessment of drug effects and abuse liability, of which 3 were used in the study: The "Euphoria Morphine-Benzedrine Group (MBG) scale, the Dysphoria (LSD) scale, and the Sedation (Pentobarbital-Chlorpromazine-Alcohol Group) PCAG scale)
- - "Subjective Drug Value" evaluations which involved a series of independent, theoretical forced choices between the drug administered and different monetary values. - Pupillometry as objective PD measure

The "Drug Liking VAS" was used as the primary endpoint. This is a bipolar VAS ("At this moment, my liking for this drug is…"), where values can range from 0 [strong disliking] to 100 [strong liking] and 50 is the neutral point.

All doses of the study drug were not associated with a relevant effect on drug liking and in the intranasal study was associated with relevant "bad effects", thus demonstrating a low potential for abuse.

A dose-response model was developed upon the data from the phase 2 dose-ranging study only. However, the model was considered equivocal when population pharmacokinetic data were modelled separately against PD endpoints of weekly average abdominal pain scores and weekly average stool consistency scores. Thus, the results were concluded to be unreliable and no definitive conclusions could be reached.

A later post-hoc PK/PD model built on the AUC and binary PD endpoints (the composite daily response used in the phase 3 studies) was able to determine a "minimally effective" dose, which was determined to be just above the 25 mg BID dose.

However, despite the improved correlation between systemic exposure and clinical response in the post hoc model, overall, the data from the Phase 2 study demonstrated no true PK/PD relationship, which was finally attributed to the local action in the GI tract.

## 2.4.4. Discussion on clinical pharmacology

The PK has been sufficiently characterised with 10 dedicated PK studies conducted. The compound possesses high solubility and low permeability. Although an i.v. formulation is not available for human use, allometric scaling has resulted in an estimated oral bioavailability of just over 1%. This is consistent with the low plasma levels observed.

The compound develops dose proportionality across the therapeutic dose-range and above, with maximum plasma levels are observed between 1,5 and 3 hours and the substance does not accumulate after repeated dosing. A significant food effect reduces oral bioavailability further.

The variability of the PK of eluxadoline is very high, and can partly be attributed to the known mechanism of excretion via OATP1B1. The compound is mainly undergoing faecal excretion, with minor amounts excreted in urine. The metabolism of the compound appears to be limited with glucuronidation being the main pathway.

Investigations into transport and metabolising pathways, and the potential induction or inhibition by the compound did reveal a minor inhibiting effect on OATB1B1 and some potential for metabolism-dependent inhibition of CYP3A4/5, but no relevant effects on other proteins investigated. In consequence, the applicant committed to conduct an in-vivo drug-drug-interaction study with the CYP 3A4-substrate midazolam the results of which will be submitted as a Post Authorisation Measure as outlined in the RMP.

Further in-vivo investigations on DDIs did not show a significant interaction for the tested substances (probenecid, oral contraceptive and rosuvastatin). However, the effect on other statins which are more sensitive OATP1B1 substrates may be more pronounced and a respective warning has been included into the SmPC.

Following a single oral 100–mg dose to-be marketed formulation in subjects with varying degrees of liver impairment and healthy subjects, mean eluxadoline plasma exposure was 6-fold, 4-fold, and 16-fold higher in mild, moderate, and severe hepatically impaired subjects (Child Pugh Class A, B, C), respectively, compared to the subjects with normal liver function.

Similarly a 4- to 6-fold elevation of rate and extent of exposure was seen in a DDI study with Cyclosporine A (CSA) confirming the primary involvement of OATB1B1 in the elimination of eluxadoline. Considering the magnitude of the influence of this effect is similar to the one seen in patients with hepatic impairment a contraindication for patients on treatment with potent inhibitors of OATP1B1 was included into the SmPC.

Renal impairment was not separately investigated, however, is not thought to relevantly influence the PK of the compound. Nevertheless, the applicant has already committed to conduct a study exploring the “worst-case” scenario in severely impaired patients to the FDA and commits to submit the results 6 months after marketing authorisation of the product as outlined in the RMP. This is acceptable to the CHMP.

A population-PK model was developed, including sparse sampling data from the phase II study, which did not show statistically significant effects of demographic parameters on the PK. With regard to this, however, the evaluation of age could not be based on any data of patients older than 65.

The primary pharmacology of the compound eluxadoline has been characterised in-vitro and in animal studies and for the effects on stool frequency and consistency only. No studies on the potential to decrease abdominal pain have been performed. In vitro radioligand binding studies and confirmatory functional assays demonstrated that eluxadoline is a mu opioid receptor (μOR) agonist and delta opioid receptor (δOR) antagonist. In vitro, it has also been shown that the substance reduced contractility and secretion of intestinal tissue. Studies in animals have shown that eluxadoline is able to normalise defecation and (inflammation induced) hyperalgesic responses, prolongs GI transit and reduces faecal output. A human study has revealed the decrease of both stool consistency and frequency, but the effects have not been shown to be dose-dependent.

The applicant postulated that the combined mixed μ-OR agonism and δ-OR antagonism possess increased analgesic potency with different GI effects as compared to pure μ-OR agonists. However, the literature

describes an increased analgesic potency of substances with a combined agonism for both the μOR and the δOR. The GI effects at the δOR are also supposed to differentiate the substance from the pure (peripheral) μ-OR agonist loperamide (which is clinically widely used for the treatment of acute as well as chronic diarrhoea, including the diarrhoea association with IBS), and which usually causes rebound constipation in a relevant percentage of patients. The experiments in mice, not showing a full inhibition of GI transit could indeed support such a conclusion.

It is noted that only limited human data are available and therefore the contribution of the two mechanisms of action to pharmacodynamics and clinical effects in humans, and the differences to known substances remain hypothetical.

With regard to secondary pharmacology, the applicant has conducted three studies, one investigating the potential for QT-prolongation, and two investigating the potential for being abused by opioid (ab-) users. The thorough QT study conducted was fully compliant with the respective regulatory guidance. The results of the study showed assay sensitivity as by the results of the active control, and a small increase in QTc for the supratherapeutic dose. The categorical analysis of QTc-interval changes did not show effects of the substance compared to placebo. A slight heart rate increase was seen with the supratherapeutic dose. The study showed that eluxadoline has a low to negligible effect on QTc prolongation.

The applicant has furthermore conducted two abuse liability studies. One study testing the oral intake with therapeutic and two supratherapeutic doses, and with an active control was conducted. The evaluation was done in participants being previous recreational users of opioids without showing opioid dependence. Standard methodology for the evaluation of patients' preferences, central effects, and choice of repeated intake were applied. PK measurements and pupillometry were also included. Whereas the active control showed a relevant differentiation from placebo for the "drug-liking-effect", this was rather marginal for eluxadoline in all doses. Relevant central effects were seen for eluxadoline high doses (albeit relevantly weaker than for the active control), whereas the therapeutic dose rather resembled placebo. IBS is associated with depression/ anxiety/ other psychological disorders and sufferers are (theoretically) more susceptible to substance dependence/ abuse.

The intranasal abuse study was conducted with a similar design to test for the potential of extemporaneous use with intranasal application. Although both, relevant CNS activity of the compound, as well as high plasma levels could be verified, the overall drug-liking preference was at the level of placebo or even below, clearly distinctive from the active control. Moreover, a relevant "dislike" was expressed by the participants ("bad effects"; potentially related to κ-OR), clearly differentiating the compound from placebo as well as the active control. Any potential for i.v. abuse is deemed unlikely based on the physic-chemical properties of the substance.



## 2.4.5. Conclusions on clinical pharmacology

The PK of the compound has extensively been evaluated showing the main feature of the compound with low bioavailability and large variability. The contributions of metabolising and transport proteins on excretion have been adequately evaluated. Special populations have adequately been addressed, with the exception of the PK in patients with renal impairment, which will be further characterised in a post authorisation study as outlined in the RMP.

The potential for drug-drug-interactions has adequately been addressed. A potential interference with CYP3A4/5 inhibition was included as missing information in the RMP and will be addressed with a DDI study post authorisation. The primary pharmacology has been elucidated in humans showing effects on stool and motility related parameters. The potential for off-target pharmacodynamics effects has been

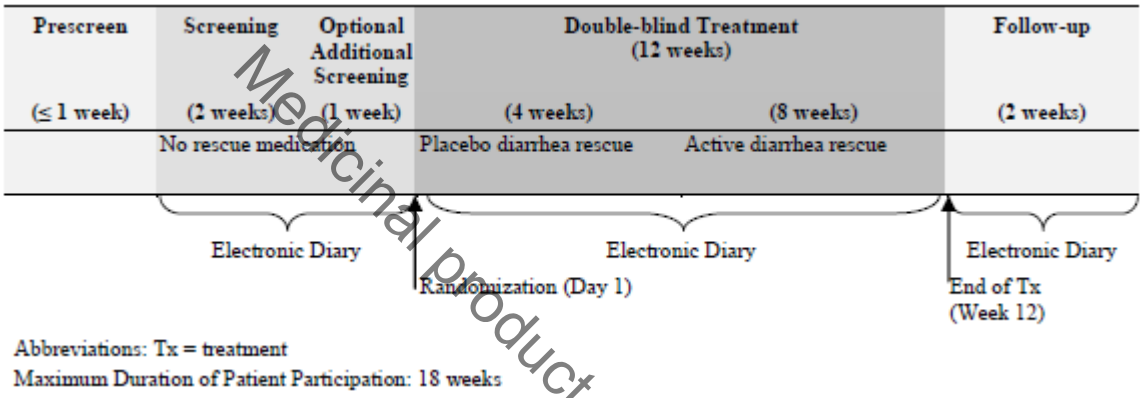
well addressed by the applicant and no potential for adverse effects with regard to CV risk and abuse have been detected.

## *2.5. Clinical efficacy*

### 2.5.1. Dose response study

Study 27018966IBS2001 (in the following: study 2001), was conducted to evaluate the clinical response relative to placebo of four different doses of eluxadoline (5 mg, 25 mg, 100 mg and 200 mg BID). Study 2001 was a multicentre (208 centres) randomised, double-blind, placebo-controlled parallel-group study with a 12 week double-blind and a 2 week open-label follow-up (without treatment) conducted in the US.

**Figure 2 - Design of phase 2 study 2001:**




Abbreviations: Tx = treatment
Maximum Duration of Patient Participation: 18 weeks



The following table shows the primary evaluation of efficacy according to the protocol:

**Table 4 - Analysis of Response rates based on primary responder definition (ITT population):**

| | 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) |
|---|---|---|---|---|---|
| **Week 4** | | | | | |
| Overall response rate | 12.4% | 12.0% | 11.0% | 13.8% | 5.7% |
| Odds ratio | 2.457 | 2.383 | 2.079 | 2.797 | |
| (95% CI) | (0.994, 6.077) | (1.036, 5.478) | (0.893, 4.842) | (1.227, 6.376) | |
| P value | 0.052 | 0.041 | 0.090 | 0.015 | |
| **Week 12** | | | | | |
| Overall response rate | 8.6% | 13.2% | 20.2% | 15.0% | 11.3% |
| Odds ratio | 0.719 | 1.208 | 2.014 | 1.395 | |
| (95% CI) | (0.306, 1.689) | (0.615, 2.373) | (1.069, 3.795) | (0.717, 2.716) | |
| P value | 0.449 | 0.583 | 0.030 | 0.326 | |

Several protocol-defined, and post-hoc defined responder analyses were performed with the results, which were almost all supporting the results shown above. The applicant decided to include the 100 mg BID dose into the phase 3 studies, but also included an intermediate 75 mg BID dose into the phase 3 studies, due to safety considerations. This was considered acceptable.

## 2.5.2. Main studies

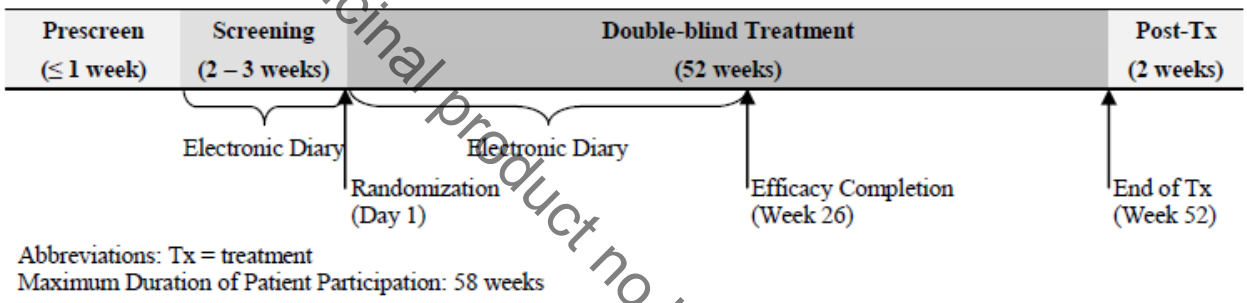
**IBS3001 / IBS3002**
**A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-27018966 in the Treatment of Patients with Diarrhea-Predominant Irritable Bowel**

***Methods***

Two phase 3 studies in support of this application are presented by the applicant. The design of the studies is similar, and both used similar inclusion criteria, methods of evaluation, and endpoints. The difference between the two trial lies in the design of the "non-confirmative" phase of the trials, which included an extension of double-blind treatment for safety up to week 52, and a 2 week withdrawal period without treatment in case of study IBS-3001, and a blinded withdrawal period of 4 weeks in case of study IBS 3002, after the double-blind period of 26 weeks used for the evaluation of efficacy. The main features of the trial will therefore be reported only once. The principal design of the two studies is shown in the following graphical display:

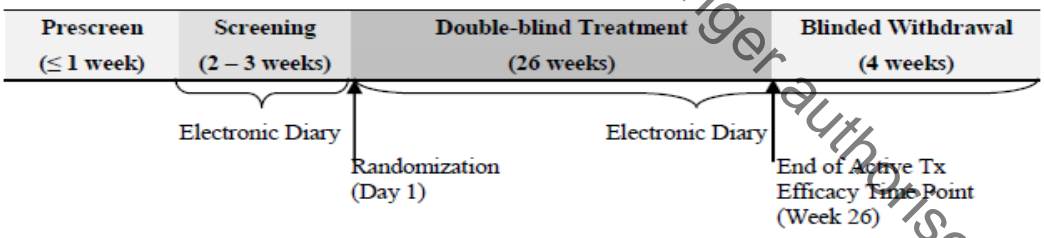


**Figure 3: Design of Phase 3 study IBS-3001:**




Abbreviations: Tx = treatment
Maximum Duration of Patient Participation: 58 weeks

**Figure 4 - Design of Phase 3 study IBS 3002:**




Abbreviations: Tx = treatment
Maximum Duration of Patient Participation: 34 weeks

***Study Participants***

The main inclusion criteria defined the eligible patient population as those between the age of 18 and 80 years with:

- A diagnosis of IBS-d according to Rome III criteria
- The requirement of a colonoscopy within 10 years without alarm features, or "since the onset of the following alarm features" defined as: documented weight loss within 6 months, nocturnal symptoms, family history of first-degree relative with colon cancer, blood in stool.
- An average of worst abdominal pain score of >3.0 during the week prior to randomisation (on a 0-10 NRS).
- An average stool consistency score of ≥5.5 and at least 5 days with a BSS score of ≥5 on the

- An average daily IBS-d global symptom score of ≥2.0 on a 0 to 4 scale over the week prior to randomisation
- Completion of at least 6 of 7 and 11 of 14 during the last week and 2 weeks before randomisation, respectively
- No use of loperamide as rescue medication within 14 days prior to randomisation
- No plans for life-style changes during the study.

Stable concomitant medication was generally allowed (including antidepressants and anti-migraine products), as well as "on-demand medication" such as antiallergics and benzodiazepines. Apart from loperamide (see above), the intake of 5HT3 antagonists was also excluded. The "usual" precautionary criteria applied for female patients in the reproductive age.

Exclusion criteria mainly referred to other GI disease, such as IBD, diverticulitis, history of intestinal obstruction, stricture, toxic megacolon, perforation, and G.I. surgery within 3 months and others. Patients with cholecystectomy were excluded if they were suffering from any history of post-cholecystectomy biliary tract pain. A history of cholecystitis was also a reason for exclusion, as well as a history for pancreatitis, biliary duct disease, and sphincter of Oddi (SO) dysfunction, elevation of lipase >2xULN, laxative abuse and history of liver disease with elevation of transaminases. A history of other relevant pre-existing disease or history of: CV event such as stroke myocyrdial infarction, congestive heart failure TIA (within 6 months), unstable renal, hepatic, metabolic, or haematologic condition, malignancy within 5 years, HIV-infection, substance dependency, alcohol abuse and others.



***Treatments***

Patients were randomly assigned to 1 of 3 treatment groups as follows:

- 75 mg eluxadoline BID (75-mg tablets)
- 100 mg eluxadoline BID (100-mg tablets)
- Placebo BID (matching tablets)

Patients took 2 tablets at each dose administration to maintain the blind. Patients took study double-blind study drug for 26 weeks. At the Week 26 visit, all patients were to be assigned kits with single-blind placebo in study 3001. In study 3002, patients took the study drug for 52 weeks.

***Objectives***

The primary objectives of the trial were defined as "to evaluate the clinical response of patients with IBS-d to eluxadoline, relative to Placebo" and "to evaluate the overall safety and tolerability of eluxadoline in the treatment of IBS-d".

The secondary objective of the studies were to further evaluate the treatment effect of eluxadoline relative to placebo based on patient reports of IBS-d symptoms (abdominal pain, abdominal discomfort, abdominal bloating, stool consistency, global symptom scores, adequate relief), bowel functioning, and quality of life.

***Outcomes/endpoints***

The primary efficacy endpoint was the composite responder proportion evaluated over the initial 12 weeks of double-blind treatment for the FDA and over 26 weeks of treatment for the EMA. A patient was counted as a composite responder if he or she met the daily response criteria for at least 50% of the days

with diary entries during the interval of interest (Weeks 1-12 or Weeks 1-26). A patient must have met BOTH of the following criteria on a 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 (average of daily worst abdominal pain the week prior to randomization).
- Daily stool consistency response: BSS score <5 (ie, score of 1, 2, 3, or 4) or the absence of a bowel movement if accompanied by ≥ 30% improvement in worst abdominal pain compared to baseline pain.

To be eligible to be a responder, a patient must have had a minimum of 60 days of diary entries over the 12-week interval and a minimum of 110 days of diary entries over the 26-week interval. Any patient with fewer than the minimum number of days of diary entries was considered a non-responder for that interval, including patients in the intent to treat (ITT) analysis who had not yet recorded post-baseline diary data.

If no diary entry was made for a given day then it was considered a missing day. If a diary entry was made and BSS was missing (eg, because no bowel movement was reported on a given day), but worst abdominal pain score was entered then so long as the pain criteria was met the patient was considered a responder for that day.



Originally, the protocol had only stated that the primary efficacy endpoint for the FDA (originally defined as the 12 week evaluation) could be regarded to be secondary for other agencies, and some of the secondary endpoints as defined in the protocol (pain and overall response) would be regarded primary in other regions. However, this was changed in the protocol Amendment No. 3 with the Scientific Advice received at that time, which was based on the (then) Draft CHMP IBS guidance. The 26 weeks composite endpoint was then defined as primary, similar to the 12 weeks evaluation.

The secondary efficacy endpoints included the following endpoints with the following definitions:

- Pain responders: defined as those patients who met the daily pain response criteria (i.e., the worst abdominal pain score in the past 24 hours improved by ≥ 30% compared to baseline, as defined in Section 9.5.3.1) for at least 50% of days with diary entries during each interval over the 12-week interval (Weeks 1-12), 26-week interval (Weeks 1-26), and each 4-week interval (Weeks 1-4, 5-8, 9-12, 13-16, 17-20, and 21-24).
- Stool consistency responders: defined as those patients who met the daily stool consistency response criteria (ie, BSS score <5 [ie, score of 1, 2, 3, or 4] or the absence of a bowel movement if accompanied by ≥ 30% improvement in worst abdominal pain compared to baseline pain) for at least 50% of days with diary entries during each interval for the 12-week interval (Weeks 1-12), 26-week interval (Weeks 1-26), and each 4-week interval (Weeks 1-4, 5-8, 9-12, 13-16, 17-20, and 21-24).
- IBS-d global symptom responders: defined as those patients who met the daily IBS-d global symptom response criteria (ie, IBS-d global symptom score of 0 [none] or 1 [mild]; or a daily IBS-d global symptom score improved by ≥ 2.0 compared to the baseline average) for at least 50% of days with diary entries during each interval over the 12-week interval (Weeks 1-12), 26-week interval (Weeks 1-26), and each 4-week interval (Weeks 1-4, 5-8, 9-12, 13-16, 17-20, and 21-24).

A patient must have had a minimum of 20 days of diary entries over any 4-week interval, a minimum of 60 days of diary entries over the 12-week interval, and a minimum of 110 days of diary entries over the 26-week interval to be a responder.

- IBS-QoL responders: defined as patients who achieved at least a 14-point improvement in IBS- QoL total score from baseline to the applicable visit (Drossman et al 2007). The “lowest possible score” and “possible raw score change” were based on the questions answered rather than all 34 questions.
- IBS-AR responders: defined as those patients with a weekly response of “Yes” to adequate relief of their IBS symptoms for at least 50% of the total weeks during the interval over the intervals from Weeks 1-12 and Weeks 1-26. A patient must have had a positive response on ≥ 6 weeks for the 12-week interval and ≥ 13 weeks for the 26-week interval, regardless of diary compliance, to be a responder. If a patient did not respond to the question for that week it was considered missing, no imputation was applied.

Other secondary efficacy endpoints included:

- Discomfort: changes from baseline in daily abdominal discomfort scores
- Bloating: changes from baseline in daily abdominal bloating scores
- Frequency: number of bowel movements per day
- Incontinence: number of bowel incontinence episodes per day and number of incontinence-free days
- Urgency: number of urgency episodes per day
- IBS-QoL: total score and scores compared to baseline

For the evaluation of most of the efficacy endpoints and the intake of loperamide rescue medication, an electronic diary (Interactive Voice Response System; IVRS) was used, which requested data input once daily. The electronic diary captured daily worst abdominal pain scores, abdominal discomfort scores, abdominal bloating scores (not applicable for the Spanish language translation), stool consistency scores (BSS), IBS-d global symptom scores, and bowel functioning (bowel movement frequency and urgency, and episodes of incontinence). Once per week (during the first 26 weeks) patients were asked if they had experienced adequate relief of their IBS symptoms (IBS-AR).

The symptoms were collected in the following way/with the following definitions for the different symptoms/evaluations:

**Worst Abdominal Pain Score:** Patients were asked to rate their worst abdominal pain in the past 24 hours daily and this was recorded on a 0 to 10 scale, where 0 corresponded to no pain and 10 corresponded to worst imaginable pain.

**Abdominal discomfort Score:** A similar scale was used for abdominal discomfort and patients were asked to rate their abdominal discomfort in the past 24 hours daily.

**Abdominal Bloating Score:** The abdominal bloating in the past 24 hours had to be rated daily also on a similar NRS scale. The abdominal bloating ratings were not asked in the Spanish language version of the electronic diary because “bloating” was not considered a term that was translatable to Spanish. There is no word in Spanish that has one-to-one equivalence to the English word “bloating” in this context.

**Bristol Stool Score**: The Bristol Stool Form Scale/Bristol Stool Score (BSS) was rated on the basis of an assessment of being “most representative of the past 24 hours). The BSS comprises a 1-7 point scale where 1 corresponds to hard stool and 7 to watery diarrhoea.

**IBS-d Global Symptom Score:** The global symptoms score was to be rated daily on a 0-4 points rating scale with the ratings “no symptoms”, “mild”, “moderate”, “severe”, and “very severe” symptoms. Additionally, a responder analysis was conducted, which defined response as 14-point improvement in the IBS-QoL score from baseline.

**Adequate Relief:** This question was asked once per week (dichotomous question).

**Freuqency, Urgency and Incontinence:** Numbers of events had to be entered into the IVRS.

**Quality of Life:** Quality of Life was only evaluated at days of visits to study centres (every 4 weeks), and the IBS-QoL was completed on paper. The IBS-QoL consists of 34 items each with a 5-point response scale, where 1 generally represents better responses on items and 5 represents worse responses.

***Sample size***

The sample size estimation for both studies assumed a 14% response rate for placebo in the primary endpoint, and a 10% superiority (treatment effect) for any active group. With an assumed 90% power and a 2-sided Cochran-Mantel-Haenszel test at a level of 0.025 (due to Bonferroni-adjustment for the two doses), the necessary sample size was estimated at 375 patients per treatment group.

***Randomisation***

The randomization schedule was generated using the SAS software (SAS Institute Inc, Cary, North Carolina) PROC PLAN Version 9.1.3. The schedule was sequestered until the study was unblinded after the last patient completed the Week 26 visit. Approximately 1125 patients were planned for randomization (in a 1:1:1 ratio) to 1 of 3 treatment groups. The overall randomization was stratified by country (US, Canada, and UK).

The randomization mechanism for the study was deployed within a telephone-based IVRS or a web-based IWRS, which were accessible 24 hours a day to authorized users. Study sites called/accessed the IVRS/IWRS to determine patient eligibility and execute each randomization on Day 1. Study site personnel, who were all blinded to treatment assignment, received a randomization notification indicating only the unique patient identifier and the date and time of randomization for each patient.



***Blinding (masking)***

This study was a double-blind study. The investigators, site personnel, and study patients were not aware of the treatment assignments. Blinding of the placebo tablets and eluxadoline tablets was maintained throughout the study by using active and placebo tablets that were identical in appearance using a double-dummy method. The randomization schedules and treatment assignments remained sequestered until the study blind was broken

The study drug was packaged in a double-dummy fashion and patients received 2 tablets at each administration.

