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LJN452

CLJN452X2202

A double blind, randomized placebo controlled crossover multiple dose study of LJN452 to assess safety, tolerability and efficacy in patients with primary bile acid diarrhea (pBAD)

Personal Data

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct.

Notification of serious adverse events

Refer to Section 9.2 of the protocol for definitions and reporting requirements for Serious Adverse Events (within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department and notify the Study Lead).

Contact information is listed in the Site Operations Manual.

Table of contents

Corporate Confidential Information

Corporate Confidential Information

Corporate Confidential Information

Corporate Confidential Information

List of tables

List of figures

List of abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
b.i.d.	twice a day
BA	bile acid
BMI	Body Mass Index
BSEP	bile salt export pump
BUN	blood urea nitrogen
CD-ROM	compact disc – read only memory
CFR	Code of Federal Regulation
CK	creatinine kinase
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CV	coefficient of variation
EC	Ethics committee
EC50	half maximal effective concentration
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
FXR	Farnesoid X-receptor
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
h	Hour
HIV	human immunodeficiency virus
i.v.	Intravenous
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDH	lactate dehydrogenase
LLN	lower limit of normal
LLQ	lower limit of quantification
mg	milligram(s)
ml	milliliter(s)
o.d.	once a day
OECD	Organization for Economic Co-operation and Development
p.o.	Oral
PA	Posteroanterior
pBAD	primary bile acid diarrhea
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
RBC	red blood cell(s)
REB	Research Ethics Board
s.c.	Subcutaneous
SAE	serious adverse event
SD	standard deviation
SeHCAT	Selenium Homocholic Acid Taurine
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SHP	Small Heterodimer Partner
TBL	total bilirubin
ULN	upper limit of normal
ULQ	upper limit of quantification
WBC	white blood cell(s)

Pharmacokinetic definitions and symbols

AUCtau	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau [mass x time / volume]
AUCtau,ss	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau at steady state [mass x time / volume]
Cav,ss	The average steady state plasma (or serum or blood) concentration during multiple dosing
CL/F	The apparent systemic (or total body) clearance from plasma (or serum or blood) following extravascular administration [volume / time]
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
Cmax,ss	The observed maximum plasma (or serum or blood) concentration following drug administration at steady state [mass / volume]
Cmin,ss	The lowest plasma (or serum or blood) concentration observed during a dosing interval at steady state [mass / volume]
Racc	The accumulation ratio
Tmax	The time to reach the maximum concentration after drug administration [time]

Protocol synopsis

Protocol number	CLJN452X2202
Title	A double blind, randomized placebo controlled crossover multiple dose study of LJN452 to assess safety, tolerability and efficacy in patients with primary bile acid diarrhea (pBAD).
Brief title	To assess safety and tolerability and establish efficacy of LJN452 in patients with primary bile acid diarrhea.
Sponsor and Clinical Phase	Novartis. Phase 2
Intervention type	Drug.
Study type	Interventional.
Purpose and rationale	To assess safety, tolerability and efficacy of LJN452 in patients with pBAD.
Primary Objective(s)	• To determine the safety and tolerability of LJN452 in patients with pBAD. • To assess the effect of LJN452 on clinical symptoms experienced by patients with pBAD.
Secondary Objectives	• To assess the pharmacokinetics of LJN452 in pBAD patients. • Assess the effect of LJN452 on use of rescue medications during the study period.
Study design	This is a multi-center, double blind (patient and investigator blind, sponsor open label), randomized placebo controlled, crossover study to assess safety, tolerability and efficacy of LJN452 in patients with primary bile acid diarrhea (pBAD).
Population	The study population will be comprised of patients with primary bile acid diarrhea. Approximately 30 patients will be enrolled in the study and randomized, with at least 24 patients expected to complete the study.
Inclusion criteria	• A history of diarrheal symptoms for at least 3 months prior to dosing - Average stool frequency of at least 3 per day when off therapy AND Average stool form of >5 on Bristol Stool Chart. • Previous laboratory or radiological confirmation of bile acid malabsorption within the last 5 years with either fecal bile acid loss of ≥2,000 µmol per 48 hours OR 7 day ^{75}Selenium homocholic acid taurine (^{75}SeHCAT) retention. • Age ≥ 18 years.
Exclusion criteria	• Patients with other diagnoses leading to diarrhea, including colorectal neoplasia, ulcerative colitis, Crohn's disease, celiac disease, chronic pancreatitis, drug-induced diarrhea or active infection *AND* Patients who have not been investigated by standard clinical assessments to exclude these disorders. • Treatment with bile acid sequestrants (colestyramine, colestipol,