***Statistical methods***

The SAP specified that the primary analysis was to evaluate the treatment effect for the ITT Analysis Set on the overall composite responders. A pair-wise, two-sided CMH test for active treatments Eluxadoline (75mg bid or 100mg bid) versus placebo was to be used.

Due to there being two active groups being tested to placebo, the classical Bonferroni adjustment was foreseen in order to preserve the family-wise error rate for the primary endpoint (i.e. each active group versus placebo comparison was assessed at the 2-sided $\alpha$=0.025 significance level). For all other endpoints, statistical analysis was performed using a 2-sided hypothesis test at the overall 5% level of significance.

Logistic regression was to be used as supportive analysis to analyze the primary endpoint, but was considered exploratory. Responder proportion at Week 12 was to be modelled using treatment as a fixed effect and using gender, baseline pain and baseline BSS scores as fixed effect covariates. A random effect for region was also to be fitted to explore possible heterogeneity of variances between regions.

Sensitivity analyses were to be conducted with 2 methods based on weekly response evaluations of the composite response one based on a BSS criterion of “5 or less if baseline average BSS is 6 or greater; or a reduction in weekly average BSS scores of at least 1 point for those with a baseline average BSS greater than or equal to 5.5 and less than 6” (method 1) or “at least a 50% decrease in the number of days in a week where the BSS is 6 or greater as compared to the number of days in the baseline week (Week -1) where the BSS is 6 or greater” (method 2).

A “worst case scenario” was to be evaluated with an absolute criterion for 42 of the 84 days having entries in the diary with a positive response, regardless of compliance. A further exploratory analysis was to be performed with a “longitudinal model”.

The sensitivity analyses or further responder analyses were to be evaluated by the same methods as the primary evaluation.

As a further post-hoc sensitivity analysis, a multiple imputation (MI) analysis was performed based on the pooled pivotal studies. The model in the MI was a logistic regression model, with treatment, day, average baseline pain score and average baseline stool consistency score as explanatory variables and including the interaction between treatment and day and a quadratic term for day. The results of 10 imputed datasets were combined and the combined estimates of the responder rates were presented, along with the odds ratio.

Sensitivity analyses were performed to evaluate the impact of IVRS/IWRS treatment misallocations on the analysis of composite response over Weeks 1-26 in Study IBS-3001 by 1) excluding affected patients from analysis, 2) setting daily response status as non-response for the affected study days, and 3) replacing data on affected days by MI techniques.

The analysis sets for the study include the enrolled patient population, ITT, modified ITT, and the Safety Analysis Set. The enrolled patient population was defined as those who received at least 1 dose of the study drug (including those that were not randomised; treatment allocation was made based on the medication received on the first day). The ITT se was defined as all patients randomized. This set excluded all patients randomised more than once. The ITT set was regarded to be the primary set of analysis.

The MITT se was defined as all patients randomly assigned who received at least one dose of the study drug and had at least baseline, and one post-randomisation diary entry. This set was mainly used for the evaluation of durability of response based on analyses over the 4-week intervals for multiple responder definitions.

The Safety Analysis Set was defined as all patients enrolled who received at least on dose of study drug. For this set, the patients with treatment misallocations (see GCP-chapter) or dispensing errors were included more than one treatment arm.

Periodic blinded data reviews were conducted before database lock and unblinding of the patients’ treatment assignments. These data reviews assessed the accuracy and completeness of the study database, patient evaluability, and appropriateness of the planned statistical methods and began after the start of enrollment. In some subsets of the blinded reviews, formal team meetings were held to review the statistical outputs. Blinded data were accessible to stipulated Furiex Pharmaceuticals personnel and other Furiex designees.

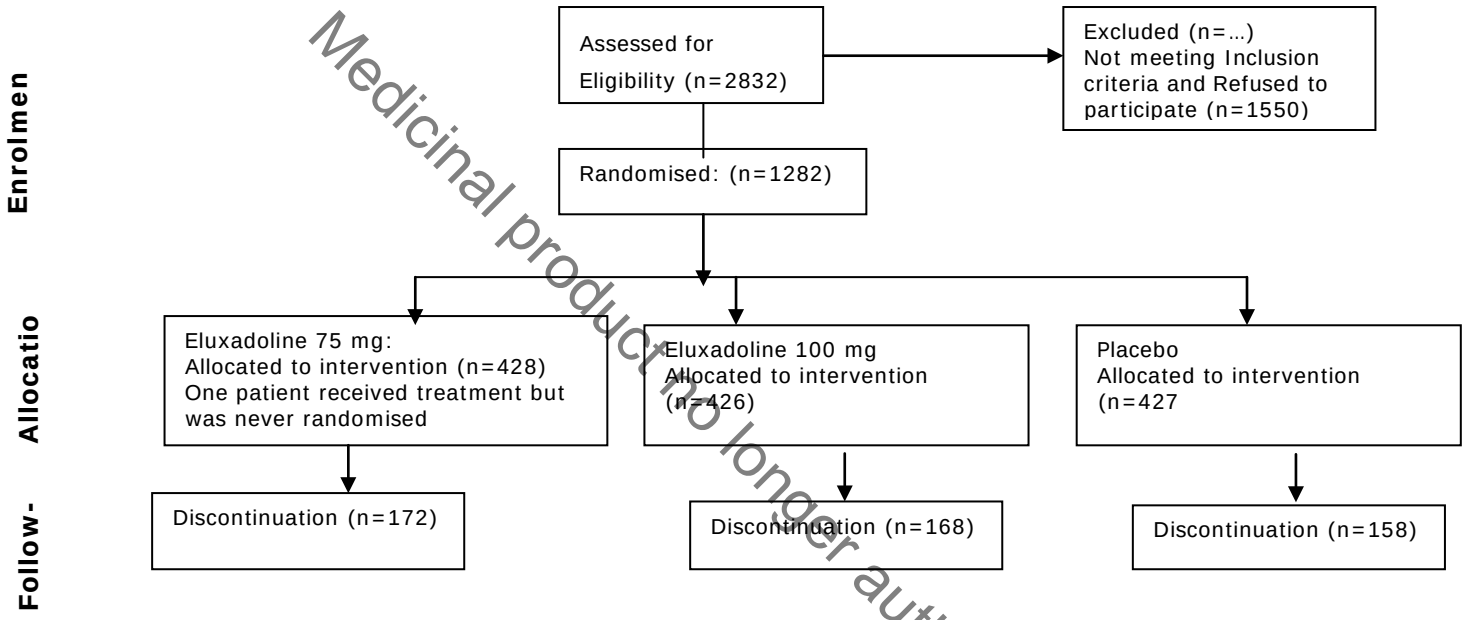
An interim analysis (pre-planned) was conducted in study 3001 which occurred at a time point when all patients had passed their week-26 visit. This therefore did not affect the evaluation of efficacy.

***Results***

The following chapters will be divided between the two pivotal studies, and the results presented separately for the studies 3001 and 3002.

**Study IBS-3001:**

**Participant flow**






- A tabular overview on patient disposition is given in the following:

**Table 5 - Patient disposition Study 3001:**

| | Number (%) of Patients | | | |
|---|---|---|---|---|
| | Eluxadoline 75 mg BID N=429 | Eluxadoline 100 mg BID N=426 | Placebo BID N=427 | Total[a] N=1282 |
| **Total Number of Patients, n (%)** | | | | |
| Randomized[b] | 428 (99.8) | 426 (100.0) | 427 (100.0) | 1281 (99.9) |
| Attended Week 12 visit | 341 (79.5) | 330 (77.5) | 342 (80.1) | 1013 (79.0) |
| Attended Week 26 visit | 289 (67.4) | 291 (68.3) | 290 (67.9) | 870 (67.9) |
| Completed study | 257 (59.9) | 257 (60.3) | 269 (63.0) | 783 (61.1) |
| Discontinued study | 172 (40.1) | 168 (39.4) | 158 (37.0) | 498 (38.8) |
| IVRS/IWRS misallocation | 53 (12.4) | 0 | 0 | 53 (4.1) |
| **Primary Reason for Discontinuation, n (%)** | | | | |
| Voluntarily withdrew | 94 (21.9) | 79 (18.5) | 96 (22.5) | 269 (21.0) |
| Adverse event or SAE | 36 (8.4) | 45 (10.6) | 16 (3.7) | 97 (7.6) |
| Lost to follow-up | 25 (5.8) | 23 (5.4) | 16 (3.7) | 64 (5.0) |
| Physician decision: other | 11 (2.6) | 14 (3.3) | 16 (3.7) | 41 (3.2) |
| Physician decision: lack of efficacy | 2 (0.5) | 3 (0.7) | 7 (1.6) | 12 (0.9) |
| Protocol violation | 3 (0.7) | 4 (0.9) | 4 (0.9) | 11 (0.9) |
| Sponsor decision | 1 (0.2) | 0 | 3 (0.7) | 4 (0.3) |



One patient was randomized twice in the study and was assigned 2 patient identification numbers. This patient's multiple randomizations were due to the patient seeking participation at multiple study centres, and not due to a site error or IVRS error. The data for 001/0027 is included in the ITT Analysis Set and data from 176/0005 is excluded from the ITT Analysis Set.

Altogether, 17 patients had entrance criteria violations, which were not thought to influence the efficacy evaluation. The violations mainly concerned previous participation in study 2001 (7 patients), and prohibited medication within 28 days of randomisation (5 patients took rifaximin).

A total of 58 patients were assigned the incorrect study drug due to an IVRS/IWRS error. Additionally there was missing notification of constipation events due to malfunctioning of the IVRS in 8 patients for 16 instances.

Moreover, 5 patients received the wrong treatment due to site kit misallocation, which was not associated with the IVRS errors.

On 19 November 2013, the managing CRO for this study (PPD) alerted Furiex that 2 callers in the IVRS/IWRS using 2 different phone numbers attempted to record a diary entry for a patient at one site (site 363) at the same time. A directed audit for this site was conducted and concluded that some staff members at this site were making patient diary entries into the system on their patient's behalf using the patient's personal ID numbers. These entries were made by site staff to assist patients with diary compliance but required the site staff to know the patient's daily symptom scores for entry. Per the protocol, site staff should not have had direct knowledge of patients' diary data. This protocol violation was submitted to the IRB and corrective and preventative actions were taken. A letter dated 16 December 2013 was sent to all sites to request verification from all site staff that no one had had access to diary data or personal identification number information.

The datasets analysed are shown in the following table:

**Table 6 - Display of analysis sets Study 3001.**

| | Number of Patients | | | |
|---|---|---|---|---|
| | Eluxadoline 75 mg BID | Eluxadoline 100 mg BID | Placebo BID | Total |
| Enrolled Set | 429 | 426 | 427 | 1282 |
| Randomized Set | 428 | 426 | 427 | 1281 |
| ITT Analysis Set | 427 | 426 | 427 | 1280 |
| Safety Analysis Set | 428 | 479 | 427 | 1276 |
| Modified ITT Analysis Set | 422 | 421 | 424 | 1267 |
| No. of patients receiving >1 treatment | | | | |
| IVRS/IWRS Misallocation[a] | | | | |
| 1st treatment received | 53 | 0 | 0 | 53 |
| 2nd treatment received | 0 | 53 | 0 | 53 |
| Site Misallocation[b] | | | | |
| 1st treatment received | 0 | 1 | 4 | 5 |
| 2nd treatment received | 2 | 2 | 1 | 5 |
| No. of patients randomized >1 time[c] | 2 | 0 | 0 | 1 |
| No. of patients treated but not randomized[d] | 1 | 0 | 0 | 1 |
| No. of patients randomized but not treated | 3 | 2 | 1 | 6 |



**Recruitment**

Study Initiation Date: 29 May 2012, first patient pre-screened

Study Completion Date: 29 July 2014, last patient completed last visit

**Conduct of the study**

During the conduct of the study 4 protocol amendments were performed. Most of the amendments concerned clarifications of methodology and definitions. Also, the consequences of the subsequent Scientific Advices (and the reflection of the changes to the IBS guideline) were implemented with the protocol amendments.

During the conduct of the two pivotal studies, a systematic error in the IVRS/IWRS occurred, which resulted in treatment misallocations in both studies. Immediate corrective actions were taken to address the error, including implementing a programming change, and no subsequent errors were identified in the final reconciliation after unblinding.

In IBS 3001, the systematic error occurred at the Week 18 visit and resulted in 53 patients taking the wrong treatment during the study. All 53 patients were randomized to the 75 mg eluxadoline group, but received kits containing 100 mg eluxadoline at the Week 18 visit. The number of days the patients received the incorrect treatment varied from 1 day to ≥ 60 days; 13 patients took the incorrect study drug for 50 to 59 days and 13 patients took the incorrect study drug for ≥ 60 days to < 132 days.

Moreover, a total of 5 patients in IBS 3001 and 3 patients in IBS 3002 were dispensed the wrong kits in error at the site. Across both studies, 6 patients who were randomized to placebo received eluxadoline from 28 to 69 days (2 of these misallocations occurred at the Week 26 visit); 1 patient randomized to 100

mg eluxadoline received placebo for 37 days; and 1 patient randomized to 100 mg eluxadoline received 75 mg eluxadoline for 34 days.

**Baseline data**

The relevant baseline characteristics were in their majority not relevantly different between treatment groups. There was a potentially relevant difference for the percentage of older patients, which was lowest in the 75 mg group (6.8%) and highest in the placebo group (11.9%). The following table shows the main demographic characteristics:

**Table 7 - Demographic characteristics (enrolled set)**

| | Eluxadoline 75 mg BID N=429 | Eluxadoline 100 mg BID N=426 | Placebo BID N=427 | Total N=1282 |
|---|---|---|---|---|
| **Age (years)** | | | | |
| Mean (SD) | 44.5 (13.18) | 44.4 (13.91) | 45.8 (14.10) | 44.9 (13.74) |
| Median | 44.0 | 45.0 | 45.0 | 45.0 |
| Min, Max | 18, 80 | 18, 79 | 18, 79 | 18, 80 |
| **Age categories (years), n (%)** | | | | |
| 18-40 | 173 (40.3) | 166 (39.0) | 159 (37.2) | 498 (38.8) |
| 41-64 | 227 (52.9) | 225 (52.8) | 217 (50.8) | 669 (52.2) |
| ≥65 | 29 (6.8) | 35 (8.2) | 51 (11.9) | 115 (9.0) |
| **Gender, n (%)** | | | | |
| Male | 151 (35.2) | 143 (33.6) | 150 (35.1) | 444 (34.6) |
| Female | 278 (64.8) | 283 (66.4) | 277 (64.9) | 838 (65.4) |
| **Race** | | | | |
| White | 374 (87.2) | 368 (86.4) | 370 (86.7) | 1112 (86.7) |
| Black | 46 (10.7) | 48 (11.3) | 46 (10.8) | 140 (10.9) |
| Asian | 3 (0.7) | 3 (0.7) | 4 (0.9) | 10 (0.8) |
| American Indian or Alaska Native | 1 (0.2) | 2 (0.5) | 1 (0.2) | 4 (0.3) |
| Native Hawaiian or Other Pacific Islander | 0 | 1 (0.2) | 0 | 1 (0.1) |
| Other | 5 (1.2) | 4 (0.9) | 6 (1.4) | 15 (1.2) |
| **Ethnicity, n (%)** | | | | |
| Hispanic or Latino | 119 (27.7) | 117 (27.5) | 125 (29.3) | 361 (28.2) |
| Not Hispanic or Latino | 310 (72.3) | 309 (72.5) | 302 (70.7) | 921 (71.8) |
| **BMI ($kg/m^2$)** | | | | |
| N | 428 | 424 | 425 | 1277 |
| Mean (SD) | 30.70 (7.421) | 31.22 (7.858) | 30.63 (7.253) | 30.85 (7.513) |
| Median | 29.45 | 30.30 | 29.80 | 29.80 |
| Min, Max | 17.8, 54.6 | 16.7, 60.9 | 16.9, 72.3 | 16.7, 72.3 |



Regarding the IBS baseline characteristics, no relevant differences were detected between the treatment groups. The patients had an average daily worst abdominal pain score of 6.19 on the 0-10 NRS scale, a BSS scale of 6.27 (on the 1-7 BSFS scale, a global average symptom severity of 2.85 (on the 0-4 scale where 0 denotes no symptoms, and 4 very severe symptoms, and 4.93 BMs per day. Almost 80% of the patients reported to have persistent symptoms, whereas about 20% described their symptoms as waxing and waning over time. About 1/3 of the patients used loperamide during the year before enrolment. Just over 20% of the patients had a history of cholecystectomy, and of these, the vast majority was female.

77.6% of the patients took concomitant medication, of which the most common single agents were: omeprazole (12.8%, ibuprofen (12.2%), paracetamol (12.6%), lisinopril (9.2%), aspirin (9.4%), multivtiamins (9.0%), metformin (8.1%), salbutamol (7.3%), loratadine (5.9%), simvastatin (5.4%), and Fitamin D (5.1%).

Treatment compliance was overall satisfactory, and overall compliance rates were around 98% in the first 12 weeks, and 82% in the following 14 weeks of the 26-week controlled period. The percentage of patients with an overall ≥80% was around 85% during the first 12 weeks, and 61% during the following 14 week period, with no relevant differences between treatment groups.

**Numbers analysed**

The ITT Analysis Set, used for the efficacy analyses, included 1280 unique patients [excluded the patient treated but never randomised and the 2nd randomisation from the individual randomised twice].

The MITT Analysis Set included 1267 patients who were randomized, received at least one dose of study drug and had at least one post-randomization diary entry. The MITT Analysis Set was used to assess durability based on analyses over the 4-week intervals for multiple responder definitions (composite, pain, stool consistency and IBS-d global symptom). The assumption was that, to evaluate a clinically meaningful assessment of durability, the patient must at least have taken a single dose of study drug during that interval.

Efficacy data for the 53 patients who received 100mg rather than 75mg eluxadoline due to the IVR/IWR system error was summarised based on the randomised treatment assignment. The number included in each analysis set was similar across treatment groups, except for the 100mg eluxadoline Safety Analysis Set which was slightly higher due to the systematic misallocations.



**Outcomes and estimation**

The following table shows the result of the composite responder evaluation representing the primary evaluation of the study:

**Table 8 - CMH analysis of composite responders (daily response criteria; ITT population)**

| Interval<br>Treatment | Number (%) | | *P* value[a] |
|---|---|---|---|
| | Responder | Non-Responder | |
| Weeks 1-12 (FDA primary endpoint) | | | |
| Eluxadoline 75 mg BID (N=427) | 102 (23.9) | 325 (76.1) | 0.014 |
| Eluxadoline 100 mg BID (N=426) | 107 (25.1) | 319 (74.9) | 0.004 |
| Placebo BID (N=427) | 73 (17.1) | 354 (82.9) | -- |
| Weeks 1-26 (EMA primary endpoint) | | | |
| Eluxadoline 75 mg BID (N=427) | 100 (23.4) | 327 (76.6) | 0.112 |
| Eluxadoline 100 mg BID (N=426) | 125 (29.3) | 301 (70.7) | <0.001 |
| Placebo BID (N=427) | 81 (19.0) | 346 (81.0) | -- |

The logistic regression model based analysis were generally in rough accordance with the results as above, with p-values of 0.015 and 0.004 for the two treatment groups at week 12, and 0.123 and <0.001 after 26 weeks.

The evaluation of the primary endpoint underwent an exploration of the longitudinal response, and with several sensitivity analyses, including the "worst-case scenario" (using the overall absolute 50% of positive daily responder criterion, and a weekly responder definition evaluation; see above). These evaluations were generally in line with the primary evaluation, however, showing somewhat more inconsistent effects for the lower dose group in the longitudinal analysis. As examples of these exercises, the overall weekly evaluation ("alternative composite responder definition"), and the longitudinal worst-case analysis are shown in the following:

**Table 9 - CMH analysis of alternative composite responder definitions (weekly response criteria; ITT analysis).**

| Interval<br>Treatment | Number (%)<br>Responder | <br>Non-Responder | *P* value[a] |
|---|---|---|---|
| **Method 1** | | | |
| Weeks 1-12 | | | |
| Eluxadoline 75 mg BID (N=427) | 143 (33.5) | 284 (66.5) | 0.013 |
| Eluxadoline 100 mg BID (N=426) | 154 (36.2) | 272 (63.8) | 0.001 |
| Placebo BID (N=427) | 110 (25.8) | 317 (74.2) | -- |
| **Method 2** | | | |
| Weeks 1-12 | | | |
| Eluxadoline 75 mg BID (N=427) | 164 (38.4) | 263 (61.6) | 0.026 |
| Eluxadoline 100 mg BID (N=426) | 178 (41.8) | 248 (58.2) | 0.001 |
| Placebo BID (N=427) | 133 (31.1) | 294 (68.9) | -- |

**Table 10 - CMH analyiss of worst-case composite responders by interval; ITT analysis):**

| Interval<br>Treatment | Number (%)<br>Responder | <br>Non-Responder | <br>*P* value[a] |
|---|---|---|---|
| Weeks 1-4 | | | |
| Eluxadoline 75 mg BID (N=427) | 86 (20.1) | 341 (79.9) | 0.002 |
| Eluxadoline 100 mg BID (N=426) | 92 (21.6) | 334 (78.4) | <0.001 |
| Placebo BID (N=427) | 53 (12.4) | 374 (87.6) | -- |
| Weeks 5-8 | | | |
| Eluxadoline 75 mg BID (N=427) | 113 (26.5) | 314 (73.5) | 0.019 |
| Eluxadoline 100 mg BID (N=426) | 123 (28.9) | 303 (71.1) | 0.002 |
| Placebo BID (N=427) | 84 (19.7) | 343 (80.3) | -- |
| Weeks 9-12 | | | |
| Eluxadoline 75 mg BID (N=427) | 107 (25.1) | 320 (74.9) | 0.122 |
| Eluxadoline 100 mg BID (N=426) | 130 (30.5) | 296 (69.5) | <0.001 |
| Placebo BID (N=427) | 88 (20.6) | 339 (79.4) | -- |
| Weeks 13-16 | | | |
| Eluxadoline 75 mg BID (N=427) | 100 (23.4) | 327 (76.6) | 0.322 |
| Eluxadoline 100 mg BID (N=426) | 127 (29.8) | 299 (70.2) | 0.002 |
| Placebo BID (N=427) | 88 (20.6) | 339 (79.4) | -- |
| Weeks 17-20 | | | |
| Eluxadoline 75 mg BID (N=427) | 119 (27.9) | 308 (72.1) | 0.011 |
| Eluxadoline 100 mg BID (N=426) | 128 (30.0) | 298 (70.0) | 0.001 |
| Placebo BID (N=427) | 87 (20.4) | 340 (79.6) | -- |
| Weeks 21-24 | | | |
| Eluxadoline 75 mg BID (N=427) | 116 (27.2) | 311 (72.8) | 0.025 |
| Eluxadoline 100 mg BID (N=426) | 124 (29.1) | 302 (70.9) | 0.004 |
| Placebo BID (N=427) | 88 (20.6) | 339 (79.4) | -- |



The study report presents – after the primary evaluation – the separate evaluation of stool consistency and pain response. However, the new European IBS guideline has defined the outcome with regard to global response as the main secondary evaluation, and therefore, these analyses are presented first in this report. The following two tables show the evaluation of the global symptom scale responders and of the “adequate relief” responders.

**Table 11 - CMH analysis of IBS-d global symptom responders (daily response criterion; ITT analysis):**

| Interval<br>Treatment | Number (%)<br>Responder | <br>Non-Responder | <br>*P* value[a] |
|---|---|---|---|
| Weeks 1-12 | | | |
| Eluxadoline 75 mg BID (N=427) | 150 (35.1) | 277 (64.9) | 0.048 |
| Eluxadoline 100 mg BID (N=426) | 148 (34.7) | 278 (65.3) | 0.063 |
| Placebo BID (N=427) | 123 (28.8) | 304 (71.2) | -- |
| Weeks 1-26 | | | |
| Eluxadoline 75 mg BID (N=427) | 155 (36.3) | 272 (63.7) | 0.221 |
| Eluxadoline 100 mg BID (N=426) | 158 (37.1) | 268 (62.9) | 0.144 |
| Placebo BID (N=427) | 138 (32.3) | 289 (67.7) | -- |

The longitudinal analysis of this endpoint shows similarly some inconsistencies in the effects, with partly better responses in the low dose-group, and with a diminished effect during the periods week 9-12, 13-6, and 17-20, with more clear effects again shown towards the end of the treatment period.

**Table 12 - CMH analysis of IBS-Adequate Relief responders (ITT analysis):**

| Interval / Treatment | Number (%) | | *P* value[a] |
|---|---|---|---|
| | Responder | Non-Responder | |
| Weeks 1-12 | | | |
| Eluxadoline 75 mg BID (N=427) | 226 (52.9) | 201 (47.1) | 0.008 |
| Eluxadoline 100 mg BID (N=426) | 231 (54.2) | 195 (45.8) | 0.002 |
| Placebo BID (N=427) | 187 (43.8) | 240 (56.2) | -- |
| Weeks 1-26 | | | |
| Eluxadoline 75 mg BID (N=427) | 195 (45.7) | 232 (54.3) | 0.097 |
| Eluxadoline 100 mg BID (N=426) | 211 (49.5) | 215 (50.5) | 0.005 |
| Placebo BID (N=427) | 171 (40.0) | 256 (60.0) | -- |



Contrary to the scale-based global response, this evaluation shows more clear effects for both treatment groups, and with a higher effect and more consistently significant effect of the high-dose group, more reflecting the results of the primary evaluation.

The analyses of the “pain responder” evaluations are shown in the following table:

**Table 13 - CMH analysis of pain responders (daily response criterion; ITT analysis):**

| Interval / Treatment | Number (%) | | *P* value[a] |
|---|---|---|---|
| | Responder | Non-Responder | |
| Weeks 1-12 | | | |
| Eluxadoline 75 mg BID (N=427) | 181 (42.4) | 246 (57.6) | 0.404 |
| Eluxadoline 100 mg BID (N=426) | 184 (43.2) | 242 (56.8) | 0.284 |
| Placebo BID (N=427) | 169 (39.6) | 258 (60.4) | |
| Weeks 1-26 | | | |
| Eluxadoline 75 mg BID (N=427) | 193 (45.2) | 234 (54.8) | 0.582 |
| Eluxadoline 100 mg BID (N=426) | 198 (46.5) | 228 (53.5) | 0.355 |
| Placebo BID (N=427) | 185 (43.3) | 242 (56.7) | |

The evaluation of the longitudinal response was generally consistent with the results of the CMH analysis, with the only p-value below 0.05 at the time interval week 1-4 for the high dose group. Generally, the overall differences between the treatment groups were small (even “negative” during weeks 13-16), and were smallest during weeks 5-16, with relevant differences in favour of the active groups only in the first and last 4 weeks. The explorative weekly responder analysis for pain was in accordance with the CMH daily analysis.

The following table shows the results with regard to stool consistency response:

**Table 14 - CMH analysis of stool consistency responders (daily response; ITT analysis)**

| Interval Treatment | Number (%) | | *P* value[a] |
|---|---|---|---|
| | Responder | Non-Responder | |
| Weeks 1-12 | | | |
| Eluxadoline 75 mg BID (N=427) | 128 (30.0) | 299 (70.0) | 0.008 |
| Eluxadoline 100 mg BID (N=426) | 146 (34.3) | 280 (65.7) | <0.001 |
| Placebo BID (N=427) | 94 (22.0) | 333 (78.0) | -- |
| Weeks 1-26 | | | |
| Eluxadoline 75 mg BID (N=427) | 120 (28.1) | 307 (71.9) | 0.186 |
| Eluxadoline 100 mg BID (N=426) | 145 (34.0) | 281 (66.0) | 0.001 |
| Placebo BID (N=427) | 103 (24.1) | 324 (75.9) | -- |

The longitudinal analysis is very much consistent with the above results, showing partly inconsistent (and inconclusive) results for the low dose-group. However, a slight reduction of the overall treatment effect (or more so an increase of the placebo response over time) is observed toward the end of the treatment. Similarly, the sensitivity analysis using the weekly responder definition was consistent with the above results, both in the CMH-based analysis, and the longitudinal one.

In the following, additional symptoms, or "numerical" evaluations of the recorded symptoms are presented.

For the numerical evaluation of the stool consistency, a decrease of the mean was noted for all treatment groups , however, with higher decreases noted in the active treatment groups. The difference was between -0.28 and -0.21 for the lower dose group, and -0.27 and -0.33 for the higher dose group with statistically significant differences for all time points evaluated (consistency p<0.001 for the high dose group).



**Ancillary analyses**

The evaluation of the abdominal bloating and abdominal discomfort scales are presented in the following. This is based on a longitudinal analysis, but not with a responder evaluation but on the changes on numerical values:

**Table 15 - Londitudinal analyis of abdominal bloating and abdominal discomfort count data (ITT analysis)**

| | | LS Mean | LS Mean Difference (95%) | | *P* value |
|---|---|---|---|---|---|
| **Abdominal bloating** | | | | | |
| Week 4 | Eluxadoline 75 mg BID | 4.17 | -0.17 | (-0.47, 0.12) | 0.252 |
| | Eluxadoline 100 mg BID | 4.07 | -0.28 | (-0.57, 0.02) | 0.069 |
| | Placebo | 4.34 | -- | -- | -- |
| Week 12 | Eluxadoline 75 mg BID | 3.78 | -0.24 | (-0.53, 0.06) | 0.116 |
| | Eluxadoline 100 mg BID | 3.73 | -0.29 | (-0.59, 0.00) | 0.053 |
| | Placebo | 4.02 | -- | -- | -- |
| Week 26 | Eluxadoline 75 mg BID | 3.10 | -0.35 | (-0.65, -0.05) | 0.022 |
| | Eluxadoline 100 mg BID | 3.13 | -0.32 | (-0.62, -0.02) | 0.034 |
| | Placebo | 3.45 | -- | -- | -- |
| **Abdominal discomfort** | | | | | |
| Week 4 | Eluxadoline 75 mg BID | 4.23 | -0.20 | (-0.46, 0.06) | 0.128 |
| | Eluxadoline 100 mg BID | 4.11 | -0.33 | (-0.59, -0.06) | 0.015 |
| | Placebo | 4.43 | -- | -- | -- |
| Week 12 | Eluxadoline 75 mg BID | 3.72 | -0.28 | (-0.54, -0.02) | 0.038 |
| | Eluxadoline 100 mg BID | 3.65 | -0.34 | (-0.60, -0.08) | 0.010 |
| | Placebo | 3.99 | -- | -- | -- |
| Week 26 | Eluxadoline 75 mg BID | 2.82 | -0.40 | (-0.67, -0.14) | 0.003 |
| | Eluxadoline 100 mg BID | 2.85 | -0.37 | (-0.64, -0.11) | 0.006 |
| | Placebo | 3.22 | -- | -- | -- |



The evaluation of the frequency of BMs, the no. of urgency episodes, and the no. of bowel incontinence episodes is shown in the following:

**Table 16 - Londitudinal analysis of bowel symptoms (count data; ITT analysis)**

| | | Risk | Risk Ratio (95% CI) | | *P* value |
|---|---|---|---|---|---|
| **Frequency of bowel movements** | | | | | |
| Week 4 | Eluxadoline 75 mg BID | 2.84 | 0.88 | (0.82, 0.93) | <0.001 |
| | Eluxadoline 100 mg BID | 2.75 | 0.85 | (0.80, 0.90) | <0.001 |
| | Placebo | 3.24 | -- | -- | -- |
| Week 12 | Eluxadoline 75 mg BID | 2.67 | 0.89 | (0.83, 0.94) | <0.001 |
| | Eluxadoline 100 mg BID | 2.61 | 0.86 | (0.81, 0.92) | <0.001 |
| | Placebo | 3.02 | -- | -- | -- |
| Week 26 | Eluxadoline 75 mg BID | 2.41 | 0.90 | (0.85, 0.96) | 0.002 |
| | Eluxadoline 100 mg BID | 2.38 | 0.89 | (0.84, 0.95) | <0.001 |
| | Placebo | 2.67 | -- | -- | -- |
| **No. of urgency episodes** | | | | | |
| Week 4 | Eluxadoline 75 mg BID | 1.01 | 0.79 | (0.68, 0.91) | 0.001 |
| | Eluxadoline 100 mg BID | 0.99 | 0.77 | (0.67, 0.89) | <0.001 |
| | Placebo | 1.28 | -- | -- | -- |
| Week 12 | Eluxadoline 75 mg BID | 0.88 | 0.78 | (0.68, 0.90) | <0.001 |
| | Eluxadoline 100 mg BID | 0.89 | 0.80 | (0.69, 0.92) | 0.002 |
| | Placebo | 1.12 | -- | -- | -- |
| Week 26 | Eluxadoline 75 mg BID | 0.69 | 0.78 | (0.67, 0.90) | <0.001 |
| | Eluxadoline 100 mg BID | 0.74 | 0.84 | (0.72, 0.97) | 0.015 |
| | Placebo | 0.89 | -- | -- | -- |
| **Bowel Incontinence** | | | | | |
| Week 4 | Eluxadoline 75 mg BID | 0.10 | 0.79 | (0.62, 0.99) | 0.044 |
| | Eluxadoline 100 mg BID | 0.10 | 0.81 | (0.64, 1.03) | 0.085 |
| | Placebo | 0.12 | -- | -- | -- |
| Week 12 | Eluxadoline 75 mg BID | 0.09 | 0.80 | (0.64, 1.02) | 0.070 |
| | Eluxadoline 100 mg BID | 0.09 | 0.84 | (0.67, 1.07) | 0.160 |
| | Placebo | 0.11 | -- | -- | -- |
| Week 26 | Eluxadoline 75 mg BID | 0.07 | 0.84 | (0.66, 1.06) | 0.147 |
| | Eluxadoline 100 mg BID | 0.08 | 0.90 | (0.71, 1.14) | 0.399 |
| | Placebo | 0.09 | -- | -- | -- |



Finally, the influence of the treatment on the Quality of Life has been evaluated by a longitudinal analysis, the results of which are presented in the following table:

**Table 17 - Longitudinal analyiss of IBS-QoL total scores (ITT analysis):**

| | | LS Mean | LS Mean Difference (95%) | | *P* value |
|---|---|---|---|---|---|
| Week 4 | Eluxadoline 75 mg BID | 63.15 | 4.18 | (1.56, 6.81) | 0.002 |
| | Eluxadoline 100 mg BID | 64.11 | 5.14 | (2.52, 7.77) | <0.001 |
| | Placebo | 58.97 | -- | -- | -- |
| Week 8 | Eluxadoline 75 mg BID | 64.19 | 4.08 | (1.52, 6.64) | 0.002 |
| | Eluxadoline 100 mg BID | 65.30 | 5.20 | (2.63, 7.76) | <0.001 |
| | Placebo | 60.11 | -- | -- | -- |
| Week 12 | Eluxadoline 75 mg BID | 65.22 | 3.98 | (1.46, 6.50) | 0.002 |
| | Eluxadoline 100 mg BID | 66.49 | 5.25 | (2.72, 7.77) | <0.001 |
| | Placebo | 61.25 | -- | -- | -- |
| Week 18 | Eluxadoline 75 mg BID | 66.26 | 3.88 | (1.37, 6.38) | 0.002 |
| | Eluxadoline 100 mg BID | 67.68 | 5.30 | (2.79, 7.80) | <0.001 |
| | Placebo | 62.39 | -- | -- | -- |
| Week 26 | Eluxadoline 75 mg BID | 67.30 | 3.77 | (1.26, 6.28) | 0.003 |
| | Eluxadoline 100 mg BID | 68.87 | 5.35 | (2.84, 7.86) | <0.001 |
| | Placebo | 63.52 | -- | -- | -- |
| Week 36 | Eluxadoline 75 mg BID | 68.33 | 3.67 | (1.13, 6.21) | 0.005 |
| | Eluxadoline 100 mg BID | 70.06 | 5.40 | (2.86, 7.93) | <0.001 |
| | Placebo | 64.66 | -- | -- | -- |
| Week 44 | Eluxadoline 75 mg BID | 69.37 | 3.57 | (0.98, 6.16) | 0.007 |
| | Eluxadoline 100 mg BID | 71.25 | 5.45 | (2.86, 8.04) | <0.001 |
| | Placebo | 65.80 | -- | -- | -- |
| Week 52 | Eluxadoline 75 mg BID | 70.41 | 3.46 | (0.80, 6.12) | 0.011 |
| | Eluxadoline 100 mg BID | 72.45 | 5.50 | (2.84, 8.16) | <0.001 |
| | Placebo | 66.94 | -- | -- | -- |



In addition, also a responder analysis was conducted on Quality of Life. This only showed partially statistical significance at week 4, week 8, and at week 52 for the high dose group only. The difference in response rates ranged between 3% and 8%, with up to 49.8% responders in the high dose group at week 8 showing the highest response rates.

At last, sensitivity analyses regarding the treatment misallocations due to the IVRS/IWRS errors are reported. For this, three different analyses were performed: a) Exclusion of the 53 affected patients, b) replacement of affected study days with non-response, and c) days set to missing and use of multiple imputation techniques. An influence was only seen for the low dose-group, as would be expected, and showed slightly diminished effects with even higher p-values. As example, the analysis with the replacement of affected study days with non-response is shown.

**Table 18 - CMH analysis of composite repsonders (ITT analysis) Study IBS-3001 comparing original analysis and sensitivity analysis with imputed non-response for patients with IVRS/IWRS misallocation.**

| | Study IBS-3001 (Original Analysis Table 2.7.3.3-12) | | | Study IBS-3001 Imputed Non-Response for Patients With IVRS/IWRS Misallocations (ISE Analysis) | | |
|---|---|---|---|---|---|---|
| Interval / Treatment | N | Responder n (%) | *P* value[a] | N | Responder n (%) | *P* value[a] |
| **Weeks 1-26** | | | | | | |
| Eluxadoline 75 mg BID | 427 | 100 (23.4) | 0.112 | 427 | 95 (22.2) | 0.237 |
| Eluxadoline 100 mg BID | 426 | 125 (29.3) | < 0.001 | 424[b] | 125 (29.5) | < 0.001 |
| Placebo BID | 427 | 81 (19.0) | -- | 427 | 81 (19.0) | -- |

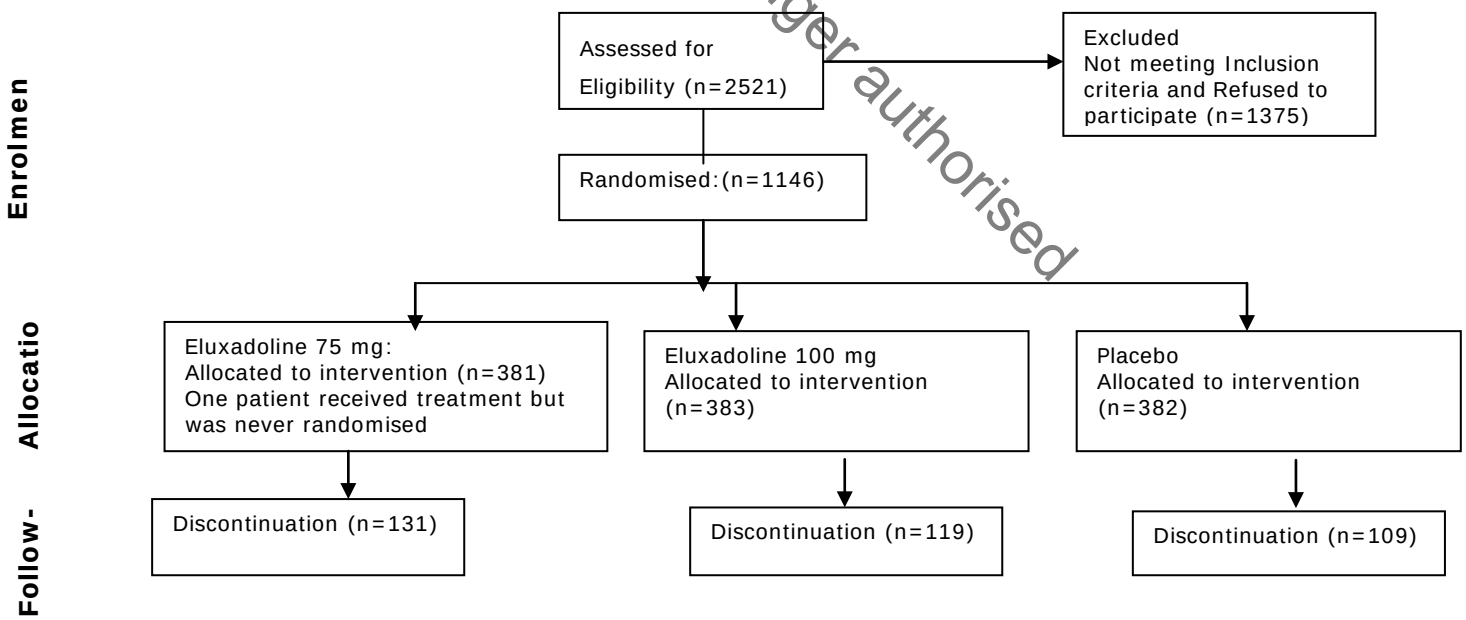


**Withdrawal effects:**

Study 3001 included a 2-week observation period after the end of double-blind treatment (lasting for 52 weeks). Efficacy related results (effects of withdrawal or occurrence of rebound) are not reported in the study report.

**Study IBS-3002:**

**Participant flow**




- A tabular overview on patient disposition is given in the following:

**Table 19 - Disposition of patients in study 3002:**

| | Number (%) of Patients | | | |
|---|---|---|---|---|
| | Eluxadoline 75 mg BID N=381 | Eluxadoline 100 mg BID N=383 | Placebo BID N=382 | Total N=1146 |
| Total Number of Patients | | | | |
| Randomized | 381 (100.0) | 383 (100.0) | 382 (100.0) | 1146 (100.0) |
| Attended Week 12 visit | 296 (77.7) | 301 (78.6) | 312 (81.7) | 909 (79.3) |
| Attended Week 26 visit | 259 (68.0) | 271 (70.8) | 278 (72.8) | 808 (70.5) |
| Completed study | 250 (65.6) | 264 (68.9) | 273 (71.5) | 787 (68.7) |
| Discontinued study | 131 (34.4) | 119 (31.1) | 109 (28.5) | 359 (31.3) |
| IVRS/IWRS misallocation | 12 (3.1) | 13 (3.4) | 0 | 25 (2.2) |
| Primary Reason for Discontinuation | | | | |
| Voluntarily withdrew | 70 (18.4) | 66 (17.2) | 74 (19.4) | 210 (18.3) |
| Adverse event or SAE | 32 (8.4) | 28 (7.3) | 19 (5.0) | 79 (6.9) |
| Physician decision: other | 10 (2.6) | 8 (2.1) | 7 (1.8) | 25 (2.2) |
| Lost to follow-up | 11 (2.9) | 5 (1.3) | 6 (1.6) | 22 (1.9) |
| Sponsor decision, specify | 7 (1.8) | 5 (1.3) | 0 | 12 (1.0) |
| Physician decision: lack of efficacy | 1 (0.3) | 5 (1.3) | 3 (0.8) | 9 (0.8) |
| Protocol violation | 0 | 2 (0.5) | 0 | 2 (0.2) |



In the included patient population, 10 patients had entry criteria violations, two of which had evidence of relevant hepatic disease, one of which had elevated serum lipase levels, and seven of which had previously taken rifaximin within the last 28 days before study entry.

A total of 26 patients were assigned the incorrect study drug due to an IVRS/IWRS error and instead of switching to placebo after the week 26 visit, continued on their originally assigned therapy. 12 patients randomized to the 75-mg treatment arm and 14 patients randomized to the 100-mg treatment arm were dispensed the wrong treatment kits at Week 26 because of 2 errors in the IVR/IWR system. At the Week 26 visit, all patients were to have been dispensed single-blind placebo. Twenty-six patients who had reached the Week 26 visit were impacted before the 2 errors were identified and corrected. One of these patients (100-mg treatment group) voluntarily withdrew from the study and was never dispensed the incorrect kit and the remaining 25 patients took the wrong treatment (i.e., remained on their randomized treatment assignment of 100-mg eluxadoline or 75-mg eluxadoline instead of placebo) during the 4-week single-blind withdrawal period. The duration of exposure to IVRS/IWRS misallocation that occurred at Week 26 was not calculated for this study, as the last 4 weeks of the study patients were to have received placebo. Immediate corrective actions were taken by the IVRS/IWRS vendor (PPD) to address the issue, including implementing a programming change to address the 2 errors with IVRS/IWRS. No subsequent IVRS/IWRS study drug dispensation errors occurred.

A systematic error in the IVR/IWR system resulted in patient contact requirement notifications not being generated if some of the trigger events (eg, a day without a bowel movement) were entered by patients a day late (a 1-day retrograde diary entry was a pre-specified allowance per the IVRS/IWRS specifications). This concerned 5 patients for the reporting of constipation, and 5 patients ( in 6 instances) for the intake of loperamide as rescue medication. The IRBs were informed of the situation and corrective actions were taken by the IVRS/IWRS vendor (PPD) to address the issue.

During the study site kit misallocations occurred for three patients, which received the wrong drug. These were dispensation errors du to site personnel only and were not associated with the IVRS system errors.

One user in the US was inappropriately given access to the eCRFs of an incorrect site in the electronic database. A user at site 783 in the US was inappropriately given access to site 763 (a site in the UK). This user (from site 783) made incorrect entries on a single day only to the eCRFs for two patients at site 763; those entries should have been made to the eCRFs for two other patients. The data entry to incorrect patients was corrected, inappropriate access to the eCRF database was rectified, and full audit trails for the changes were verified and monitored to confirm that the data in the eCRFs were correct at both sites.

The datasets analysed are shown in the following table:

**Table 20 - Display of analysis sets Study 3002.**

| | Number of Patients | | | |
|---|---|---|---|---|
| | Eluxadoline 75 mg BID | Eluxadoline 100 mg BID | Placebo BID | Total |
| Enrolled Set | 381 | 383 | 382 | 1146 |
| Randomized Set | 381 | 383 | 382 | 1146 |
| ITT Analysis Set | 381 | 382 | 382 | 1145 |
| Safety Analysis Set | 379 | 380 | 381 | 1137 |
| Modified ITT Analysis Set | 376 | 376 | 379 | 1131 |
| No. of patients receiving >1 treatment | | | | |
| IVRS/IWRS Misallocation[a] | | | | |
| 1st treatment received | 12 | 13 | 0 | 25 |
| 2nd treatment received | 12 | 13 | 0 | 25 |
| Site Misallocation[b] | | | | |
| 1st treatment received | 0 | 1 | 2 | 3 |
| 2nd treatment received | 2 | 1 | 0 | 3 |
| No. of patients randomized >1 time[c] | 1 | 1 | 0 | 1 |
| No. of patients treated but not randomized | 0 | 0 | 0 | 0 |
| No. of patients randomized but not treated | 4 | 4 | 1 | 9 |



**Recruitment**

Study Initiation Date: 29 May 2012, first patient pre-screened

Study Completion Date: 09 January 2014, last patient completed last visit

**Conduct of the study**

The original study protocol 27018966IBS3002 dated 04 March 2012, was amended 4 times- Similar to study 3001, the amendments were either relating to clarifications of methodology and definitions, or can be seen as the consequences of the changes in the regulatory requirements.

During the conduct of the two pivotal studies, a systematic error in the IVRS/IWRS occurred, which resulted in treatment misallocations in both studies. Immediate corrective actions were taken to address the error, including implementing a programming change, and no subsequent errors were identified in the final reconciliation after unblinding.

In IBS 3002, the systematic error occurred at the Week 26 visit when all patients were to have received single-blind placebo and did not impact the analysis of efficacy results (Weeks 1 12 or Weeks 1 26) for this study. Overall, 25 patients in IBS 3002 continued to take their assigned active study drug (12 patients took 75 mg eluxadoline instead of placebo and 13 patients took 100 mg eluxadoline instead of placebo) during the 4-week single-blind withdrawal period due to the IVRS/IWRS issue.

Moreover, a total of 5 patients in IBS 3001 and 3 patients in IBS 3002 were dispensed the wrong kits in error at the site. Across both studies, 6 patients who were randomized to placebo received eluxadoline from 28 to 69 days (2 of these misallocations occurred at the Week 26 visit); 1 patient randomized to 100 mg eluxadoline received placebo for 37 days; and 1 patient randomized to 100 mg eluxadoline received 75 mg eluxadoline for 34 days.

**Baseline data**

The relevant baseline characteristics were in their majority not relevantly different between treatment groups. There was a potentially relevant difference for the percentage of older patients, which was lowest in the 75 mg group (9.4%) and highest in the placebo group (13.4%). The following table shows the main demographic characteristics:



**Table 21 - Demographic characteristics (enrolled set)**

| | Eluxadoline 75 mg BID N=381 | Eluxadoline 100 mg BID N=383 | Placebo BID N=382 | Total N=1146 |
|---|---|---|---|---|
| **Age** | | | | |
| Mean (SD) | 45.0 (13.17) | 45.7 (13.31) | 47.1 (13.82) | 45.9 (13.45) |
| Median | 45.0 | 45.0 | 47.5 | 45.5 |
| Min, Max | 18, 77 | 19, 75 | 19, 77 | 18, 77 |
| **Age categories (years), n (%)** | | | | |
| 18-40 | 139 (36.5) | 146 (38.1) | 133 (34.8) | 418 (36.5) |
| 41-64 | 206 (54.1) | 198 (51.7) | 198 (51.8) | 602 (52.5) |
| ≥65 | 36 (9.4) | 39 (10.2) | 51 (13.4) | 126 (11.0) |
| **Gender, n (%)** | | | | |
| Male | 120 (31.5) | 126 (32.9) | 132 (34.6) | 378 (33.0) |
| Female | 261 (68.5) | 257 (67.1) | 250 (65.4) | 768 (67.0) |
| **Race** | | | | |
| White | 327 (85.8) | 318 (83.0) | 329 (86.1) | 974 (85.0) |
| Black | 46 (12.1) | 51 (13.3) | 43 (11.3) | 140 (12.2) |
| Asian | 2 (0.5) | 7 (1.8) | 6 (1.6) | 15 (1.3) |
| American Indian or Alaska Native | 3 (0.8) | 3 (0.8) | 1 (0.3) | 7 (0.6) |
| Native Hawaiian or Other Pacific Islander | 0 | 1 (0.3) | 2 (0.5) | 3 (0.3) |
| Other | 3 (0.8) | 3 (0.8) | 1 (0.3) | 7 (0.6) |
| **Ethnicity, n (%)** | | | | |
| Hispanic or Latino | 98 (25.7) | 99 (25.8) | 101 (26.4) | 298 (26.0) |
| Not Hispanic or Latino | 283 (74.3) | 284 (74.2) | 281 (73.6) | 848 (74.0) |
| **BMI ($kg/m^2$)** | | | | |
| Mean (SD) | 30.79 (8.167) | 30.45 (7.738) | 29.79 (6.866) | 30.34 (7.614) |
| Median | 29.30 | 28.90 | 29.00 | 29.05 |
| Min, Max | 15.5, 65.8 | 16.0, 63.5 | 14.8, 69.6 | 14.8, 69.6 |

The IBS characteristics at baseline were also comparable between the treatment groups. During the last 7 days prior to Day 1, the mean worst abdominal pain score was 6.00 (on the 0-10 NRS scale), the average daily BSS score was 6.22 (on the 0-7 BSFS score), and 2.79 on the IBS-d global symptom score (on the 0-4 scale). The number of BMs at baseline was 4.78 per day. 78% of the patients had persistent symptoms, whereas about 22% described their symptoms as “waxing and waning” over time. The use of loperamide during the past years was reported by about just over a third of the patients, without relevant differences between treatment groups.

Again, roughly 20% of the patients had a history of cholecystectomy, and these were in their majority female.

Just over 80% of the patients took concomitant medications, with the most common medications being ibuprofen (14.9%), omeprazole (10.9%), multivitamins (10.7%), paracetamol (10.6%) aspirin (10.1%), l9isinopril (9.3%), metformin (7.9%), salbutamol (7.2%), ergocalciferol (7.0%), simvastatin (6.9%), fish oil (6.5%), alprazolam (5.2%), and hydrochlorothiazide (5.1%). The proportion for at least ibuprofen, omeprazole, paracetamol, and aspirin were similar across the treatment groups.

During the first week the average total unit doses of loperamide rescue medication used were 0.7, 1.0, and 1.2 doses in the 75-mg, 100-mg, and placebo groups, respectively. From Week 2 through Week 26 the use of loperamide for diarrhoea was uncommon and averaged <1 unit dose per week for both eluxadoline treatment groups as well as placebo. The proportion of patients with excessive use of loperamide follow-ups was 5.0%, 6.9%, and 6.8% for the 75-mg, 100-mg, and placebo groups, respectively.

Treatment compliance was generally again reported to be high with an average of around 90%, and about 85% of the patients (around 84% in the active treatment groups, and 89% in the placebo group) taking more than 80% of the trial medication during the first 12 weeks. The figures for the overall period were also about 90% mean compliance, with about 84% of the patients having an overall >80% compliance in the two active treatment groups, and about 89% in the placebo group.



**Numbers analysed**

The Enrolled Set comprised 1146 randomised patients. The ITT Analysis Set included 1145 patients with data presented according to their randomisation assignment (for the patient randomised twice, only data from the first randomisation were included). The MITT Analysis Set included 1131 patients (please refer to table 60 in above chapter participations flow).

**Outcomes and estimation**

The evaluation of the primary endpoint (both for FDA and EMA) is shown in the following table:

**Table 22 - CMH analysis of composite responders (daily response criteria; ITT set):**

| Interval Treatment | Number (%) | | *P* value[a] |
|---|---|---|---|
| | Responder | Non-Responder | |
| **Weeks 1-12 (FDA primary endpoint)** | | | |
| Eluxadoline 75 mg BID (N=381) | 110 (28.9) | 271 (71.1) | <0.001 |
| Eluxadoline 100 mg BID (N=382) | 113 (29.6) | 269 (70.4) | <0.001 |
| Placebo BID (N=382) | 62 (16.2) | 320 (83.8) | |
| **Weeks 1-26 (EMA primary endpoint)** | | | |
| Eluxadoline 75 mg BID (N=381) | 116 (30.4) | 265 (69.6) | 0.001 |
| Eluxadoline 100 mg BID (N=382) | 125 (32.7) | 257 (67.3) | <0.001 |
| Placebo BID (N=382) | 77 (20.2) | 305 (79.8) | |

The logistic regresssion model based analysis were generally in rough accordance with the results as above, with p-values of <0.001 for the high dose throughout and between <0.001 and 0.007 for the low dose group.

The evaluation of the primary enpoint underwent an exploration of the longitudinal response, and with several sensitivity analyses, including the "worst-case scenario" (using the overall absolute 50% of positive daily responder criterion, and a weekly repsonder definition evaluation; see above). These evaluations were generally in line with the primary evaluation, however, showing somewhat more inconsistent effects for the lower dose group (after 26 weeks in the weekly response definition evaluation, and during the last 4 weeks in the "worst case" scenario). As examples of these exercises, the overall weekly evaluation ("alternative composite responder definition"), and the longitudinal worst-case analysis are shown in the following:

**Table 23 - CMH analysis of alternative composite responder definitions (weekly response criteria; ITT analysis).**

| Interval Treatment | Number (%) | | *P* value[a] |
|---|---|---|---|
| | Responder | Non-Responder | |
| **Method 1** | | | |
| Weeks 1-12 | | | |
| Eluxadoline 75 mg BID (N=381) | 138 (36.2) | 243 (63.8) | 0.004 |
| Eluxadoline 100 mg BID (N=382) | 144 (37.7) | 238 (62.3) | <0.001 |
| Placebo BID (N=382) | 101 (26.4) | 281 (73.6) | -- |
| **Method 2** | | | |
| Weeks 1-12 | | | |
| Eluxadoline 75 mg BID (N=381) | 147 (38.6) | 234 (61.4) | 0.091 |
| Eluxadoline 100 mg BID (N=382) | 172 (45.0) | 210 (55.0) | <0.001 |
| Placebo BID (N=382) | 125 (32.7) | 257 (67.3) | -- |

**Table 24 - CMH analyiss of worst-case composite responders by interval; ITT analysis):**

| Interval Treatment | Number (%) Responder | Non-Responder | *P* value[a] |
|---|---|---|---|
| **Weeks 1-4** | | | |
| Eluxadoline 75 mg BID (N=381) | 94 (24.7) | 287 (75.3) | <0.001 |
| Eluxadoline 100 mg BID (N=382) | 98 (25.7) | 284 (74.3) | <0.001 |
| Placebo BID (N=382) | 43 (11.3) | 339 (88.7) | -- |
| **Weeks 5-8** | | | |
| Eluxadoline 75 mg BID (N=381) | 119 (31.2) | 262 (68.8) | <0.001 |
| Eluxadoline 100 mg BID (N=382) | 127 (33.2) | 255 (66.8) | <0.001 |
| Placebo BID (N=382) | 70 (18.3) | 312 (81.7) | -- |
| **Weeks 9-12** | | | |
| Eluxadoline 75 mg BID (N=381) | 123 (32.3) | 258 (67.7) | <0.001 |
| Eluxadoline 100 mg BID (N=382) | 122 (31.9) | 260 (68.1) | <0.001 |
| Placebo BID (N=382) | 78 (20.4) | 304 (79.6) | -- |
| **Weeks 13-16** | | | |
| Eluxadoline 75 mg BID (N=381) | 119 (31.2) | 262 (68.8) | <0.001 |
| Eluxadoline 100 mg BID (N=382) | 134 (35.1) | 248 (64.9) | <0.001 |
| Placebo BID (N=382) | 79 (20.7) | 303 (79.3) | -- |
| **Weeks 17-20** | | | |
| Eluxadoline 75 mg BID (N=381) | 121 (31.8) | 260 (68.2) | 0.002 |
| Eluxadoline 100 mg BID (N=382) | 122 ( 31.9) | 260 (68.1) | 0.001 |
| Placebo BID (N=382) | 83 (21.7) | 299 (78.3) | -- |
| **Weeks 21-24** | | | |
| Eluxadoline 75 mg BID (N=381) | 110 (28.9) | 271 (71.1) | 0.011 |
| Eluxadoline 100 mg BID (N=382) | 125 (32.7) | 257 (67.3) | <0.001 |
| Placebo BID (N=382) | 80 (20.9) | 302 (79.1) | -- |



The analysis of the primary endpoints according to the old IBS guideline are presented in the following, with the global response again reported with the scale-based evaluation as well as the “adequate relief” evaluation.

**Table 25 - CMH analysis of IBS-d global symptom responders (daily response criterion; ITT analysis)**

| Interval Treatment | Number (%) Responder | Non-Responder | *P* value[a] |
|---|---|---|---|
| **Weeks 1-12** | | | |
| Eluxadoline 75 mg BID (N=381) | 166 (43.6) | 215 (56.4) | <0.001 |
| Eluxadoline 100 mg BID (N=382) | 162 (42.4) | 220 (57.6) | <0.001 |
| Placebo BID (N=382) | 113 (29.6) | 269 (70.4) | -- |
| **Weeks 1-26** | | | |
| Eluxadoline 75 mg BID (N=381) | 172 (45.1) | 209 (54.9) | 0.002 |
| Eluxadoline 100 mg BID (N=382) | 165 (43.2) | 217 (56.8) | 0.012 |
| Placebo BID (N=382) | 131 (34.3) | 251 (65.7) | -- |

The analysis of the time course of this global response endpoint shows consistently significant p-values for all time intervals evaluated. The numerical differences are generally around 10%, reaching just under 8% in the worst case (for the high dose during weeks 17-20, and for both dose groups during weeks 21-24). The longitudinal analysis (based on numerical evaluation) was generally in line with the CMH evaluation of responders.

**Table 26 - CMH analysis of IBS-Adequate Relief responders (ITT analysis)**

| Interval / Treatment | Number (%) | | |
|---|---|---|---|
| | Responder | Non-Responder | *P* value[a] |
| **Weeks 1-12** | | | |
| Eluxadoline 75 mg BID (N=381) | 229 (60.1) | 152 (39.9) | 0.003 |
| Eluxadoline 100 mg BID (N=382) | 223 (58.4) | 159 (41.6) | 0.011 |
| Placebo BID (N=382) | 188 (49.2) | 194 (50.8) | -- |
| **Weeks 1-26** | | | |
| Eluxadoline 75 mg BID (N=381) | 201 (52.8) | 180 (47.2) | 0.013 |
| Eluxadoline 100 mg BID (N=382) | 205 (53.7) | 177 (46.3) | 0.006 |
| Placebo BID (N=382) | 167 (43.7) | 215 (56.3) | -- |

The analysis of the pain response is shown in the following:

**Table 27 - CMH analysis of pain responders (daily response criterion; ITT analysis):**

| Interval / Treatment | Number (%) | | |
|---|---|---|---|
| | Responder | Non-Responder | *P* value[a] |
| **Weeks 1-12** | | | |
| Eluxadoline 75 mg BID (N=381) | 183 (48.0) | 198 (52.0) | 0.448 |
| Eluxadoline 100 mg BID (N=382) | 195 (51.0) | 187 (49.0) | 0.111 |
| Placebo BID (N=382) | 173 (45.3) | 209 (54.7) | -- |
| **Weeks 1-26** | | | |
| Eluxadoline 75 mg BID (N=381) | 181 (47.5) | 200 (52.5) | 0.448 |
| Eluxadoline 100 mg BID (N=382) | 191 (50.0) | 191 (50.0) | 0.148 |
| Placebo BID (N=382) | 171 (44.8) | 211 (55.2) | -- |



The evaluation of the different time-intervals was generally in line with these (non-significant) results. Also, the weekly evaluation (done for the first 12 weeks only) did not show significant results. The longitudinal evaluation of the pain scores, however, (based on the numerical evaluation) showed partly results with p-values <0.05 over time (for the high dose at all time-points except week 4, and for the low dose group at week 4 and 8).

The following table show the evaluation of the stool consistency response:

**Table 28 - CMH analysis of stool consistency responders (daily response criterion; ITT analysis)**

| Interval / Treatment | Number (%) | | |
|---|---|---|---|
| | Responder | Non-Responder | *P* value[a] |
| **Weeks 1-12** | | | |
| Eluxadoline 75 mg BID (N=381) | 141 (37.0) | 240 (63.0) | <0.001 |
| Eluxadoline 100 mg BID (N=382) | 136 (35.6) | 246 (64.4) | <0.001 |
| Placebo BID (N=382) | 80 (20.9) | 302 (79.1) | -- |
| **Weeks 1-26** | | | |
| Eluxadoline 75 mg BID (N=381) | 131 (34.4) | 250 (65.6) | <0.001 |
| Eluxadoline 100 mg BID (N=382) | 152 (39.8) | 230 (60.2) | <0.001 |
| Placebo BID (N=382) | 90 (23.6) | 292 (76.4) | -- |

The analysis of the time course of this response criterion shows highly consistent results across all intervals (all p-values <0.001). Also, the sensitivity analysis regarding weekly responder rates are consistent with this analysis (albeit with slightly higher p-values for the low dose group), and the longitudinal analysis (on the numerical stool consistency scores at certain time-points) are fully consistent with p-values <0.001 throughout. The numerical differences at all time points between the two active and placebo groups were about -0.52 (throughout) for the lower dose group and -0.52 rising to -0.59 for the higher dose group.

**Ancillary analyses**

The evaluation of the abdominal bloating and abdominal discomfort scales are presented in the following. This is based on a longitudinal analysis, but not with a responder evaluation but on the changes on numerical values:

**Table 29 - Londitudinal analysis of abdominal bloating and abdominal discomfort (count data; ITT analysis)**

| | | LS Mean | LS Mean Difference (95%) | *P* value |
|---|---|---|---|---|
| **Abdominal bloating** | | | | |
| **Week 4** | Eluxadoline 75 mg BID | 4.05 | -0.06 (-0.37, 0.24) | 0.683 |
| | Eluxadoline 100 mg BID | 3.91 | -0.20 (-0.50, 0.10) | 0.194 |
| | Placebo | 4.11 | -- | -- |
| **Week 12** | Eluxadoline 75 mg BID | 3.79 | -0.03 (-0.33, 0.28) | 0.861 |
| | Eluxadoline 100 mg BID | 3.54 | -0.28 (-0.59, 0.02) | 0.064 |
| | Placebo | 3.82 | -- | -- |
| **Week 26** | Eluxadoline 75 mg BID | 3.35 | 0.04 (-0.27, 0.34) | 0.818 |
| | Eluxadoline 100 mg BID | 2.88 | -0.43 (-0.74, -0.13) | 0.005 |
| | Placebo | 3.31 | -- | -- |
| **Abdominal discomfort** | | | | |
| **Week 4** | Eluxadoline 75 mg BID | 3.92 | -0.31 (-0.58, -0.03) | 0.028 |
| | Eluxadoline 100 mg BID | 3.95 | -0.28 (-0.56, 0.00) | 0.047 |
| | Placebo | 4.23 | -- | -- |
| **Week 12** | Eluxadoline 75 mg BID | 3.55 | -0.32 (-0.59, -0.04) | 0.025 |
| | Eluxadoline 100 mg BID | 3.51 | -0.36 (-0.63, -0.08) | 0.011 |
| | Placebo | 3.86 | -- | -- |
| **Week 26** | Eluxadoline 75 mg BID | 2.90 | -0.33 (-0.60, -0.05) | 0.021 |
| | Eluxadoline 100 mg BID | 2.73 | -0.50 (-0.77, -0.22) | <0.001 |
| | Placebo | 3.22 | -- | -- |



The evaluation of the frequency of BMs, the no. of urgency episodes, and the no. of bowel incontinence episodes is shown in the following:

**Table 30 - Longitudinal analysis of bowel symptoms (count data; ITT analysis):**

| | | Risk | Risk Ratio (95% CI) | *P* value |
|---|---|---|---|---|
| **Frequency of bowel movements** | | | | |
| **Week 4** | Eluxadoline 75 mg BID | 2.61 | 0.87 (0.82, 0.93) | <0.001 |
| | Eluxadoline 100 mg BID | 2.67 | 0.89 (0.83, 0.95) | <0.001 |
| | Placebo | 3.00 | -- | -- |
| **Week 12** | Eluxadoline 75 mg BID | 2.46 | 0.86 (0.81, 0.92) | <0.001 |
| | Eluxadoline 100 mg BID | 2.50 | 0.88 (0.83, 0.94) | <0.001 |
| | Placebo | 2.84 | -- | -- |
| **Week 26** | Eluxadoline 75 mg BID | 2.21 | 0.85 (0.80, 0.91) | <0.001 |
| | Eluxadoline 100 mg BID | 2.23 | 0.87 (0.81, 0.92) | <0.001 |
| | Placebo | 2.58 | -- | -- |
| **No. of urgency episodes** | | | | |
| **Week 4** | Eluxadoline 75 mg BID | 0.77 | 0.66 (0.55, 0.79) | <0.001 |
| | Eluxadoline 100 mg BID | 0.78 | 0.67 (0.56, 0.80) | <0.001 |
| | Placebo | 1.17 | -- | -- |
| **Week 12** | Eluxadoline 75 mg BID | 0.67 | 0.64 (0.53, 0.77) | <0.001 |
| | Eluxadoline 100 mg BID | 0.67 | 0.65 (0.54, 0.78) | <0.001 |
| | Placebo | 1.04 | -- | -- |
| **Week 26** | Eluxadoline 75 mg BID | 0.52 | 0.61 (0.50, 0.73) | <0.001 |
| | Eluxadoline 100 mg BID | 0.52 | 0.61 (0.51, 0.73) | <0.001 |
| | Placebo | 0.85 | -- | -- |
| **Incontinence** | | | | |
| **Week 4** | Eluxadoline 75 mg BID | 0.05 | 0.79 (0.62, 1.01) | 0.059 |
| | Eluxadoline 100 mg BID | 0.06 | 0.87 (0.68, 1.11) | 0.252 |
| | Placebo | 0.07 | -- | -- |
| **Week 12** | Eluxadoline 75 mg BID | 0.05 | 0.77 (0.61, 0.98) | 0.035 |
| | Eluxadoline 100 mg BID | 0.05 | 0.80 (0.63, 1.02) | 0.067 |
| | Placebo | 0.06 | -- | -- |
| **Week 26** | Eluxadoline 75 mg BID | 0.04 | 0.74 (0.58, 0.94) | 0.014 |
| | Eluxadoline 100 mg BID | 0.04 | 0.69 (0.54, 0.88) | 0.003 |
| | Placebo | 0.05 | -- | -- |



The evaluation of the incontinence free days did see increasing differences over time for the high dose group, with Odds Ratios rising from 1.48 (at week 4) to 2.27 at the end of treatment ($p<0.001$) whereas the results for the low dose group were more inconsistent and slightly decreasing Odds Ratios were observed, with none of the results being significant.

Finally, the influence of the treatment on the Quality of Life has been evaluated by a longitudinal analysis, the results of which are presented in the following table:

**Table 31 - Longitudinal analyiss of IBS-QoL total scores (ITT analysis):**

| | | LS Mean | LS Mean Difference (95%) | | *P* value |
|---|---|---|---|---|---|
| **Week 4** | Eluxadoline 75 mg BID | 67.84 | 5.64 | (2.92, 8.37) | <0.001 |
| | Eluxadoline 100 mg BID | 66.79 | 4.60 | (1.89, 7.31) | <0.001 |
| | Placebo | 62.19 | -- | -- | -- |
| **Week 8** | Eluxadoline 75 mg BID | 68.90 | 5.22 | (2.58, 7.85) | <0.001 |
| | Eluxadoline 100 mg BID | 67.68 | 3.99 | (1.38, 6.61) | 0.003 |
| | Placebo | 63.68 | -- | -- | -- |
| **Week 12** | Eluxadoline 75 mg BID | 69.96 | 4.79 | (2.20, 7.37) | <0.001 |
| | Eluxadoline 100 mg BID | 68.56 | 3.39 | (0.82, 5.96) | 0.010 |
| | Placebo | 65.17 | -- | -- | -- |
| **Week 18** | Eluxadoline 75 mg BID | 71.02 | 4.36 | (1.78, 6.95) | <0.001 |
| | Eluxadoline 100 mg BID | 69.45 | 2.79 | (0.21, 5.36) | 0.034 |
| | Placebo | 66.66 | -- | -- | -- |
| **Week 26** | Eluxadoline 75 mg BID | 72.08 | 3.94 | (1.30, 6.57) | 0.003 |
| | Eluxadoline 100 mg BID | 70.33 | 2.19 | (-0.44, 4.81) | 0.103 |
| | Placebo | 68.15 | -- | -- | -- |
| **Week 30** | Eluxadoline 75 mg BID | 73.14 | 3.51 | (0.77, 6.25) | 0.012 |
| | Eluxadoline 100 mg BID | 71.21 | 1.58 | (-1.14, 4.30) | 0.254 |
| | Placebo | 69.63 | -- | -- | -- |

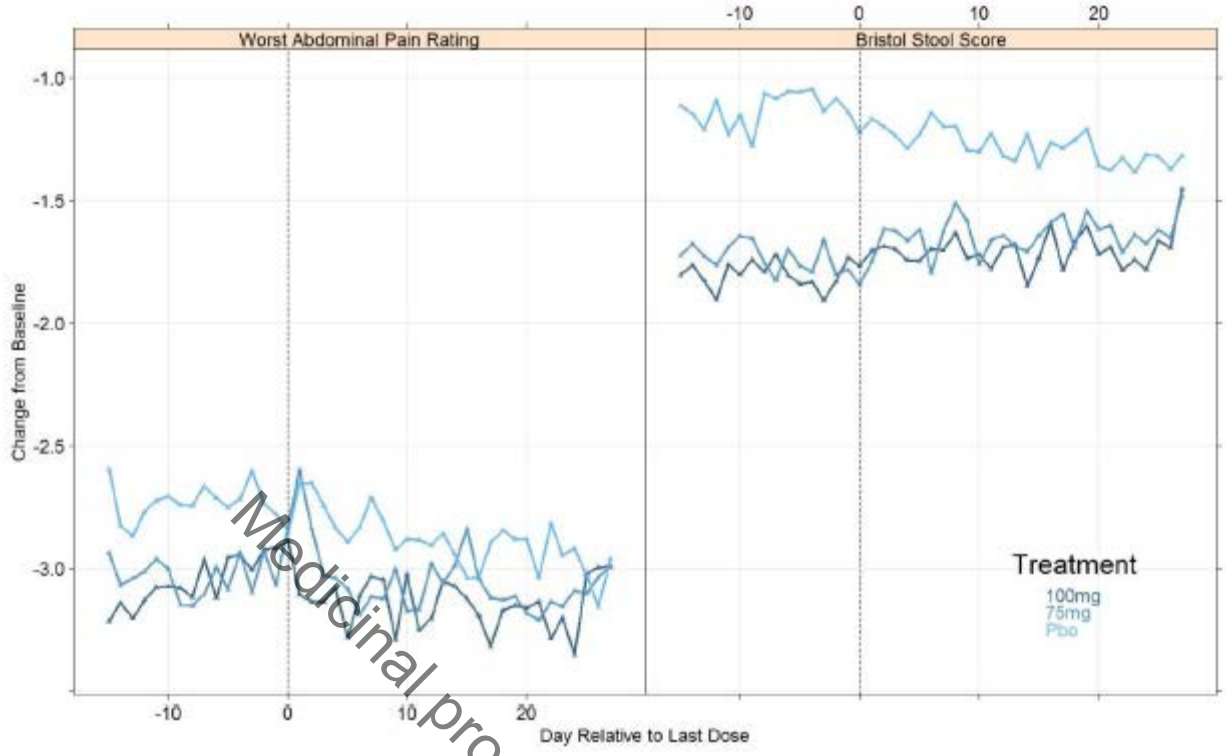
The responder evaluation of the IBS-QoL did not show statistically significant difference to placebo at any time point, and consistent across both active treatment groups. The differences to placebo were numerically small at all time-points, ranging from 3% to 5%.

**Withdrawal and rebound effects:**

Study 3002 included a 4-week (single-blind) withdrawal period and a further evaluation of the endpoints until the 30 week final examination. The study report, however, does not clearly describe the development of the endpoints after withdrawal of active medication.

The Summary of Efficacy includes a description and graphical display of the abdominal pain and stool consistency scores after the cessation of treatment (the last 20 days of double-blind treatment and the 30 days of “placebo”-treatment). Overall abdominal pain scores for both eluxadoline and placebo groups tended to remain relatively stable or even continued to decline during the placebo withdrawal period. By contrast, stool consistency scores for the placebo group tended to remain relatively stable or continued to decline during the withdrawal period while patients who were previously treated with eluxadoline saw a slow, gradual worsening of their stool consistency. Importantly, the regression of the stool consistency scores for the eluxadoline group was not abrupt, and scores remained below Baseline values. Overall these data indicate no “rebound” or worsening of abdominal pain or diarrheal symptoms.

**Figure 5 - Changes in daily abdominal pain and stool consistency scores upon cessation of double-blind treatment (IBS-3002)**






**Summary of main study(ies)**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 32 - Summary of Efficacy for Trial IBS-3001**

| | | | |
|---|---|---|---|
| **Title**: A Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-27018966 in the Treatment of Patients with Diarrhoea-Predominant Irritable Bowel Syndrome | | | |
| Study identifier | 27018966-IBS3001 (IBS-3001) | | |
| Design | Randomized, double blind, parallel group, placebo-controlled | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | 52 weeks<br>not applicable<br>not applicable |
| Hypothesis | Superiority | | |
| Treatments groups | Eluxadoline 100 mg BID | | Eluxadoline 100 mg BID, 52 weeks, 426 randomized |
| | Eluxadoline 75 mg BID | | Eluxadoline 75 mg BID, 52 weeks, 428 randomized |
| | Placebo BID | | placebo, 52 weeks, 427 randomized |
| Endpoints and definitions | Primary endpoint | Composite responder | The primary efficacy endpoint was the composite responder proportion evaluated over the initial 12 weeks of double-blind treatment for the Food and Drug Administration (FDA) and over the initial 26 weeks of treatment for the European Medicines |

| | | | |
|---|---|---|---|
| | | | Agency (EMA). Responder rates were compared based on patients who met the daily composite response criteria (pain and stool consistency) for at least 50% of the days with diary entries from Weeks 1-12 and Weeks 1-26. A patient must have met BOTH of the following criteria on any given day to be a daily responder:<br>• Daily pain response: worst abdominal pain scores in the past 24 hours improved by ≥30% compared to baseline pain (average of week prior to randomization)<br>• Daily stool consistency response: BSS score <5 or the absence of a bowel movement if accompanied by ≥30% improvement in worst abdominal pain compared to baseline<br>To be eligible to be a composite responder, a patient must have had a minimum of 60 days of diary entries over Weeks 1-12 and a minimum of 110 days of diary entries over Weeks 1-26. |
| | Secondary endpoint | Pain responders | A responder was defined as a patient who met the daily pain response criterion (as described above for composite response) for at least 50% of the days over each interval. To be eligible to be a pain responder, a patient must have had a minimum of 60 days of diary entries over Weeks 1-12 and a minimum of 110 days of diary entries over Weeks 1-26. |
| | Secondary endpoint | Stool consistency responders | A stool consistency responder was defined as a patient who met the stool consistency response criteria (as described above for composite response) for at least 50% of the days over each interval. To be eligible to be a stool consistency responder, a patient must have had a minimum of 60 days of diary entries over Weeks 1-12 and a minimum of 110 days of diary entries over Weeks 1-26. |
| | Secondary endpoint | IBS-d (irritable bowel syndrome-diarrhea predominant) global symptom responders | Those patients who met the daily IBS-d global symptom response criteria (ie, IBS-d global symptom score of 0 [none] or 1 [mild]; or a daily IBS-d global symptom score improved by ≥2.0 compared to the baseline average) for at least 50% of days with diary entries during each interval over the 12-week interval (Weeks 1-12), 26-week interval (Weeks 1-26), and each 4-week interval (Weeks 1-4, 5-8, 9-12, 13-16, 17-20, and 21-24) |
| Database lock | 08 August 2014 | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis (Cochran-Mantel-Haenszel [CMH]): Composite Responders** |
|---|---|
| Analysis population and time point description | Intent-to-Treat (ITT); Weeks 1-26 and Weeks 1-12 |

| | | | | | |
|---|---|---|---|---|---|
| Effect estimate per comparison | Treatment group | | Eluxadoline 100 mg BID | Eluxadoline 75 mg BID | Placebo BID |
| | Number of subjects | | 426 | 427 | 427 |
| | Composite Responders | Weeks 1-26 | **29.3%** | **23.4%** | **19.0%** |
| | | P-value | **<0.001** | **0.112** | **—** |
| | | Weeks 1-12 | 25.1% | 23.9% | 17.1% |
| | | P-value | 0.004 | 0.014 | **—** |
| Notes | Treatment effect was assessed via pair-wise, 2-sided Cochran-Mantel-Haenszel (CMH) tests for active treatments (75 mg BID or 100 mg BID eluxadoline) versus placebo for composite responders (Weeks 1-12 and Weeks 1-26). To account for 2 active treatment groups, multiplicity of hypothesis tests for the primary endpoints was controlled for by employing the Bonferroni procedure, thereby maintaining the family-wise α-level. | | | | |
| **Analysis description** | **Secondary analyses (CMH Analyses): Pain Responders; BSS (Stool Consistency) Responders; IBS-d Global Symptom Responders** | | | | |
| Analysis population and time point description | ITT; Weeks 1-26 and Weeks 1-12 | | | | |
| Effect estimate per comparison | Treatment group | | Eluxadoline 100 mg BID | Eluxadoline 75 mg BID | Placebo BID |
| | Number of subjects | | 426 | 427 | 427 |
| | Pain Responders | Weeks 1-26 | **46.5%** | **45.2%** | **43.3%** |
| | | P-value | **0.355** | **0.582** | **—** |
| | | Weeks 1-12 | 43.2% | 42.4% | 39.6% |
| | | P-value | 0.284 | 0.404 | — |
| | Number of subjects | | 426 | 427 | 427 |
| | BSS Responders | Weeks 1-26 | **34.0%** | **28.1%** | **24.1%** |
| | | P-value | **0.001** | **0.186** | **—** |
| | | Weeks 1-12 | 34.3% | 30.0% | 22.0% |
| | | P-value | <0.001 | 0.008 | **—** |
| | Number of subjects | | 426 | 427 | 427 |
| | IBS-d Global Symptom Responders | Weeks 1-26 | **37.1%** | **35.1%** | **32.3%** |
| | | P-value | **0.144** | **0.221** | **—** |
| | | Weeks 1-12 | 34.7% | 36.3% | 28.8% |
| | | P-value | 0.063 | 0.048 | **—** |
| | Number of subjects | | 426 | 427 | 427 |
| Notes | The same analyses performed for the primary composite responder endpoint were performed for the secondary responder endpoints. | | | | |

**Table 33 - Summary of Efficacy for Trial IBS-3002**

| | | | |
|---|---|---|---|
| **Title**: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-27018966 in the Treatment of Patients with Diarrhea-Predominant Irritable Bowel Syndrome | | | |
| Study identifier | 27018966-IBS3002 (IBS-3002) | | |
| Design | Randomized, double blind, parallel group, placebo-controlled | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | 26 weeks<br>not applicable<br>4 weeks (single-blind placebo treatment for safety only) |
| Hypothesis | Superiority | | |
| Treatments groups | Eluxadoline 100 mg BID | | Eluxadoline 100 mg BID, 26 weeks, 383 randomized |
| | Eluxadoline 75 mg BID | | Eluxadoline 75 mg BID, 26 weeks, 381 randomized |
| | Placebo BID | | placebo, 26 weeks, 382 randomized |
| Endpoints and definitions | Primary endpoint | Composite responder | The primary efficacy endpoint was the composite responder proportion evaluated over the initial 12 weeks of double-blind treatment for the FDA and over the initial 26 weeks of treatment for the EMA. Responder rates were compared based on patients who met the daily composite response criteria (pain and stool consistency) for at least 50% of the days with diary entries from Weeks 1-12 and Weeks 1-26. A patient must have met BOTH of the following criteria on any given day to be a daily responder:<br>• Daily pain response: worst abdominal pain scores in the past 24 hours improved by ≥30% compared to baseline pain (average of week prior to randomization)<br>• Daily stool consistency response: BSS score <5 or the absence of a bowel movement if accompanied by ≥30% improvement in worst abdominal pain compared to baseline<br>To be eligible to be a composite responder, a patient must have had a minimum of 60 days of diary entries over Weeks 1-12 and a minimum of 110 days of diary entries over Weeks 1-26. |
| | Secondary endpoint | Pain responders | A responder was defined as a patient who met the daily pain response criterion (as described above for composite response) for at least 50% of the days over each interval. To be eligible to be a pain responder, a patient must have had a minimum of 60 days of diary entries over Weeks 1-12 and a minimum of 110 days of diary entries over Weeks 1-26. |
| | Secondary endpoint | Stool consistency responders | A stool consistency responder was defined as a patient who met the stool consistency response criteria (as described above for composite response) for at least 50% of the days over each interval. To be eligible to be a stool consistency responder, a patient must have had a minimum of 60 days of diary entries over Weeks 1-12 and a minimum of 110 days of diary entries over Weeks 1-26. |

| | | | |
|---|---|---|---|
| | Secondary endpoint | IBS-d (irritable bowel syndrome-diarrhea predominant) global symptom responders | Those patients who met the daily IBS-d global symptom response criteria (ie, IBS-d global symptom score of 0 [none] or 1 [mild]; or a daily IBS-d global symptom score improved by ≥2.0 compared to the baseline average) for at least 50% of days with diary entries during each interval over the 12-week interval (Weeks 1-12), 26-week interval (Weeks 1-26), and each 4-week interval (Weeks 1-4, 5-8, 9-12, 13-16, 17-20, and 21-24) |
| Database lock | 22 January 2014 | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis (CMH): Composite Responders** | | | |
|---|---|---|---|---|
| Analysis population and time point description | ITT; Weeks 1-26 and Weeks 1-12 | | | |
| Effect estimate per comparison | Treatment group | | Eluxadoline 100 mg BID | Eluxadoline 75 mg BID | Placebo BID |
| | Number of subjects | | 382 | 381 | 382 |
| | Composite Responders | Weeks 1-26 | **32.7%** | **30.4%** | **20.2%** |
| | | P-value | **<0.001** | **0.001** | — |
| | | Weeks 1-12 | 29.6% | 28.9% | 16.2% |
| | | P-value | <0.001 | <0.001 | — |
| Notes | Treatment effect was assessed via pair-wise, 2-sided CMH tests for active treatments (75 mg BID or 100 mg BID eluxadoline) versus placebo for composite responders (Weeks 1-12 and Weeks 1-26). To account for 2 active treatment groups, multiplicity of hypothesis tests for the primary endpoints was controlled for by employing the Bonferroni procedure, thereby maintaining the family-wise α-level. | | | | |
| **Analysis description** | **Secondary analyses (CMH): Pain Responders; BSS (Stool Consistency) Responders; IBS-d Global Symptom Responders** | | | |
| Analysis population and time point description | ITT; Weeks 1-26 and Weeks 1-12 | | | |
| Effect estimate per comparison | Treatment group | | Eluxadoline 100 mg BID | Eluxadoline 75 mg BID | Placebo BID |
| | Number of subjects | | 382 | 381 | 382 |
| | Pain Responders | Weeks 1-26 | **50.0%** | **47.5%** | **44.8%** |
| | | P-value | **0.148** | **0.448** | — |
| | | Weeks 1-12 | 51.0% | 48.0% | 45.3% |
| | | P-value | 0.111 | 0.448 | — |
| | Number of subjects | | 382 | 381 | 382 |
| | BSS Responders | Weeks 1-26 | **39.8%** | **34.4%** | **23.6%** |
| | | P-value | **<0.001** | **<0.001** | — |
| | | Weeks 1-12 | 35.6% | 37.0% | 20.9% |
| | | P-value | <0.001 | <0.001 | — |

| | | | | | |
|---|---|---|---|---|---|
| | Number of subjects | | 382 | 381 | 382 |
| | IBS-d Global Symptom Responders | Weeks 1-26 | **43.2%** | **45.1%** | **34.3%** |
| | | P-value | **0.012** | **0.002** | **—** |
| | | Weeks 1-12 | 42.4% | 43.6% | 29.6% |
| | | P-value | <0.001 | <0.001 | — |
| Notes | The same analyses performed for the primary composite responder endpoint were performed for the secondary responder endpoints. | | | | |

**Analysis performed across trials (pooled analyses and meta-analysis)**

The following numbers of patients in the different older age groups were included into the phase II and phase III trials:

**Table 34 - Summary of number of patients in older age group categories (pooled phase II and III studies)**

| | Age 65-74 (Older subjects number /total number) | Age 75-84 (Older subjects number /total number) | Age 85+ (Older subjects number /total number) |
|---|---|---|---|
| Controlled Trials | 218/3235 | N= 28/3235 | None |
| Non Controlled trials | None | None | None |



The differences found in these analyses for gender, BMI, race, baseline abdominal pain severity, characteristics of IBS complaints (continuous vs. wax/wane) and cholecystectomy status did not reveal relevant influences of these characteristics on the overall results, at least for the high dose. The non-US population was too small to draw any reliable conclusions. The effect size for the 100mg dose in the non-US (38.5%; 15/39 patients) was similar to the US population. However, the placebo response rate over Week 1-26 was higher in the non-US (10/38; 26.3%) compared to the US population (148/771; 19.2%).

The pooled analysis revealed a trend regarding age (split <65 vs>65years) similar to each trial analysed separately. The applicant has additionally evaluated the risk-benefit ratio in the older population, showing that the administration of the lower dose in the older population while showing similar or somewhat increased efficacy, has a smaller increase in adverse events (as compared to the younger age groups). The composite response rate difference for the older patients was higher than 20% for both doses, and even the abdominal pain response rate difference was >10% in the older population. Contrary to the population aged <65 years of age, where some difference in overall AE rates between active and placebo has been seen, the overall AE rate in older patients appears to be very similar to placebo (but the overall rate of AEs is increased compared to the younger population, which has to be attributed to the overall poorer health status of this population).

The evaluation of ethnicity showed a marked reduction of efficacy in the Hispanic/Latino population, which was even more pronounced, when the population with the use of a Spanish version of the IVRS system was evaluated in addition.

The cholecystectomy population had a marked reduction of efficacy for the lower dose group.

An additional responder analysis for abdominal pain with stricter success criteria (40% and 50% improvement) showed a more clear differentiation between the groups, with statistical significance in the high dose group, however, with the magnitude of effect still having questionable clinical relevance only (clearly under 10%).

**Clinical studies in special populations**

No studies in special patient populations have been conducted with regard to efficacy. However, the applicant has analysed potential factors for efficacy like BMI, gender, and age for the pooled data of the two pivotal studies (please refer to above chapter on Analysis performed across trials).

**Supportive studies**

No further studies supporting efficacy have been conducted.

## 2.5.3. Discussion on clinical efficacy

**Design and conduct of clinical studies**

The applicant has conducted three clinical trials during phase 2b and phase 3 of the drug development.

During phase 2, a dose-finding and preliminary efficacy and safety trial with a 3-month duration was conducted which included 4 doses of active treatment (range of 5 mg to 200 mg) in randomised, double-blind, placebo-controlled manner. The trial included a 2-week screening phase, a 12-week double-blind phase and a 2 week follow-up phase and was conducted in the USA.

For the inclusion of patients, the Rome III criteria were used as the basis, and minimum requirements for pain severity and stool consistency abnormalities were defined. The original protocol, including the definition of endpoints, was developed in close collaboration with and reflecting the ongoing discussions within the FDA on the design of trials in IBS at that time. Whereas the principal requirement of demonstrating efficacy and dose-response via the evaluation of pain and stool consistency response was not questioned during the trial, the final evaluation of the trial used the final FDA guidance compliant endpoints which were slightly different from those defined in the protocol. Further endpoints included frequently used scales such as the IBS-SSS and global response evaluations, as well as measures of quality of life. The overall design of the trial and the choice of endpoints – as well as the evaluations finally performed – are considered suitable to fulfil the purposes of the study. The trial is considered suitable to fulfil the aim of the investigation of dose-response and the choice of a suitable dose for the later development. The choice of the patient population is likewise considered to be acceptable.

The study included 807 patients. At a pre-planned interim analysis (after 425 patients had completed 4 weeks of treatment), the lowest included dose (5 mg BID) was abandoned due to missing efficacy. The overall statistical planning and methodology for evaluation of the trial are considered adequate. Sparse blood sampling in order to further elucidate PK via PK modelling was also included.

The design of the two phase 3 trials conducted was set up in close collaboration with the FDA and according to the design proposed in the final FDA IBS guideline. Due to the fact, however, that the CHMP IBS guideline at that time showed major discrepancies to the final FDA guideline, the applicant also developed the phase 3 programme according to the Scientific Advice received from the CHMP. This led to the design of two identical, placebo-controlled trials of 6 months duration of the controlled trial phase. This is therefore the first application

for a new compound in the treatment of IBS which presents indeed 2 trials with the extended duration of 6 months as requested by the CHMP (old and revised) IBS-guideline. The proposed primary endpoints were at that time planned with different evaluations for the FDA and the CHMP. However, the fact that the CHMP guideline has in fact been aligned with the requirements laid down in the FDA guideline, has finally enabled the presentation of similar evaluations for both the FDA and the CHMP, the only difference remaining the timing of the primary evaluation, which was 12 weeks for the FDA and 26 weeks for the CHMP.

Both phase 3, studies IBS-3001 and IBS-3002, included a 2-3 week screening phase, and a 26 weeks double-blind placebo-controlled treatment phase. Study 3001 was continued in blinded manner until week 52, although the detailed efficacy evaluations were abandoned during the second 6 months. The study ended with a 2 weeks post-treatment observation phase. Study 3002 included a 4-weeks single-blind withdrawal phase, during which all patients received placebo.

The study population included was diagnosed with IBS on the basis of the Rome III criteria and minimum requirements with regard to a minimal pain score, and the stool consistency at bowel movements, with additional requirements during the run-in phase in order to ensure the presence of the symptoms at inclusion. Although the IBS guideline requests the inclusion of an appropriate population according to the character of the complaints (i.e. a population with continuous symptoms for long-term trials) the inclusion criteria did not take account of this. However, the results achieved showed that the vast majority of patients were suffering from continuous symptoms, and the response to treatment was not relevantly different in those with “waxing and waning” character of the symptoms as opposed to those with a continuous clinical picture. The further in- and exclusion criteria (e.g. with regard to other relevant diseases) were considered also to be appropriate. Therefore, the included patient population is adequate, with the major exception that the patients were not tested for the presence of bile acid malabsorption (BAM), which causes watery diarrhoea and is commonly misdiagnosed as IBS-d. In fact it is widely accepted that up to one third of patients diagnosed with IBS-d do have BAM. The request to diagnose and exclude these patients from trials in IBS-d has only been recently taken up into the revised IBS-guideline, and the applicant was therefore unable to account for this requirement on time. Because it is currently unknown whether BAM in these patients is the causative factor of the complaints, or exists as an “epiphenomenon” or an additional entity “only” in these patients, and the proposed treatment of these patients with bile-acid complexing agents (such as colesevelam etc.) has not been investigated in fully satisfactory manner, the omission of the requirement to exclude these patients from the trials is considered acceptable, but remains to be a problem to be addressed in the future. From a regulatory point of view, and considering the fact of a relevantly reduced efficacy in patients without gallbladder (which is known to be risk-factor for BAM), this point addresses not only a question of general scientific interest, but the important regulatory question of identifying a subgroup with relevantly altered magnitude of effect(s). The conduct of further studies is given as a recommendation to the Applicant.



Of note, the exclusion criteria also included potential “off-target” effects/diseases of the pharmacodynamics of the compound, such as patients with a history of cholecystitis, pancreatitis, post-cholecystectomy syndromes, biliary duct disease, and Sphincter of Oddi (SO) dysfunction.

The primary endpoints used in both studies were in full compliance with the CHMP revised IBS guideline and based on a composite 50% response in abdominal pain and stool consistency. Interactive Voice Response Systems were used to collect daily symptoms during the trial. Secondary endpoints were further responder evaluations with regard to pain, stool consistency, and global symptoms, as well as numerical evaluations of the development of scales for the symptoms discomfort, bloating, frequency of stools, occurrence of incontinence and urgency and the development of Quality of Life. The choice of endpoints is considered to be fully acceptable.

The statistical analysis foreseen in the protocol and conducted for the evaluation of the results is considered adequate and an adequate set of sensitivity analyses has shown consistency of the effects.

***Efficacy data and additional analyses***

The results of the phase 2 trial were not entirely conclusive with regard to the superiority of one or more dose groups to placebo, and only "trending results" were achieved for certain doses and at certain time-points of evaluation for the responder based analyses. Overall, the results of the study demonstrated that the compound in the dose of 100 mg BID had relevantly higher response rates in the different evaluations used, showing a difference to placebo in responder rates in the range of 7-20%, with a slower onset of the response in pain. It could be demonstrated that both the responses for the 25 mg dose as well as the 200 mg dose did not exceed the effects seen for the 100 mg dose (in fact the lower dose was clearly inferior). The post-hoc analysis linked improvement in abdominal pain and BSS on the same day and produced higher overall response rates that were statistically significant for the 100mg and 200mg eluxadoline doses in comparison to placebo (28.0%, 28.7% and 13.9% respectively, p=0.002 for both).

The 100 mg BID dose was chosen for further development. Considerations on safety and the minimally effective dose (determined to be 25 mg BID) led to the conclusion to include both a 100 mg BID and a 75 mg BID dose into the phase 3 trials. The magnitude of the effect was expected to lie in the range of 10-15% and the potential problems with regard to showing "clinical relevance" were discussed in a Scientific Advice with the CHMP. At that time, the acceptance of a superiority below a threshold of 15% superiority over placebo was not excluded by the CHMP depending on the overall safety evaluation.

1282 and 1146 patients were included into the studies IBS 3001 and 3002. The patient population was relatively young of age (mean age of about 40), with relatively high BMI. Also, because patients above 80 years of age were excluded, the overall number of patients with an age over 65, and all the more those with an age above 75 were low. However, the recruited numbers of patients above 65 and 75 years of age do appropriately reflect the epidemiology of the disease and are therefore considered acceptable. The exclusion of the very old subjects has been adequately justified based on the high requirements on compliance/use of electronic IVRS.

The results of the phase 3 trials showed a statistically highly significant superiority of both active doses over placebo in the primary evaluation. The magnitude of the treatment effect in comparison to placebo was higher in Study IBS-3002 than IBS-3001 across multiple analyses. Similar results were achieved for most of the secondary evaluations, including the symptoms abdominal discomfort, stool consistency, stool frequency, bloating, and urgency of stools. The magnitude of effect for the primary evaluation was in the range expected and showed a (pooled) 11.5% superiority over placebo. This is considered of limited clinical relevance. Also, it has to be considered that the response rates according to this evaluation do not exceed 32%, meaning that indeed at least 2/3 of the treated population do not experience (full) response. Even if the highest rates of response (in the "adequate relief" category) are taken, about half of the patient population will be left without a (sufficient) response. The magnitude of the effect for the lower dose (75 mg BID) was generally numerically smaller and showing more inconsistencies with regard to statistical significance. There was a trend towards a greater increase in the proportion of responders to placebo than to active treatment (particularly 75mg eluxadoline) between the 12 week (US) and the 26 week (EU) efficacy analysis. The 75 mg dose, however, shows an acceptable level of superiority in the subgroup of patients aged 65 and older, which was accepted as the reasons to include this lower dose as a treatment option in these patients, despite the fact that this was based on a post-hoc analysis in a minority of patients only.

Regarding the individual components of the primary endpoint the compound showed clearly disappointing results in the evaluation of pain (independent of the effects on stool consistency), but demonstrated a statistically significant difference from placebo for the 100mg dose in both trials over Weeks 1 -26 for the stool consistency endpoint.

The 75mg dose was statistically significantly different from placebo for the primary composite response endpoint over Weeks 1-26 in IBS-3002 and both studies combined (26.7% vs. 19.5%, p<0.001) but not IBS-3001 alone. The trials also revealed partly conflicting results with regard to the global response evaluations and the development of Quality of Life. Concerning the global response criteria (which showed statistical significance in one trial and in the pooled evaluation), a comparison with previous substances filed for evaluation (e.g. alostetron, tegaserod) was possible, and it was shown that the results were not relevantly different from those with tegaserod, but somewhat inferior to alosetron. Additional analyses with regard to the pain response showed that the difference to placebo in pain response is dependent on the definition of response, and appears to be a bit more clinically relevant if defined more strictly, however, with a treatment magnitude which is still clearly below 10%.

With regard to the missing statistical significance of the pain response, and its questionable clinical relevance, the issue is also raised whether the pharmacology and thus the efficacy of the compound could be any different from the one for loperamide, the peripheral μ-OR used in clinical practice for IBS-d and recommended by learned societies for the symptomatic treatment of diarrhoea in IBS. For the comparison to loperamide, the applicant makes the case that there is currently no evidence for any effect of loperamide on pain, which is agreed to after a review of the available literature data.

However, additional analyses showed that stool consistency response seems to be a pre-condition of pain response, and that based on these results, pain response has to be regarded to be secondary to the normalisation of the stool related parameters only and also that only a stool response can be expected to occur without having a pain response. Contrary to this, a pain response independent of the stool (consistency) response is not achieved by the compound.

In addition, even if loperamide might have some effects on pain, there is the clear advantage for eluxadoline that efficacy has been documented according to nowadays standards. The trials conducted with loperamide were relevantly shorter (and would be considered to be insufficiently short nowadays) and used partly questionable methodology, not to speak of the incomplete documentation of the literature reports. Therefore, the “superiority” of eluxadoline over loperamide lies in the very superior documentation with two adequately designed and fully powered trials. Moreover, the patient population also included a sub-population of patients being refractory to treatment with loperamide, for which the compound has been proven to be similarly effective as compared to the effects in the total study population.

Concerning the questionable relevance of the pain response, and the inconsistency in the global responder evaluations, it also has to be stated that the results of the trials would have almost excluded the approval of the compound if evaluated according to the requirements of the former CHMP IBS guideline, which requested a co-primary evaluation of pain and global symptoms.

Contrary to what would be expected, the proportion of patients that required follow–up for excessive loperamide rescue medication use was marginally greater with active treatment than placebo in study IBS -3001 (6.1%, 4.0% and 3.8% for the 75mg, 100mg and placebo groups respectively) and little different in study IBS-3002 (5.0%, 6.9% and 6.8% respectively).The applicant has shown high consistency of the (pooled) results with regard to most subgroups. Whereas gender, race, and BMI, as well as baseline severity, the character of the IBS symptom presentation (continuous or waxing/waning), the refractoriness to loperamide, and history of GERD

and depression did show high consistency of the results, this was not so much the case with regard to ethnicity and cholecystectomy status.

With regard to the further evaluation of age, no statistically significant benefit was seen in patients below the age of 40 in IBS-3001 whilst the 100mg dose showed a statistically significant benefit in IBS-3002; although response rates were lower (composite response 23.3% vs. 13.5% for 100mg eluxadoline vs. placebo in patients <40 years in IBS-3002). In additional analyses, the applicant has demonstrated that this subpopulation did indeed differ in two characteristics, namely the baseline severity, especially abdominal pain, and compliance with the collection of diary data. For both factors, the applicant was able to show that these possess a relevant influence on the overall response rates, and has thus made likely that at least a part of the reduced effects in the subpopulation can be explained by these factors. In addition, the pooled analysis of the composite response rate has shown that the magnitude of the treatment effect appear not to be substantially different from the overall results.

Conversely, the proportion of responders appeared greater with the 75mg than the 100mg dose in patients over the age of 65 years in both trials individually and the combined analysis. Although speculative, there is a suggestion that patients are more sensitive to the effects of eluxadoline with increasing age. This has been taken into account in recommending that the 75 mg dose should be included as a treatment option in the population above 65 years of age.



In addition, geographic region has been analysed, but the patients with UK been pooled with those from Canada, whereas for geographic region it would be expected that North America is compared to Europe. Additional analyses according to country showed that the results achieved in the European population for the 100 mg BID dose do not deviate relevantly from the overall results. If any deviation exists, it is the one that the magnitude of effect appears to be greater in the UK compared to the overall population. Further justification on the acceptability of the US population has also been given and found to be acceptable according to the relevant guidance documents (EMEA/CHMP/EWP/292702/2008 and ICHE5).

The reduced response rates in the post-cholecystectomy population (mainly confined to the low dose, which was, however, proposed to be the regular dose in this population due to safety reasons in the proposal of the applicant) was seen as one of the main reasons the exclusion of these patients from treatment.

This lower dose is also proposed to be an alternative option for those with tolerability problems with the regular dose of 100 mg BID. Although no data on efficacy of the 75 mg dose in those previously having tolerability problems with the regular dose are available, and – as shown by the overall results – the efficacy of the compound is slightly inferior in the low-dose, the applicant has made likely that the severity of adverse events, especially in those that could finally be attributed to be causally related and are included as undesirable effects in the prescribing information occur with a lower grade of severity, and a switch in the dose is indeed considered to be an option.

The 4-week extension period of study 3002 could not detect any potential for withdrawal and rebound effects.

## 2.5.4. Conclusions on the clinical efficacy

In summary, the applicant has conducted an adequate clinical programme, with two well-designed phase 3 studies in a patient population being fully compliant with the IBS-guideline (however, bile acid malabsorption not excluded). The results achieved showed high statistical significance in the primary evaluation and several secondary endpoints, and also a relatively high consistency of the effects across sub-populations. The Quality of Life – although with conflicting results in one trial – was shown to be improved. However, the effects achieved

are considered to be of lesser clinical relevance only with regard to most endpoints especially for the abdominal pain response, which is one of the main features of the disease. Overall, the effects seen for the lower dose were smaller than those achieved with the high dose.

## *2.6. Clinical safety*

### Patient exposure

In the 10 Phase 1 oral administration studies, 373 subjects were enrolled and 330 subjects received at least 1 oral dose of eluxadoline (Safety Set). For those who received eluxadoline in the Phase 1 studies, 319 (96.7%) subjects completed the study and 11 (3.3%) subjects discontinued from the study. An AE led to discontinuation for 5 (1.5%) subjects.

The Phase 2 and 3 Enrolled Set included a total of 3235 patients (of which 3202 were unique). The study was completed by 45.0% (50/111), 75.3% (131/174), 62.6% (507/810), 65.4% (644/985), and 59.2% (103/174) patients in the 5 mg, 25 mg, 75 mg, 100 mg, and 200 mg dose groups, respectively, and by 67.3% (660/981) patients who were in the placebo group (figures given on individual study data, including those randomised more than once). An AE led to discontinuation for 1.8%, 2.9%, 8.4%, 8.0%, and 12.6% of patients in the 5 mg, 25 mg, 75 mg, 100 mg, and 200 mg eluxadoline dose groups, respectively, and 42 (4.3%) patients in the placebo group.

The total exposure for the phase 1-3 amounted to 2562 single subjects.

The figures of the duration of exposure for the phase 2 and 3 studies with unique exposures are shown in the following table:

**Table 35 - Disposition, pooled analysis of phase 2 and 3 studies (safety analysis set):**

| | Eluxadoline 5 mg BID[a] (N=109) | Eluxadoline 25 mg BID (N=173) | Eluxadoline 75 mg BID (N=807[b]) | Eluxadoline 100 mg BID (N=1032[b]) | Eluxadoline 200 mg BID (N=171) | Placebo BID (N=975[b]) | Total (N=3202) |
|---|---|---|---|---|---|---|---|
| **Overall duration of exposure (days)** | | | | | | | |
| n[c] | 109 | 172 | 803 | 976 | 170 | 972 | 3202 |
| Mean (SD) | 65.5 (25.19) | 72.8 (25.06) | 211.9 (121.80) | 186.0 (123.42) | 63.6 (31.66) | 190.9 (121.28) | 177.3 (122.49) |
| Median | 78.0 | 85.0 | 183.0 | 183.0 | 84.0 | 183.0 | 181.0 |
| Min, Max | 4, 97 | 1, 95 | 1, 384 | 1, 399 | 1, 103 | 1, 390 | 1, 399 |



### Adverse events

The evaluation of the safety documented in the phase I studies does overall comply with the adverse event profile of the phase 2 and 3 studies. Some of the studies investigating supratherapeutic doses, however, showed a clear dose-dependent effect on the occurrence of adverse events, especially with regard to gastrointestinal and CNS-related events.

The evaluation of the overall adverse event profile is therefore mainly based on the pooled evaluation of the phase 2 and phase 3 studies. An overview on these studies is given in the following table. For the interpretation, the different exposure of the patients in the phase 2 only (i.e. the 5 mg, 25 mg, and 200 mg) should be considered:

1. 75 mg and 100 mg compared to placebo.

**Table 36 - Overview of adverse events (safety analysis set) – pooled phase 2 and phase 3 studies:**

| | Eluxadoline 5 mg BID (N=109) | | Eluxadoline 25 mg BID (N=173) | | Eluxadoline 75 mg BID (N=807) | | Eluxadoline 100 mg BID (N=1032) | | Eluxadoline 200 mg BID (N=171) | | Placebo BID (N=975) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n (%) | Events | n (%) | Events | n (%) | Events | n (%) | Events | n (%) | Events | n (%) | Events |
| Adverse events | 48 (44.0) | 100 | 86 (49.7) | 224 | 486 (60.2) | 1556 | 575 (55.7) | 1804 | 91 (53.2) | 238 | 533 (54.7) | 1573 |
| Serious AEs | 1 (0.9) | 1 | 3 (1.7) | 4 | 34 (4.2) | 40 | 41 (4.0) | 65 | 3 (1.8) | 3 | 25 (2.6) | 28 |
| Related serious AEs | 0 | 0 | 0 | 0 | 5 (0.6) | 5 | 5 (0.5) | 7 | 0 | 0 | 0 | 0 |
| Deaths[a] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Adverse events leading to treatment discontinuation | 2 (1.8) | 3 | 5 (2.9) | 7 | 67 (8.3) | 68 | 80 (7.8) | 84 | 22 (12.9) | 48 | 42 (4.3) | 46 |

A more detailed evaluation of the adverse event profile is shown in the following table, which included all adverse events with a frequency of or above 2%:

**Table 37 - Adverse events reported by ≥2% of patients in any eluxadoline treatment group and at a greater incidence than placebo (safety analysis set) – pooled phase 2 and 3 studies.**

| | Number (%) of Patients | | | | | |
|---|---|---|---|---|---|---|
| System Organ Class<br>Preferred Term | Eluxadoline 5 mg BID (N=109) | Eluxadoline 25 mg BID (N=173) | Eluxadoline 75 mg BID (N=807) | Eluxadoline 100 mg BID (N=1032) | Eluxadoline 200 mg BID (N=171) | Placebo BID (N=975) |
| Total number of AEs | 100 | 224 | 1556 | 1804 | 238 | 1573 |
| Number of patients with ≥1 AE | 48 (44.0) | 86 (49.7) | 486 (60.2) | 575 (55.7) | 91 (53.2) | 533 (54.7) |
| **Gastrointestinal disorders** | **20 (18.3)** | **38 (22.0)** | **242 (30.0)** | **273 (26.5)** | **48 (28.1)** | **185 (19.0)** |
| Nausea | 6 (5.5) | 10 (5.8) | 65 (8.1) | 73 (7.1) | 18 (10.5) | 49 (5.0) |
| Constipation | 2 (1.8) | 5 (2.9) | 60 (7.4) | 84 (8.1) | 6 (3.5) | 24 (2.5) |
| Abdominal pain | 3 (2.8) | 6 (3.5) | 33 (4.1) | 47 (4.6) | 13 (7.6) | 25 (2.6) |
| Vomiting | 1 (0.9) | 7 (4.0) | 32 (4.0) | 43 (4.2) | 12 (7.0) | 12 (1.2) |
| Flatulence | 1 (0.9) | 3 (1.7) | 21 (2.6) | 33 (3.2) | 4 (2.3) | 17 (1.7) |
| Abdominal distension | 0 | 0 | 21 (2.6) | 28 (2.7) | 1 (0.6) | 15 (1.5) |
| Dry mouth | 1 (0.9) | 4 (2.3) | 15 (1.9) | 13 (1.3) | 5 (2.9) | 15 (1.5) |
| Diarrhea | 0 | 8 (4.6) | 14 (1.7) | 13 (1.3) | 2 (1.2) | 10 (1.0) |
| Gastroesophageal reflux disease | 2 (1.8) | 5 (2.9) | 11 (1.4) | 13 (1.3) | 1 (0.6) | 10 (1.0) |
| **Infections and infestations** | **18 (16.5)** | **30 (17.3)** | **199 (24.7)** | **222 (21.5)** | **25 (14.6)** | **230 (23.6)** |
| Upper respiratory tract infection | 3 (2.8) | 5 (2.9) | 27 (3.3) | 53 (5.1) | 1 (0.6) | 38 (3.9) |
| Nasopharyngitis | 5 (4.6) | 8 (4.6) | 33 (4.1) | 31 (3.0) | 6 (3.5) | 33 (3.4) |
| Sinusitis | 5 (4.6) | 6 (3.5) | 27 (3.3) | 27 (2.6) | 1 (0.6) | 35 (3.6) |
| Bronchitis | 4 (3.7) | 4 (2.3) | 26 (3.2) | 30 (2.9) | 1 (0.6) | 21 (2.2) |
| Gastroenteritis viral | 1 (0.9) | 3 (1.7) | 22 (2.7) | 14 (1.4) | 4 (2.3) | 18 (1.8) |
| Urinary tract infection | 0 | 2 (1.2) | 17 (2.1) | 18 (1.7) | 4 (2.3) | 17 (1.7) |
| **Nervous system disorders** | **8 (7.3)** | **17 (9.8)** | **81 (10.0)** | **112 (10.9)** | **24 (14.0)** | **99 (10.2)** |
| Headache | 3 (2.8) | 12 (6.9) | 32 (4.0) | 44 (4.3) | 7 (4.1) | 44 (4.5) |
| Dizziness | 4 (3.7) | 4 (2.3) | 21 (2.6) | 33 (3.2) | 11 (6.4) | 21 (2.2) |
| Somnolence | 1 (0.9) | 1 (0.6) | 1 (0.1) | 11 (1.1) | 4 (2.3) | 3 (0.3) |
| **Investigations** | **5 (4.6)** | **8 (4.6)** | **77 (9.5)** | **70 (6.8)** | **4 (2.3)** | **78 (8.0)** |
| Alanine aminotransferase increased | 2 (1.8) | 0 | 17 (2.1) | 26 (2.5) | 1 (0.6) | 14 (1.4) |
| **General disorders and administration site conditions** | **5 (4.6)** | **9 (5.2)** | **47 (5.8)** | **64 (6.2)** | **15 (8.8)** | **65 (6.7)** |
| Fatigue | 2 (1.8) | 3 (1.7) | 21 (2.6) | 20 (1.9) | 4 (2.3) | 23 (2.4) |
| **Respiratory, thoracic, and mediastinal disorders** | **4 (3.7)** | **10 (5.8)** | **58 (7.2)** | **55 (5.3)** | **7 (4.1)** | **66 (6.8)** |
| Cough | 0 | 5 (2.9) | 13 (1.6) | 9 (0.9) | 1 (0.6) | 19 (1.9) |
| **Vascular disorders** | **0** | **4 (2.3)** | **25 (3.1)** | **25 (2.4)** | **7 (4.1)** | **25 (2.6)** |
| Hypertension | 0 | 3 (1.7) | 20 (2.5) | 14 (1.4) | 5 (2.9) | 16 (1.6) |

AEs were most commonly reported within the GI disorders (25.2% of patients overall) and infections and infestations (22.5% of patients) SOCs. The GI disorders AEs with the highest incidence for the 75-mg and 100-mg eluxadoline doses were experienced by similar percentages of patients between these 2 dosage groups and included nausea, constipation, abdominal pain, vomiting, flatulence and abdominal distension. Within the first 2 weeks of dosing, the most commonly reported AEs were related to the GI disorders SOC and the incidence was comparable between the 75-mg (16.0%) and 100-mg (14.8%) eluxadoline groups and higher for 200mg eluxadoline (21.1%) during this time. During the first 2 weeks of dosing, nausea was the most commonly reported GI AE and was experienced by 4.7%, 4.6% and 2.8% of patients who received 75 mg eluxadoline, 100 mg eluxadoline and placebo, respectively. Abdominal pain was reported for 1.7%, 2.8%, and 0.7% of patients, respectively, in these 3 groups.

Following at least 1 year of treatment, the proportion of patients with AEs was 62.9% (154/245), 60.9% (148/243) and 56.2% (145/258) for the 75-mg, 100-mg and placebo groups, respectively. For these patients, the most commonly reported AEs were consistent with those for the full safety set, and involved the GI disorders and infections and infestations SOCs.



**Serious adverse event / deaths / other significant events**

During the duration of the study programme, including phase 1, 2 and 3, there were no deaths reported. 1 patient died 3 weeks after having completed study 3001. The death was considered unrelated to the study drug.

SAEs in the phase I study included four patients, with only one of them being assessed as related (ileus in a patients with hepatic impairment; these patients will be contraindicated).

Overall, a total of 141 SAEs were reported for 107 of 3202 (3.3%) patients during the phase 2 and 3 studies. Only 7 patients treated with either 5 mg, 25 mg, or 200 mg eluxadoline in the Phase 2 study experienced SAEs. For the other treatment groups, the proportions of patients with SAEs were 4.2% for the 75 mg group, 4.0% for the 100 mg group, and 2.6% for the placebo group.

While the SAE incidence rate among all patients was low, SAEs were most often reported within the GI disorders SOC (0.9% of all patients). GI disorders SAEs occurred in similar proportions of patients in the 75-mg and 100-mg treatment groups (1.0% and 1.3%, respectively), compared with 0.4% of placebo patients. The SAE with the overall highest incidence was pancreatitis (this includes the terms "pancreatitis," "acute pancreatitis," and "alcoholic pancreatitis"). A total of11 cases of pancreatitis were reported all of which occurred with the intake of eluxadoline.

**Laboratory findings**

Generally, no treatment-related trends were observed in mean serum chemistry results over time and the mean values observed at EOT/Early Withdrawal were generally similar to those observed at baseline for each treatment group. The parameters investigated comprised Albumin, ALP, ALT, AST, BUN, Calcium, bicarbonate, Chloride, Creatinine, Glucose, LDH, Phosphorus, Sodium, Potassium, Bilirubin, and Total Protein. The only imbalances in comparison to placebo occurred with increases in ALT, where especially the high increases in ALT occurred in the active treatment groups only (3 cases in the active treatment groups with ALT <10xULN compared to none for placebo; overall number of ALT increases 114 (14.1%), 126 (12.2%) and 128 (13.1%); ALT increases reported as AEs: 17 (2.1%), 26 (2.5%), and 14 (1.4%) for the 75 mg, 100 mg and placebo

groups, respectively). ALT increases were generally associated with the status of being post-cholecystectomy. The construct of an e-DISH-plot did not reveal any “Hy’s Law” cases with the simultaneous increase of >3xULN of ALT and <2xULN of bilirubin. ALT increase is therefore considered to be associated with biliary obstruction (based on SO-spasm) rather than liver cell toxicity. A similar trend as for ALT was also observed for ALP.

No treatment-related trends were observed in mean haematology results over time and the mean values observed at EOT/Early Withdrawal were similar to those observed at Baseline for each treatment group. Anaemia events reported as AE, however, will need further evaluation.

Results for vital sign measurements were similar across treatment groups and no remarkable findings for mean vital sign measurements or change from Baseline were observed.

**Safety in special populations**

The applicant evaluated the following factors for an influence on the number and rates of adverse events: Gender, Age, Race, BMI, IBS symptom history, cholecystectomy status, hepatic and renal dysfunction, history of GERD and depression.

In these evaluations, it was shown that the event frequency in females and in older people were increased, as well as those with prior cholecystectomy. However, due to the higher occurrence also in the placebo group this obviously reflects the overall disposition of the patients. In the latter population of post-cholecystectomy patients, the difference to placebo was increased for the GI event rate, as well as for SAEs. With regard to the older population, it could be shown – within the uncertainties of the relatively small number of older patients included – that the AE rates do not differ to placebo for the lower dose, despite the overall higher rate of AEs in this population.

No increase in the overall incidence of AEs based on renal or hepatic dysfunction status (mild or moderate impairment) was observed but data is limited in those with renal impairment and an increase was seen in those with hepatic impairment for the GI events nausea and constipation.

The applicant has identified AEs of special interest, which are investigated further, and which relate to the pharmacological class of eluxadoline (mixed opioid agonism/antagonism). These concern the following: Constipation, Sphincter of Oddi Spasm related events (including pancreatitis and biliary syndrome events), events of fall, syncope, and road traffic accidents, and cardiac and chest pain events.

The evaluation of constipation events showed an overall decrease of events over time, which is, however, questioned by the evaluation of the stool frequencies according to the IVRS system, which enabled the detection of similar rates of events across different periods of the studies, obviously pointing to some kind of negligence in the registration of these events. According to the IVRS diary records, severe constipation (no BM for $\geqslant$4 consecutive days based on non-missing diary entries) was experienced by 2.9%, 3.8% and 2.6% of patients across the 75-mg, 100-mg and placebo groups respectively during the first 13 weeks with a similar rate during the second three months of treatment. No serious complications of constipation were mentioned in the phase 2/3 studies. Small bowel obstruction developed after 362 days of eluxadoline 100mg but the patient had a tubal ligation 30 years previously and ileal stricture at laparotomy.

The evaluation of pancreatitis and hepatobiliary events and their correlation with potential causation by Sphincter of Oddi spasm (which is a well known effect of opioids) has revealed that all these events occurred in the active treatment groups only. None of the patients was treated with placebo, even if including the pancreatitis cases that could not be clearly related to a SO spasm mechanism. In the evaluation of the hepatobiliary events, and in those pancreatitis events for which SO spasm was adjudicated as the causative

factor it was revealed that cholecystectomy appears a clear risk factor, in as all 12 (or 11, if the one pancreatitis case with potential ethylic aetiology is not counted) but 1 had a prior cholecystectomy (and in the remaining patient, the status was unknown). Of the 6 non-SO cases of pancreatitis, 4/6 were directly related to high alcohol consumption, 1/6 was off eluxadoline for 2 weeks while also taking clarithromycin, a compound reported to cause pancreatitis, and 1/6 had biliary sludge as a predisposing factor.

As a consequence of these events, the risk factors identified, as well as the overall "borderline" relevance of efficacy results, it is decided that patients without a gallbladder, with previous bile-duct related disease, or with regular high intake of alcohol should not be treated with the compound and a contra-indication has been imposed consequently.

The conclusion from this analysis has been confirmed by an analysis of the first 4 ½ months of post-marketing data obtained from the US, which showed that out of 65 events reported as either pancreatitis or SO-spasm, only three were reported in patients with an intact gallbladder (albeit in about half of the cases the gallbladder status was unknown), and these cases were poorly documented.

With regard to CNS effects and their consequences fall, syncope and road traffic accidents, the incidence of these events was low. Fall was reported in 1.6%, 0.9% and 0.4% of patients in the 75mg, 100mg and placebo groups respectively. There were 10 road traffic accident events, 6 in patients taking eluxadoline, none of whom were considered to have had prior CNS-related AEs that might have diminished their ability to drive. Syncope was reported in 0.2%, 0.3% and 0.2% of patients and vasovagal syncope for 0.1%, 0% and 0% in the 75mg, 100mg and placebo groups respectively. With regard to cardiac and chest pain events, the overall incidence of cardiac disorder AEs were 1.5%, 1.8% and 1.1% of the 75mg, 100mg and placebo groups respectively. Despite this imbalance, it can be concluded that there was no reasonable possibility that eluxadoline was a causal factor contributing to these events. However, a slightly higher and dose-dependent incidence of events of sedation/somnolence has been seen in the phase 2 and 3 trials, which was therefore included into the list of undesirable effects.

The evaluation of the withdrawal periods did not show reasons for concern. No clear rebound symptoms or increased frequency of AEs occurred, and no opioid withdrawal symptoms were detected.



**Immunological events**

No immunological events were investigated separately. By nature of the compound, an immunological risk is not expected. In the pooled phase 2 and 3 trials, the number of events reported in the SOC "Immune System Disorders" was generally very low.

**Safety related to drug-drug interactions and other interactions**

The applicant has analysed the potential for increased AE occurrence in patients concomitantly taking "CNS risk medications", and for patients concomitantly taking potentially hepatotoxic drugs as well as those taking OATB1B1 substrates (such as e.g. statins and sartans). The subpopulation with the CNS risk medication included 432, 531, and 516 patients in the 75 mg, 100 mg, and placebo groups, the numbers of the potentially hepatotoxic drugs were 116, 119, and 121 and the potential interacting medication subgroup comprised 53, 65, and 67. The analysis of the full range of adverse events for the CNS risk medication population revealed that the most common adverse events (e.g. nausea, constipation and abdominal pain) were similar to overall trial population. The analysis of the course of the ALT values revealed isolated cases of increases relative to baseline. The analysis of the potentially interacting medication did not yield any meaningful increase in adverse events.

**Discontinuation due to adverse events**

The overall rate of discontinuations due to AEs was almost similar between the two active doses (8.3% and 7.8%) and about doubled the rate of placebo (4.3%). The most frequent single AEs leading to discontinuation were abdominal pain, constipation, and nausea. The profile of AEs leading to discontinuation did not relevantly differ from the overall AE profile.

**Post marketing experience**

The compound has been licensed in the US in May 2015, which was the first world-wide approval of the compound.

The applicant analysed the events from spontaneous post-marketing data related to pancreatitis and SO-spasm. The database was also updated with a new cut-off on 30 April 2016, which now includes 4.5 months of marketing the compound in the US.

The reported number of events relating to pancreatitis and SO-spasm has increased from about 30 events to a total of 65 events out of a total of 292 reports received in total (=22%). About 20% of this total of 292 was reported in men (with only 2.7% with unknown gender). The distribution according to age appears to be more uncertain, with more than half of the reports not including the gender of the patients. Of the rest of the 122 reports (41.8% of the total), 41% were reported in the population aged 65 and above, which appears to a relatively high share, considering the epidemiology of the underlying disease. However any conclusion on this appears to be premature, due to the high amount of missing data, and the unknown exposure data according to age.

The overall adverse event profile of the compound, both from the clinical studies and from the previous post-marketing report was confirmed, with the majority of events reported for abdominal pain, constipation, nausea and vomiting, and diarrhoea, but also dizziness, feeling abnormal, malaise, chest pain, fatigue, feeling drunk and dyspnoea. These events are at this point of time not evaluated for causality.

Of the 65 events of suspected pancreatitis and SO-spasm, the male to female ratio was again “in favour” of the female population, including an even higher percentage of 88% of the total cases. Whereas the age of a considerable proportion of patients is again unknown (54%), the population older than 65 years of age seems again to be affected by a relatively high incidence (33% of the total events were in patients >65 years).

About at least one third of the events occurred in a close time-relation to the first intake of the compound, clearly favouring a causal association with the intake. Reassuring appears also the fact that – of those with a known outcome of the event – the vast majority had recovered from the event, however, there were 8 cases included in the databased for which the event was “ongoing” at the time of the data cut-off.

Most importantly, the analysis of the cholecystectomy status of the patients revealed that – of the 38/65 patients for which this status was known – only 3 did have a gallbladder at the time of the occurrence of the event. The three cases which occurred in patients with a gallbladder, relatively poor information is available, with no clear confirmation of the event.

## 2.6.1. Discussion on clinical safety

The clinical development programme for eluxadoline included a total of 3608 subjects of which 373 were included into 10 phase 1 trials, and 3235 were included into the phase 2 and the two phase 3 trials. 330 subjects received at least 1 does in the phase 1 trials, and 2250 in the phase 2 and 3 trials. The median duration of

exposure was more than 180 days in both doses proposed for marketing and for the placebo group. Of the 1282 patients randomised into study 3001, 783 completed the study, meaning that this is the number of patient treated for 1 year. The number of patients treated for one year for the two doses of active medication was 257 and 257 for 75 and 100 mg and thus well exceeds the minimal requirements according to ICH E1. The requirements for the 6 months time-point were also easily met, because both phase 3 trials had a duration of at least 6 months controlled treatment and about 2/3 of the patients completed the 6 months trial period.

During the phase 2 and phase 3 trials, in the two doses proposed for marketing, the overall incidence of Adverse Events (AEs) was in the range of 55.7% and 60.2% (in the 100 mg and 75 mg dosing groups), whereas the rate for placebo was almost similar to the lower range (54.7%). Most adverse events were occurring at the beginning of treatment, and the majority of the events had occurred during the first 3 months already. The occurrence of adverse events in the second 6 months of treatment (from study 3001) appears to be greatly decreased. It can be anticipated that the registration of events, and the attention of both the patients and the investigator to adverse events was diminished the longer the study was ongoing.

The most frequent events during the phase 2 and 3 trials occurred in the SOC Gastrointestinal Disorders, followed by Infections and Infestations, and Nervous System Disorders. The most frequent single events were nausea (around 7-8%), constipation (also 7-8%), abdominal pain, and vomiting (both just above 4%), as well as upper respiratory infections, and headache. Adverse events occurring in higher frequency in the active as compared to the placebo group have been identified as nausea, constipation, abdominal pain, and vomiting. Also, a clear difference is seen for ALT increase.

The proposed SmPC also includes the events, sphincter of Oddi spasm, pancreatitis, and gastroesophageal reflux disease (which includes the terms “gastritis” and “dyspepsia”) as well as rash and dizziness, which has been adequately justified by the evaluation of comparative rates of occurrence, and assessment of causality. The need to include the events somnolence/sedation was finally concluded based on the observed dose-dependent increase in the occurrence of events of somnolence with active treatment during the phase 2/3 studies .During the studies, no patient died. There was one study where death was recorded 3 weeks after study termination. This was obviously unrelated to the intake of study drug.

During the phase 2 and 3 programme, a total of 141 SAEs occurred in 107 patients (3.3%). The occurrence rates in the dose groups of 75 mg, 100 mg and placebo were 4.2%, 4.0%, and 2.6% and thus showing a somewhat higher incidence in the active treatment groups. This was even more clearly visible if analysed for those patients treated for a whole year. The slight discrepancies can be tracked back to a different rate of occurrence of SAE-cases of pancreatitis, and abdominal pain, as well as diverticulitis, angina pectoris, and road traffic accidents. The SAE pancreatitis had the highest incidence of all SAEs. The SAE cases also include the cases of respiratory failure, of which the detailed analysis of the cases however, concluded that these were unrelated to the intake of the study drug. The analysis of the road traffic accidents has shown that a causal relation to the study drug is unlikely and further investigation of cardiac events has revealed that most events were unlikely related to the intake of the study drug.

The evaluation of AEs leading to discontinuation showed an overall rate of about 8% in the active treatment groups, compared to 4% in the placebo group. Most of the events leading to discontinuation were in the GI SOC, of which the events abdominal pain, constipation, and nausea were most frequent.

The evaluation of laboratory values was unremarkable, with the exception of ALT increases of which those cases potentially clinically relevant were increased in the active groups compare to placebo, and which were mostly associated with events of Sphincter of Oddi spasm and/or patients with cholecystectomy. No cases of relevant concomitant increases in ALT and bilirubin (Hy’s Law cases) were detected, pointing to the conclusion that ALT

increases were associated with biliary events, rather than being hepatotoxic. Blood chemistry and haematology evaluations did not show abnormalities considered to be clinically relevant. The evaluation of vital signs, physical findings, and other observations was unremarkable.

The applicant has identified potential AEs of special interest which were analysed more closely and which included constipation, Sphincter of Oddi Spasm related events (including pancreatitis and biliary syndrome events), events of fall, syncope, and road traffic accidents, and cardiac and chest pain events. Additionally, a subgroup analysis with regard to safety has been performed for age groups with a cut-off at 65 years of age, race, body mass, IBS symptoms history (wax/wane vs. continuous), cholecystectomy status, medical history of GERD or depression, and hepatic or renal dysfunction.

Regarding the analysis of subgroups it was shown that AEs occurred at higher frequencies in females, which was for the most part attributable to constipation events. Similarly, there was a higher frequency of all AEs in the population over 65, but the increase (for the overall event rate) was similar for the placebo group, thus potentially (only) reflecting the poorer health status of an older population. There was, however, a suggestion of a dose response in the elderly regarding SAEs, AEs leading to treatment discontinuation, GI AEs and GI SAEs; the incidence of these events appeared higher in the older population with the 100mg dose compared to the 75mg dose, unlike in the younger population below 65 years of age where the incidence of these events was similar if not slightly higher with the 75mg compared to the 100mg dose. As mentioned earlier, an assessment of safety differences for patients older than 75, or those above 85 was not possible due to the low number of patients included. Race, BMI, the presence of mild renal dysfunction, a history of GERD or depression and the character of the IBS symptoms appeared not to influence the adverse event profile.

The applicant has also proposed to include the possibility to use a reduced dose of 75 mg BID in those patients with tolerability problems while receiving the regular (recommended) dose of 100 mg BID. The empirical database for the assumption that patients with tolerability problems with the higher dose might experience a better tolerability with the lower dose, while maintaining their benefits, is limited because any data with a switch in the dosing regime was not included into any of the trials concluded, and the overall AE results do not point into a better tolerability of the lower dose. However, the applicant has presented data showing that the frequency of AEs experienced as severe is clearly lower in the low dose group as compared to the high dose group. This effect is then also seen for the overall GI events, and for the selected single GI events abdominal pain and constipation, which have been one of the most frequently seen AEs during the trials. Therefore, the 75 mg BID dose is given as additional treatment option in patients experiencing problems with tolerability.

A major factor influencing the overall number and frequency of adverse events, however, was identified to be cholecystectomy. Patients with a previous cholecystectomy were generally at higher risk of experiencing adverse events. Whereas for the total of the events this was also the case for the placebo treatment, a clear increase in the difference of AE rates compared to placebo was detected for SAEs, and those AEs leading to discontinuation, most of which could be attributed to the GI SOC, and of those a clear correlation was seen to the high frequency of events connected to SO spasm.

A safety-focused adjudication committee (the HPAC) was established outside of the protocols to evaluate whether blinded AEs in Studies IBS-3001 and IBS-3002 met pre-specified case definitions for pancreatitis and acute hepatobiliary events, and to determine the potential aetiology of SO spasm in these events. In total, 11 cases were identified, of which 9 were adjudicated as pancreatitis. All of these events occurred in the active treatment groups. A similar result was seen for the 9 events adjudicated as acute hepatobiliary event, for which also no event was identified in the placebo treated patients. The vast majority of all these events occurred in post-cholecystectomy patients, and if all cases are counted, the resulting overall frequency of these serious, and even potentially life-threatening events amounts to 3.7%. The rate of these events is lower for the lower dose

of eluxadoline, and the applicant has taken the decision to propose this lower dose for those with prior cholecystectomy. However, the total number of events for the lower dose is not zero, and a frequency of >1% is still present for this subgroup, with the consequentially increased uncertainties due to the lower numbers overall.

The conclusion of the Applicant that a relevant reduction of these events in patients with cholecystectomy can be achieved by reducing the dose was not shared. Considering the overall moderate beneficial effects on the disease, and the potential for serious and severe events based on SO spasm in those with prior cholecystectomy, it is considered that the benefit-risk ratio for these patients is negative and the use in patients without gall bladder was contraindicated. The 75 mg dose is therefore only foreseen to be given to patients >65 years of age and those in the general (non-cholecystectomy) population in case of tolerability problems as additional treatment option.

A more confident conclusion that the occurrence of SO-spasm events can be reduced can be drawn if cholecystectomy is labelled as a contraindication because no such event was observed in a population with intact biliary tract. The cases of pancreatitis diagnosed 'separately' from SO spasm appeared in the main to be linked to alcohol excess. Given the limited clinical relevance of the efficacy results, all populations at increased risk of SO-spasm and pancreatitis (with previous such disease, high alcohol intake and without gall-bladder) are consequently excluded from the treatment. This assumption has found preliminary confirmation through the evaluation of the early post-marketing data from the US (where no such contra-indication is impose) and which show reports of pancreatitis and/or SO-spasm events, with their overwhelming majority affecting patients without gallbladder.

The closer analysis of falls, syncope and road traffic accidents has revealed that syncope events and road traffic accidents were unlikely to be associated with the study drug. However, the dose-related consistent increase of events in somnolence has triggered the additional mentioning of this event in the SmPC.

The adverse event analysis of the withdrawal periods in all studies did not show any relevant concerns. Neither was there any indication of rebound-related events, nor was there any indication of opioid-withdrawal symptoms.

From the safety database all the adverse reactions reported in clinical trials <and post-marketing> have been included in the Summary of Product Characteristics



## 2.6.2. Conclusions on the clinical safety

The safety of the compound has been adequately documented in a sufficient number of patients. The safety profile mainly corresponds well to the expected effects of the pharmacology of the compound, with gastrointestinal events, such as nausea, abdominal pain, and constipation being the most frequent and most clearly related events.

Also, as expected from the pharmacology, events of SO spasm occurred at relevant frequency and caused events of bile duct obstruction, as well as pancreatitis, despite the exclusion of relevant risk-populations from the study. For these events, prior cholecystectomy status has been identified to be a relevant risk factor, and – considering the overall moderate beneficial effects of the compound – these patients are therefore excluded from the treatment with the compound.

After excluding the relevant risk population, the adverse event profile is concluded to be acceptable.

## 2.7. Risk Management Plan

***Safety concerns***

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | Decreased GI motility shown as constipation<br>SO spasm<br>• Pancreatitis<br>• Hepatic enzyme elevations associated with biliary-type pain |
| Important potential risks | Potential complications of decreased GI motility (e.g. serious FI, obstruction, ileus, secondary bowel ischemia, intestinal ulceration/perforation, or TM)<br>Pancreatitis independent of SO spasm<br>Asthma exacerbation<br>Abuse<br>Use in patients ≥65 years of age<br>CNS effects as a result of extended systemic exposure in patients with hepatic impairment or concomitant treatment with OATP1B1 inhibitors |
| Missing information | Use in the paediatric population<br>Use in pregnancy and lactation<br>Use in patients with renal impairment<br>Use in patients of ethnic origin other than whites<br>Use in patients with impaired intestinal barriers (IBD and Coeliac Disease)<br>Drug-drug interactions with drugs metabolized by CYP1A2 or 3A4/5. |



***Pharmacovigilance plan***

| **Study / activity Type, title and category (1-3)** | **Objectives** | **Safety concerns addressed** | **Status (planned, started)** | **Date for submission of interim or final reports (planned or actual)** |
|---|---|---|---|---|
| Renal impairment study (category 3) - A Single-Dose, Open-Label, Pharmacokinetic Study of Eluxadoline in Healthy Subjects with Normal Renal Function and Patients with Severely Impaired Renal Function, multicentre study | To assess the PK, safety and tolerability profiles of eluxadoline following single-dose oral administration in male and female patients with severely impaired renal function compared with matched healthy subjects with normal renal function. | Use in patients with renal impairment | Planned | Planned Submission of final study report 9 months after approval |
| In-vivo drug-drug-interaction with midazolam | Conduct an in-vivo drug-drug-interaction study to evaluated eluxadoline as a potential time dependent inhibitor of CYP3A4 with the substrate midazolam | Drug-drug interactions with drugs metabolized by CYP1A2 or 3A4/5 | Planned | Submission of final study report 9 months after approval |
| In vitro drug-drug | A study to evaluate the | Drug-drug interactions | Planned | Submission |

| Study / activity Type, title and category (1-3) | Objectives | Safety concerns addressed | Status (planned, started) | Date for submission of interim or final reports (planned or actual) |
|---|---|---|---|---|
| interaction study to evaluate the potential for eluxadoline to induce CYP3A4 and 1A2 | potential for eluxadoline to induce CYP3A4 and 1A2 in vitro using human hepatocytes. | with drugs metabolized by CYP1A2 or 3A4/5 | | of final study report 6 months after approval |
| DUS (category 3) | Define the compliance of health care providers to eluxadoline contraindications (i.e., history of cholecystectomy, pancreatitis or sphincter of Oddi disease) over time. | SO spasm<br>▪ Pancreatitis<br>▪ Hepatic enzyme elevations associated with biliary-type pain | Planned | Submission of first draft of protocol 3 months after approval |



***Risk minimisation measures***

| Safety concern | Routine RMMs | Additional RMMs |
|---|---|---|
| Decreased gastrointestinal motility shown as constipation (Important Identified risk) | *The SmPC states:*<br>*Section 4.3 Contraindications:*<br>*A history of chronic or severe constipation or sequelae from constipation, or known or suspected mechanical gastrointestinal obstruction. These patients may be at risk for severe complications of bowel obstruction.*<br>*Section 4.4 Special warnings and precautions for use*<br>*Constipation*<br>*There is a potential for increased risk of constipation when taking eluxadoline. If patients develop severe constipation for a duration of more than 4 days, they should be instructed to stop eluxadoline and seek medical attention.*<br>*Risk of constipation with eluxadoline in patients with other IBS sub-types is unknown, but may be increased. Caution should be exercised when administering eluxadoline in IBS patients whose bowel habits vary over time.*<br>*Section 4.5 Interaction with other medicinal products and other forms of interaction*<br>*Medicinal products that cause constipation* | Not required |

| Safety concern | Routine RMMs | Additional RMMs |
|---|---|---|
| | *Although no direct drug-drug interactions have been demonstrated, chronic use of loperamide with eluxadoline should be avoided as this may increase the risk of constipation. The use of eluxadoline with other medicinal products that may cause constipation (for example anticholinergics, opioids etc) should also be avoided.*<br><br>*Section 4.8 Undesirable effects*<br><br>*Summary of the safety profile*<br><br>*The most common adverse reactions (incidence of >5%) reported were constipation (7% and 8% of patients receiving 75 mg and 100 mg respectively), nausea (8% and 7% of patients receiving 75 mg and 100 mg respectively) and abdominal pain (6% and 7% of patients receiving 75 mg and 100 mg respectively).*<br><br>*Tabulated list of adverse reactions*<br><br>*Gastrointestinal disorders*<br><br>*Constipation – Common*<br><br>*Description of selected adverse reactions*<br><br>*Constipation*<br><br>*Approximately 50% of constipation events occurred within the first 2 weeks of treatment.*<br><br>*Rates of severe constipation were less than 1% in patients receiving 75 mg and 100 mg eluxadoline and there were no serious complications of constipation related to eluxadoline use in pivotal studies. 1 % of patients receiving 75 mg and 2% of patients receiving 100 mg discontinued treatment or temporarily suspended dosing secondary to constipation, respectively, compared to <1% of patients treated with placebo. Patients should be instructed to stop the medicinal product and seek medical attention if they develop severe constipation for more than 4 days.* | |
| SO spasm<br>- Pancreatitis<br>- Hepatic enzyme elevations associated with biliary-type pain (Important Identified risk) | <u>(Proposed) text in SmPC</u><br><br>Section 4.3 of the SmPC states:<br>*Contraindications*<br>*• Alcoholism, alcohol abuse, alcohol addiction or chronic or acute excessive alcohol use. These patients are at increased risk for acute pancreatitis.*<br>*• Known or suspected biliary duct obstruction or sphincter of Oddi disease or dysfunction. These patients are at increased risk for* | Not required |

| Safety concern | Routine RMMs | Additional RMMs |
|---|---|---|
| | *sphincter of Oddi spasm.• Patients without a gallbladder ( e.g. due to cholecystectomy or agenesis). These patients are also at increased risk for sphincter of Oddi spasm.*<br>*• A history of pancreatitis; or known or suspected structural diseases of the pancreas, including pancreatic duct obstruction. These patients are at increased risk for acute pancreatitis.*<br><br>Section 4.4 of the SmPC states:<br>*Warnings and Precautions for Use*<br>*Sphincter of Oddi Spasm*<br>*Given the mu opioid receptor agonism of eluxadoline, there is a potential for increased risk of sphincter of Oddi spasm, resulting in pancreatitis or hepatic enzyme elevation associated with acute abdominal pain (eg, biliary-type pain) in patients taking eluxadoline, especially in patients without a gallbladder. Patients with known or suspected sphincter of Oddi disease or dysfunction and/or biliary tract or pancreatic disease, including a history of pancreatitis, and those who have had a cholecystectomy or are missing a gallbladder due to other reasons, must not receive this medicinal product.*<br>*Patients should be instructed to stop the treatment and seek medical attention if they experience symptoms suggestive of sphincter of Oddi spasm such as acute worsening of abdominal pain (e.g. acute epigastric or biliary [i.e., right upper quadrant] pain) that may radiate to the back or shoulder, with or without nausea and vomiting. Eluxadoline should not be restarted in patients who developed biliary duct obstruction or sphincter of Oddi spasm while taking [eluxadoline.*<br><br>Section 4.8 of the SmPC:<br>*Summary of the safety profile*<br>*Serious adverse reactions of pancreatitis (0.2% and 0.3% of patients receiving 75 mg and 100 mg respectively) and sphincter of Oddi spasm (0.2% of patients receiving 75 mg and 0.8% of patients receiving 100 mg) may also occur.*<br><br>*Sphincter of Oddi spasm*<br>*In clinical studies, events of sphincter of Oddi spasm manifested as elevated hepatic enzymes associated with abdominal pain in 8 patients, pancreatitis in 1 patient, and abdominal pain with lipase elevation less than 3 times the upper limit of normal in 1 patient. 80% (8/10) of sphincter of Oddi spasm events presented within the first week of treatment. All events resolved upon discontinuation of Truberzi, with symptoms typically improved by the following day. All events of sphincter of Oddi spasm occurred in patients without a gallbladder. Therefore, eluxadoline is contraindicated in this population as well as in those with previous biliary tract problems (see sections 4.2, 4.3 and 4.4). The occurrence of such events in patients with an intact biliary tract cannot be excluded.*<br><br>*Pancreatitis*<br>*Additional cases of pancreatitis not associated with sphincter of Oddi spasm were reported in clinical studies. Of the 5 cases reported, 3 were associated with excessive alcohol intake, 1 was associated with biliary sludge, and in one case the patient discontinued eluxadoline 2 weeks prior to the onset of symptoms.* | |

| Safety concern | Routine RMMs | Additional RMMs |
|---|---|---|
| | *All pancreatic events, whether or not associated with sphincter of Oddi spasm, were retrospectively evaluated as mild, indicating an absence of organ failure and local or systemic complications. All pancreatic events resolved with lipase normalization upon discontinuation of eluxadoline with 80% (4/5) resolving within 1 week of treatment discontinuation*<br><br>*Tabulated list of adverse reactions*<br>*Gastrointestinal disorders*<br>*Uncommon: Sphincter of Oddi spasm, Pancreatitis*<br><br><u>Other routine RMMs</u><br>Prescription only medicine | |
| Complications of decreased GI motility (serious FI, obstruction, ileus, secondary bowel ischemia, intestinal ulceration/perforation, TM) (Important Potential risk) | <u>(Proposed) text in SmPC</u><br>Section 4.3 of the SmPC:<br>*Contraindications*<br>*A history of chronic or severe constipation or sequelae from constipation, or known or suspected mechanical gastrointestinal obstruction. These patients may be at risk for severe complications of bowel obstruction.*<br><br>Section 4.4 of the SmPC:<br>*Warnings and Precautions for Use*<br><u>Constipation:</u><br>*There is a potential for increased risk of constipation when taking eluxadoline. If patients develop severe constipation for a duration of more than 4 days, they should be instructed to stop the treatment and seek medical attention.*<br>*Risk of constipation with eluxadoline in patients with other IBS subtypes is unknown, but may be increased. Caution should be exercised when administering eluxadoline in IBS patients whose bowel habits vary over time.*<br><br>Section 4.5 of the SmPC:<br>*Interaction with other medicinal products and other forms of interaction*<br>*Medicinal products that cause constipation*<br>*Although no direct drug-drug interactions have been demonstrated, chronic use of loperamide with eluxadoline should be avoided as this may increase the risk of constipation. The use of eluxadoline with other medicinal products that may cause constipation (for example anticholinergics, opioids etc.) should also be avoided.*<br><br>Section 4.8 of the SmPC:<br>*The most common adverse reactions (incidence of >5%) reported were constipation (7% and 8% of patients receiving 75 mg and 100 mg respectively), nausea (8% and 7% of patients receiving 75 mg and 100 mg respectively) and abdominal pain (6% and 7% of patients receiving 75 mg and 100 mg respectively).*<br><br>*Constipation*<br>*Approximately 50% of constipation events occurred within the first 2 weeks of treatment Rates of severe constipation were less than 1% in patients receiving 75 mg and 100 mg eluxadoline and there were no serious complications of constipation related to* | Not required |

| Safety concern | Routine RMMs | Additional RMMs |
|---|---|---|
| | *eluxadoline use in pivotal studies. 1 % of patients receiving 75 mg and 2% of patients receiving 100 mg discontinued treatment or temporarily suspended dosing secondary to constipation, respectively, compared to <1% of patients treated with placebo. Patients should be instructed to stop the medicinal product and seek medical attention if they develop severe constipation for more than 4 days.*<br><br>*Tabulated list of adverse reactions*<br>*Gastrointestinal disorders*<br>*Common: Constipation*<br><br><u>Other routine RMMs</u><br>Prescription only medicine | |
| Pancreatitis independent of SO spasm (Important Potential risk) | *Section 4.3 Contraindications*<br><br>*A history of pancreatitis; or known or suspected structural diseases of the pancreas, including pancreatic duct obstruction. These patients are at increased risk for acute pancreatitis.*<br><br>*Section 4.4 Special warnings and precautions for use*<br><br>*Pancreatitis*<br><br>*There is a potential for increased risk of pancreatitis, not associated with sphincter of Oddi spasm, when taking eluxadoline. All patients should be instructed to avoid chronic or acute excessive alcohol use while taking eluxadoline Patients should be monitored for new or worsening abdominal pain, that may radiate to the back or shoulder, with or without nausea and vomiting. Patients should be instructed to stop the medicinal product and seek medical attention if these symptoms develop while taking eluxadoline.*<br><br>*Section 4.8 Undesirable effects*<br><br>*Summary of the safety profile*<br><br>*Serious adverse reactions of pancreatitis (0.2% and 0.3% of patients receiving 75 mg and 100 mg respectively) and sphincter of Oddi spasm (0.2% of patients receiving 75 mg and 0.8% of patients receiving 100 mg) may also occur.*<br><br>*Tabulated list of adverse reactions*<br><br>*Gastrointestinal disorders*<br><br>*Pancreatitis – Uncommon* | None |

| Safety concern | Routine RMMs | Additional RMMs |
|---|---|---|
| | *Pancreatitis*<br><br>*Additional cases of pancreatitis not associated with sphincter of Oddi spasm were reported in clinical studies. Of the 5 cases reported, 3 were associated with excessive alcohol intake, 1 was associated with biliary sludge, and in one case the patient discontinued eluxadoline 2 weeks prior to the onset of symptoms.*<br><br>*All pancreatic events, whether or not associated with sphincter of Oddi spasm, were retrospectively evaluated as mild, indicating an absence of organ failure and local or systemic complications. All pancreatic events resolved with lipase normalization upon discontinuation of eluxadoline with 80% (4/5) resolving within 1 week of treatment discontinuation.* | |
| Asthma exacerbation (Important Potential risk) | None proposed | None |
| Abuse (Important Potential risk) | Proposed text in SmPC<br>*Drug dependence and potential for abuse*<br>*Based on the physical-chemical and biopharmaceutical properties (very low oral bioavailability), eluxadoline is expected to have minimal abuse or dependence liability.*<br><br>Other routine RMMs<br>Prescription only medicine | None |
| Use in patients ≥65 years of age (Important Potential risk) | Proposed text in SmPC<br>Section 4.2 of the SmPC:<br>*Posology and method of administration*<br>*The recommended dose is 200 mg daily (one 100 mg tablet twice daily).*<br>*For patients who are unable to tolerate the 200 mg daily dose (one 100 mg tablet, twice daily) the dose can be lowered to 150 mg daily (one 75 mg tablet twice daily).*<br><br>*Elderly*<br>*In principle, general dose recommendations also apply to patients aged 65 years and above.*<br>*However, given the potential for increased sensitivity to experience undesirable effects, it may be considered to initiate eluxadoline treatment in a dosage of 150 mg daily (one 75 mg tablet twice daily). If this dosage is well tolerated, but not sufficiently effective, dosage may subsequently be increased to 200 mg daily (one 100 mg tablet twice daily).*<br><br>Section 4.4 of the SmPC:<br>*Warnings and Precautions for Use*<br>*Special population*<br>*Elderly*<br>*Overall there was an increased frequency of adverse events reported for patients aged 65 years or greater in the clinical studies. However, patients 65 years of age and older, treated with the 75-mg dose twice daily have experienced a reduced rate of serious adverse events as well as adverse events leading to discontinuation compared to patients treated with 100mg twice daily. Therefore, the 75 mg dose twice daily can be considered for this population, but its benefit risk ratio should be periodically* | None |

| Safety concern | Routine RMMs | Additional RMMs |
|---|---|---|
| | *assessed in the context of their symptoms severity.*<br><br>Section 4.8 of the SmPC:<br>*Elderly*<br>*Of 1,795 IBS-D patients who were enrolled in clinical studies of eluxadoline and assigned to 75 mg or 100 mg twice daily, 139 (7.7%) were at least 65 years of age, while 15 (0.8%) were at least 75 years old. There was an overall increased frequency of adverse events in the older population compared to patients <65 years which was comparable across all treatment groups, including placebo.*<br>*The frequency of serious adverse events, gastrointestinal events, and events leading to discontinuation tended to be lower for the 75 mg dose compared to the 100 mg dose. Therefore, in this population, the 75 mg dose twice daily can be used.*<br><br>Section 5.2 of the SmPC:<br>*Specific populations*<br>*Age and gender*<br>*Given eluxadoline's local action in the GI tract, low $F_{oral}$ and lack of metabolism, prospective clinical studies regarding differences in age, body mass index (BMI), ethnicity, and gender were deemed unnecessary. Pharmacokinetic data for healthy volunteers pooled across Phase 1 studies (using the 100 mg single oral dose) and analysed for potential differences based on sex, age, race, and BMI demonstrated no significant differences.*<br><br><u>Other routine RMMs</u><br>Prescription only medicine | |
| CNS effects as a result of extended systemic exposure in patients with hepatic impairment or concomitant treatment with OATP1B1 inhibitors (Important Potential risk) | <u>Proposed text in SmPC</u><br><br>Section 4.3 of the SmPC:<br>*Contraindications*<br>*Hepatic impairment (Child-Pugh Class A-C). These patients are at risk for significantly increased plasma concentrations of eluxadoline.*<br><br>*Patients on treatment with potent inhibitors of OATP1B1 (e.g. cyclosporine).*<br><br>Section 4.4 of the SmPC:<br>*Warnings and precautions for use*<br>*Hepatic impairment*<br>*Eluxadoline must not be used in patients with a history of or known or suspected hepatic impairment (Child-Pugh Class A-C).*<br><br>*Somnolence and sedation*<br>*There is a potential for increased risk of somnolence and sedation when taking eluxadoline in patients who may experience increased plasma levels, such as in patients with a genetic predisposition for poor function of OATP1B1 transporter. As patient's genetic disposition may be unknown, it is recommended that patients be monitored for impaired mental or physical abilities needed to perform potentially hazardous activities such as driving a car or using machines.*<br><br>*Effect of OATP1B1 transporter function variability on plasma* | None |

| Safety concern | Routine RMMs | Additional RMMs |
|---|---|---|
| | *levels*<br>*The plasma levels in patients with a genetic predisposition for poor function of OATP1B1 transporter are increased, and in these patients a higher rate of adverse events, especially with regard to gastrointestinal events, as well as CNS effects might be expected.*<br><br>*Section 4.5 of the SmPC:*<br>*OATP1B1 inhibitors*<br>*Co-administration of OATP1B1 inhibitors (cyclosporine, gemfibrozil, antiretrovirals (atazanavir, lopinavir, ritonavir, saquinavir, tipranavir), rifampin) with eluxadoline may increase exposure to eluxadoline. Eluxadoline should not be administered concomitantly with such medicinal products.*<br><br>Section 5.2 of the SmPC:<br>*Hepatic impairment*<br>*The apparent clearance of eluxadoline is markedly reduced and half-life increases in hepatic-impaired patients. Following single oral 100 mg dose in subjects with varying degrees of liver impairment and healthy subjects, eluxadoline plasma levels were on average 6-fold, 4-fold, and 16-fold elevated in mild, moderate, and severe hepatic-impaired subjects (Child Pugh Class A, B, C), respectively, while half-life increased 3-5 fold.*<br><br>*OATP1B1 inhibitors*<br>*Eluxadoline is a substrate of the hepatic uptake transporter OATP1B1. Co- administration of eluxadoline with cyclosporine (an OATP1B1 inhibitor) increased eluxadoline exposure by approximately 5- fold.*<br><br>*OATP1B1 poor function haplotypes*<br>*The plasma levels in patients with a genetic predisposition for poor function of OATP1B1 transporter are increased and in these patients a higher rate of adverse events, especially with regard to gastrointestinal events, as well as CNS effects might be expected.*<br><br><u>Other routine RMMs</u><br>Prescription only medicine | |
| Use in the paediatric population (Missing information) | <u>(Proposed) text in SmPC</u><br>*Section 4.2 Posology and method of administration*<br>*Paediatric population*<br>*The safety and efficacy of eluxadoline in children aged 0 to18 years have not yet been established. No data are available.*<br><br>*Section 4.4 Warnings and Precautions for Use*<br>*Paediatric population*<br>*Eluxadoline should not be used in children and adolescents as it has not been studied in this population*<br><br><u>Other routine RMMs</u><br>Prescription only medicine | Not required |
| Use in pregnancy and lactation (Missing information) | <u>(Proposed) text in SmPC</u><br>*Section 4.6 Fertility, pregnancy and lactation*<br>*Pregnancy*<br>*There is limited amount of data from the use of eluxadoline in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section* | Not required |

| Safety concern | Routine RMMs | Additional RMMs |
|---|---|---|
| | *5.3). As a precautionary measure, it is preferable to avoid the use of Truberzi during pregnancy.*<br><br>*Breast-feeding*<br>*It is unknown whether eluxadoline is excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of eluxadoline in milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Truberzi therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.*<br><br>*Section 5.3 of the SmPC states:*<br>*5.3 Preclinical safety data*<br>*Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development. In rat, eluxadoline was excreted into milk in an approximately dose proportional manner with maximal concentrations less than plasma concentrations.*<br><br><u>Other routine RMMs</u><br>Prescription only medicine | |
| Use in patients with renal impairment (Missing information) | <u>(Proposed) text in SmPC</u><br>*Section 4.2 Posology and method of administration*<br>*Patients with renal impairment*<br>*The safety and pharmacokinetics of eluxadoline in patients with renal impairment have not yet been established. With the renal route being a minor route of elimination for eluxadoline, no dose adjustment based on renal function may be necessary.*<br><br>*Section 4.4 Special warnings and precautions for use*<br>*Renal impairment*<br>*No data on the pharmacokinetics of eluxadoline in patients with renal impairment are available. Due to minimal absorption and the negligible role for renal elimination, an influence of renal impairment on the plasma levels of eluxadoline is not expected.*<br><br>*Section 5.2 Pharmacokinetic properties*<br>*Renal Impairment*<br>*Eluxadoline has not been specifically studied in patients who have renal impairment. Given the low oral bioavailability ($F_{oral}$ 1.34%) of eluxadoline and limited renal elimination, renal impairment is not expected to affect clearance of eluxadoline.*<br><br><u>Other routine RMMs</u><br>Prescription only medicine | Not required |
| Use in patients of ethnic origin other than whites (Missing information) | None proposed<br><br><u>Other routine RMMs</u><br>Prescription only medicine | None |
| Use in patients with impaired intestinal barriers (IBD and Coeliac Disease) (Missing information) | None proposed<br><br><u>Other routine RMMs</u><br>Prescription only medicine | None |

| Safety concern | Routine RMMs | Additional RMMs |
|---|---|---|
| Drug-drug interactions with drugs metabolized by CYP1A2 or 3A4/5 | (Proposed) text in SmPC<br><br>*Section 4.5 Interaction with other medicinal products and other forms of interaction*<br><br>*CYP3A substrates*<br><br>*Eluxadoline may increase the exposure of co administered medicinal products metabolised by Cytrochrome CYP3A4. Caution should be exercised when administering such products (e.g. midazolam, erythromycin, nifedipine), especially for those with a narrow therapeutic index (e.g. alfentanil, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus). The concentration of these co-administered medicinal products with a narrow therapeutic index or their other pharmacodynamic markers should be monitored when concomitant use with eluxadoline is initiated or discontinued.*<br><br>*Section 5.2 Pharmacokinetic properties*<br><br>*Eluxadoline's systemic exposure following oral administration is low and is consistent with its local action in the GI tract. The active substance has linear pharmacokinetics with no accumulation upon repeated twice daily dosing. Mean plasma elimination half -life is 5 hours with high inter-subject variability. Eluxadoline is primarily cleared as such via the biliary system with the kidney playing a minimal role in elimination. Eluxadoline is not an inducer/inhibitor of major CYP enzymes, however, eluxadoline has some potential for the metabolism based inactivation of CYP3A4. It is a substrate and an inhibitor of the hepatic uptake transporter OATP1B1; and a substrate for the hepatic efflux transporter MRP2. Hepatic impairment or coadministration with cysclosporine results in significant increases in plasma concentrations of eluxadoline.*<br><br>*In vitro assessment of drug interactions*<br><br>*In vitro studies indicate that eluxadoline is neither an inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4, nor an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2C8 and CYP2D6 at clinically relevant concentrations. CYP2E1 was slightly inhibited (50% inhibitory concentration [IC50] of approximately 20 µM [11 µg/mL]), although this is not expected to result in any clinically meaningful interactions. In vitro studies in liver microsomes showed that eluxadoline is not an inhibitor of CYP3A4 at clinically relevant concentrations, but in intestinal microsomes, eluxadoline inhibited CYP3A4 with a Ki of 450 µM (256 µg/mL). Potentially high (up to 700 µM) eluxadoline concentrations in gut may affect the pharmacokinetic of concomitantly administered CYP3A4 substrates.* | None |

***Conclusion***

The CHMP and PRAC considered that the risk management plan version 1.5 is acceptable.

## *2.8. Pharmacovigilance*

**Pharmacovigilance system**

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

## *2.9. Product information*

### 2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

### 2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Truberzi (eluxadoline) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.



# 3. Benefit-Risk Balance

***Benefits***

**Beneficial effects**

The clinical efficacy has been evaluated in two well-designed placebo controlled studies. Both studies included a patient population which was generally compliant with the current guidance available with the exception of not excluding patients with bile acid malabsorption. The population was, however, acceptable with regard to its clinical features and mostly acceptable due to the results for the baseline characteristics. The study design of both studies is compliant with the current CHMP IBS-guideline. Appropriate statistical methods have been chosen for the evaluation of the data. Two doses have been chosen to be included in the confirmatory testing, which is considered reasonable.

The primary endpoint was met for the higher dose investigated in both pivotal studies conducted, but only in one study for the lower dose. The treatment with 100 mg BID showed superiority in the simultaneous increase of days with no diarrhoea and a clinically significant improvement of pain. The rate of those which had such days for at least 50% of the time of 26 weeks was about 11.5% higher than with placebo treatment, whereas the difference amounted to about 5% for the 75 mg dose group. However, in patients above 65 years of age, the response rates were generally sufficiently high for this smaller dose, for which the lower dose is therefore accepted as additional treatment option. The rate of superiority over placebo was stable over time, and showed a minor decrease across the 26 weeks of treatment, mainly due to an increase in the placebo response. This analysis was shown to be robust even if analysed using a so-called “worst-case” analysis, an analysis accounting for treatment misallocations, and with different imputation methods for response (daily versus weekly).

The primary endpoint also showed robustness with regard to the analysis in subpopulations regarding gender, race, BMI, and such baseline characteristics as IBS history (severity of pain, and character of complaints (wax/wane vs. continuous), refractoriness to loperamide treatment, and history of GERD or depression.

When the response rates of the patients were split between the stool consistency response and the pain response, it could be shown that the pain response was only marginally superior to placebo and did not reach statistical significance. The numerical advantage over placebo amounted to less than 5%. The definition of more stringent response criteria regarding pain (defining response at a 40% or 50% improvement) showed statistical significance for the pooled analysis but still, the advantage over placebo was less than 10%. The numerical evaluation of the pain scores, however, showed a statistically significant difference between the improvements of the active medication and placebo, which was, however, at a level of -0.4 on the 11-point NRS-scale. Contrary to this, the analysis of the stool consistency response clearly supported the primary analysis. The numerical superiority of the stool responder rates was about 13%. The average improvement in the stool consistency scores was almost -0.5 on a 7-point scale. Additional analyses showed that the pain response was fully dependent on the stool consistency response, and there was no pain response without co-existing stool consistency response. The pain response must therefore be regarded as secondary consequence of the effects on motility and stool related parameters.

The analysis of the pooled global responder rates showed a 7% superiority of the high dose over placebo (6% in the low dose), which was statistically significant. The analysis of “adequate relief responders”, based on a dichotomous evaluation of global efficacy, showed a 10% superiority over placebo for the high dose, and an 8-9% superiority for the low dose, both of which were again statistically significant.

Further symptom evaluations which were based on the numerical evaluation of severity scales, showed a highly statistically significant improvement for the symptoms such as bloating, abdominal discomfort, frequency of bowel movements, and number of urgency episodes for the high dose. The lower dose reached still statistically significant results. The rate of responders which were free of urgency was doubled in the high dose group, and almost doubled in the low dose group, both of which were highly statistically significant. The reduction of incidences of bowel incontinence was inconsistent between the two studies, whereas in one study no significant effect could be shown, this was highly statistically significant in the other study. Additional responder analyses on the pooled population with these secondary endpoints showed highly consistent results.

A similar split between the studies could be shown for the evaluation of Quality of Life. Whereas in one study a consistent (over time) and highly statistically significant effect could be shown for both doses (with the high dose being numerically better), the improvements in Quality of Life lost statistical significance in the high dose group towards the end of the treatment, whereas the improvements seen for the low dose showed highly statistically significant difference throughout the study.

The compound appears to be devoid of rebound effects, and only a gradual deterioration was seen after the cessation of treatment during a 4-week observation period.

**Uncertainty in the knowledge about the beneficial effects**

The magnitude of the treatment effect has to be assessed as being moderate only, and the clinical relevance of a less than 12% superiority in response rates for the primary endpoint is considered to be limited. According to the primary endpoint, almost 70% of the patients are left without an adequate composite response over the 26 week treatment period, and even for the highest responder rates achieved (in the dichotomous "adequate relief" response), almost half of the patients remain without response over the treatment period. The comparison of the global response rates – especially those using the "adequate relief" criterion – made the results comparable to compounds that had previously attempted to gain MAA (tegaserod, alosetron), and it was shown that the response rates achieved were obviously smaller with eluxadoline. However, the controlled trial/observation period for eluxadoline was, of course, doubled compared to the other compounds.

The effects with regard to the composite response appear to mainly be exerted by the effects on stool consistency, because the separate evaluation of stool consistency and pain revealed only marginal effects with regard to responder rates for pain alone and the additional analyses conducted revealed that pain response is clearly dependent on stool consistency response. Whether eluxadoline relevantly differs from effects of the peripheral μ-OR agonist loperamide cannot be fully answered. However, it can be concluded that eluxadoline has similar effects in patients with prior unsuccessful use of loperamide and any effect of loperamide on IBS is uncertain.

The studies did not explicitly exclude patients with bile acid malabsorption (BAM). These individuals are often misdiagnosed with IBS-d and constitute 20-30% of the IBS-d population. Bile acid sequestrants are considered the standard treatment for these patients. It is unknown whether these patients would have a different response to eluxadoline and the efficacy results of a "true" IBS-d population would be altered. Because this question concerns the identification of a potentially relevant subgroup of patients with different efficacy, the applicant is recommended to undertake additional efforts to address this question in a Post Marketing study.

The number of patients above the age-cut off of 65 was about 7%, and the number of patients belonging to the considerably older patient population (above 75 years, or above 85 years) was marginal. Hence, the efficacy and safety of the compound in a population aged above 80 is currently unknown and adds up to the missing PK data in the patients above 65. Efficacy appeared to be higher with 75mg than 100mg in the older population, raising the possibility that sensitivity to the effect of eluxadoline increases with therefore this dose can be given as additional option in this population. The reason for this effect remain undetected, however, the additional treatment option is regarded to increase the flexibility of the prescriber in this population.

***Risks***

**Unfavourable effects**

The safety of the compound was evaluated in a total of 3608 patients, of which 2580 were exposed to eluxadoline. 2284 patients in the clinical setting during the phase 2 and 3 studies received eluxadoline, and the number of patients included in the two phase 3 studies and receiving eluxadoline was 1795, of which 1110 took the study medication for ½ a year, and 783 for one year. Exposure numbers were therefore fully compliant with the requirements of the ICH E 1 guideline.

The overall rate of adverse events during the phase 3 programme was between 55% and 60%, only slightly higher than the rate observed for placebo. The highest rates of adverse events during these studies occurred in the gastrointestinal SOC, with nausea, constipation, abdominal pain, vomiting, and flatulence (between 3% and 8%) being the most frequent events, and showing a clear difference to placebo in occurrence rate. They tended to occur early in the course of treatment, particularly within the first 2 weeks. These events have therefore been attributed to be undesirable effects of the compound, fully reflecting the pharmacology of the compound as a peripherally acting opioid. The rate of events was also high for the SOC infections and infestations, mainly attributable to events of upper respiratory tract infections. However, there was no consistent increase in these events in the active treatment groups, as compared to the placebo group.

Nervous system disorders SOC events also occurred at similar rates in the active and placebo groups, although the overall rate was relatively high with 10% in this SOC. A slight and consistent increase compared to placebo in the adverse event rate could only be detected for the AE dizziness and somnolence and sleepiness, which occurred in about 3% and 1.1%, respectively of the patients. No consistent differences could be detected for all other SOCs.

Single PT AEs for which a clear and consistent (for both doses) difference to placebo was detected were ALT increases. The causation of relevant hepatotoxicity has been made unlikely, in as no “Hy’s law” cases could be detected, as well as almost all liver enzyme elevations observed could be attributed to the cases with definite or suspected SO spasm.

The rate of SAEs was generally relatively low during the phase 3 studies, but appeared to be almost doubled in the active treatment groups compared to placebo (4.1% vs. 2.6%). The most frequent and clear differences for SAEs were seen for cases of abdominal pain and pancreatitis. No serious complications of constipation were described in the phase 2/3 studies.

Adverse events leading to discontinuation were also doubled during the phase 3 studies, with about 8% compared to 4% with placebo. The main single events leading to discontinuation were attributable to the above mentioned gastrointestinal adverse effects.

No deaths occurred during the study, the only death recorded was a patient that died 3 weeks after cessation of treatment and clearly unrelated to the intake of the study drug.

A clear attribution of cases of ALT increases and pancreatitis to the active treatment could be found, which were mainly events of Sphincter of Oddi spasm, and which could also be regarded to be expected events for this class of substance. All cases of pancreatitis associated with SO spasm, and all other cases of potential SO spasm events were occurring in the active treatment group. The overall rate of such events appears to be almost 4%. In the further analysis of these events despite the relatively strict exclusion criteria applied during the studies, which tried to exclude relevant risk populations, such as history of post-cholecystectomy syndrome, SO dysfunction, alcohol abuse, history of pancreatitis or biliary tract disease etc. The further analysis revealed that all of these events occurred in a patient population without gallbladder (in one patient, the status was unknown), either with cholecystectomy or congenital agenesis. The applicant has therefore previously recommended the use of the lower dose of 75 mg BID for this population. However, the occurrence of these events in the 75 mg treatment group was not zero, and whereas a reduction of the events by administering the lower dose appears to be uncertain, it is considered definite that these events will not be abolished with a reduction of the dose. A contra-indication has therefore been regarded to be necessary.

**Uncertainty in the knowledge about the unfavourable effects**

Although the PK/PD investigations showed that the compound does not reach the CNS in clinically relevant amounts by oral intake events, of dizziness and somnolence occurred with higher frequency in the active treatment groups, and it remains uncertain whether other CNS-related effects can also be triggered by the compound. The applicant has also investigated the occurrence of falls, syncope and traffic accidents as potential consequences of CNS effects. For the time being it could be shown that these events were not related to the study drug but precautionary statements were included in the SmPC in particular for patients who may experience increased plasma levels.

Patients ≥65 years of age had an overall increased frequency of adverse drug reactions in clinical trials but ADRs were qualitatively not different to ADRs seen in younger patients and treated with the 75 mg dose experienced a reduced rate of serious adverse events as well as adverse events leading to discontinuation compared to patients treated with 100 mg dose. Therefore, the 75 mg dose twice daily can be considered for this population. However the number of older patients, especially those with an age above 75 was low and a clear assessment whether these patients would be at increased risk of undesirable effects from the medication (e.g. with regard to GI events, or with regard to CNS effects) is hampered. Therefore treatment in Patients ≥65 years of age was made a potential risk in the RMP and a warning was included in section 4.4 of the product information concerning use in the elderly, recommending this dose reduction for elderly patients and to assess periodically the benefit risk ratio of this treatment.



***Effects Table***

**Table 38 - Effects Table for Eluxadoline**

| Effect | Short Description | Unit | 75 mg BID | 100 mg BID | Plac. | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | | |
| Composite pain and stool consistency response rate | Daily reduction of pain of >30% and stool consistency no compatible with diarrhoea | % | 26.7 | 31.0 | 19.5 | Strong evidence, no uncertainty, clinical relevance moderate | Studies IBS-3001 and IBS 3002 pooled results |
| Stool consistency response rate | No diarrhoea | % | 33.3 | 34.7 | 21.5 | Strong evidence, no uncertainty, clinical relevance moderate to strong | |
| Pain response rate | Reduction of 30% | % | 46.3 | 48.3 | 44.0 | No statistical significance; clinical relevance low | |
| Global response rate (Likert scale) | Score of 0 (none) or 1 (mild) overall symptoms | % | 40.5 | 40.1 | 33.3 | Strong evidence, clinical relevance limited | |
| Global response rate (dichotomous evaluation) | Adequate relief yes/no | % | 52.8 | 53.7 | 43.7 | Strong evidence clinical relevance limited | |

| Effect | Short Description | Unit | 75 mg BID | 100 mg BID | Plac. | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|---|
| Improvement in Quality of Life | Changes from baseline in IBS-QoL score (mean difference to placebo) | 34 item Score | 3.77 | 5.35 | N/A | Strong evidence, clinical relevance uncertain | Study IBS 3001 |
| | | | 3.94 | 2.19 | | Strong evidence low dose, moderately strong evidence for high dose, clinical relevance uncertain | Study IBS 3002 |
| **Unfavourable Effects** | | | | | | | |
| GI effects (Constipation, vomiting, abdominal pain, flatulence) | Adverse event | Frequency (%) | 18.1% | 20.1% | 11.9% | Evidence strong due to compatibility with mechanism of action and consistency across groups | Pooled studies IBS 2001, 3001 and 3002 |
| Dizziness | | | 2.6 | 3.2 | 2.2 | Moderately strong evidence due to consistency across groups | |
| Somnolence/Sedation | | | 0.3 | 1.1 | 0.3 | Moderately strong evidence based on correlation of frequency of CNS effects with dose | |
| Serious adverse events (total) | SAE | Frequency (%) | 4.2 | 4.0 | 2.6 | Moderately strong evidence for slight increase | |
| Adverse events leading to discontinuation | Any event leading to discontinuation | Frequency (%) | 8.3 | 7.8 | 4.3 | Strong evidence for moderate increase | |
| Pancreatitis (reported as SAEs) | Definition according to investigator | Number | 2 | 3 | 0 | High uncertainty due to low numbers, pathophysiological mechanism partly identified to be SO-spasm; intended to be reduced by contraindications; uncertainty with regard to magnitude of reduction by contraindication | |
| Hepatobiliary events consistent with SO spasm | Adjudicated events | Number | 1 | 7 | 0 | Strong hints, uncertainty high due to low | |

| Effect | Short Description | Unit | 75 mg BID | 100 mg BID | Plac. | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|---|
| | | | | | | numbers; clear risk factor identified to be cholecystectomy; intended to be reduced by contraindication, uncertainty with regard to magnitude of reduction by contraindication | |



***Balance***

**Importance of favourable and unfavourable effects**

IBS is a functional disease, and is not associated with a reduction in survival over time. However, it has been shown that patients have a decreased Quality of Life, which is similar to patients suffering from depression or diabetes, and higher than the one in patients with chronic renal failure. For the diarrhoea-predominant form of IBS, there is currently no treatment licensed within the EU. The importance of the favourable effects is therefore limited by their magnitude, but strengthened by the lack of treatment alternatives, and the obvious need for treatment.

The compound eluxadoline shows an expected undesirable effects profile relating to the peripheral agonism at the μ-opioid receptor. The known adverse effects of opioids with regard to the gastrointestinal tract are obviously caused by the compound at rates that occur in up to almost 10% of the patients, and which comprise constipation, nausea and vomiting, abdominal pain and flatulence. The character of these events appears to be relatively “benign” and they are not considered to put the patients in undue danger.

Due to the physicochemical properties of the compound the availability in plasma is limited, and obviously relevant amounts of the compound do not enter the CNS at therapeutic doses; also a potential for abuse by opioid users has been adequately excluded. Despite this postulate supported by early PK and PD trials some effects on CNS seem to be occurring.

In accordance with the pharmacology of the compound, eluxadoline was also able to cause SO-spasm related events, ranging from transient biliary obstruction with ALT elevation to manifest pancreatitis (although mild in severity according to official classification), despite exclusion of a “risk population” with pre-existing biliary or pancreatic disease. All these events appeared to occur in patients without gall bladder (cholecystectomy or agenesis) in which the treatment has been contraindicated.

**Benefit-risk balance**

The evaluation of the clinical data has shown a strong proof of superiority of both doses of eluxadoline compared to placebo in the statistical sense. The two symptom-components included in the primary endpoint are considered highly relevant for the patients. However, the magnitude of the effect questions its overall clinical

relevance. The evaluation of the primary endpoint showed high robustness of the results with regard to changes in mode of data input and definition of response, and showed high consistency across most subgroups. This high level evidence was supported by some other secondary endpoints, among them being relevant clinical endpoints such as bloating and occurrence of urgency. An improvement of Quality of Life was seen, which was, however, somewhat discrepant between the studies. Global response rates, despite mostly being statistically significant, did only show clinically questionably relevant superiority over placebo.

One of the main secondary endpoints (pain) did not achieve statistical significance but showed limited effects only. The improvement of pain appears to be a secondary consequence of the influence of the compound on the stool related parameters only.

The unfavourable effect identified with sufficient certainty seem to be class-related, and appears to be more or less limited to the gastrointestinal tract, where a couple of complaints are occurring which are mostly mild in nature and functional in the sense that no permanent sequelae are left.

As expected from this class of medicines, relevant and potentially clinically severe and serious adverse effects can be caused by triggering events of SO spasm, where a potential at risk population had been excluded, for which, however, those with prior cholecystectomy have been definitely identified to be an at risk population. Similarly, patients with high levels of alcohol intake have also been identified as population at risk for pancreatitis (with or without SO-spasm). Both populations should not receive the compound and it is expected that the occurrence of these relevant events is greatly reduced by the implemented contraindication. Effects relating to CNS appear currently to be limited to somnolence and dizziness only and can be managed by the implemented statements in the SmPC.

The compound therefore is regarded to exert moderately beneficial effects overall with borderline clinical relevance, and presents a risk-profile that includes mainly “functional” gastrointestinal complaints.

The beneficial effect, although moderate in magnitude, do exceed the identified risks which are considered balanced with the implemented routine risk minimisation measures.

***Discussion on the benefit-risk assessment***

The clinical trial programme conducted with the substance eluxadoline has overall shown a relatively strong evidence for efficacy in a formal sense, whereas the clinical benefits observed have been shown to be moderate only, and of borderline clinical relevance. This pertains mainly to one of the main features of IBS, the abdominal pain, but also the overall assessment of the primary endpoint used, and to the global assessment of efficacy by the patient. However, there is a clear unmet medical need in the indication proposed for licensing with no substance available. Compared to substances not licensed for the specific indication but used to treat some symptoms of the disease, the compound has the advantage of data being available that show effects on the totality of the symptoms of the disease entity. The compound is therefore considered adequate to fill the unmet need. The general adverse events profile appears to be mainly limited to the gastrointestinal tract, resembling the expected action from the pharmacology of the compound.

The risk factors identified for the causation of events of SO spasm (including biliary obstruction and pancreatitis) have been identified to be cholecystectomy and high alcohol intake. These patient populations were therefore be contraindicated which makes the risk of occurrence of these events controllable. Furthermore it is considered acceptable to give this lower dose as a treatment option; i.e. 75 mg for the treatment of patients with tolerability problems to the 100 mg dose and for patients older than 65 years of age.

# 4. Recommendations

***Outcome***

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Truberzi for the treatment of adults with irritable bowel syndrome with diarrhoea (IBS-D) is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

***Conditions or restrictions regarding supply and use***

Medicinal product subject to medical prescription.

***Conditions and requirements of the Marketing Authorisation***

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

***Conditions or restrictions with regard to the safe and effective use of the medicinal product***

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

***New Active Substance Status***

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that Eluxadoline is qualified as a new active substance.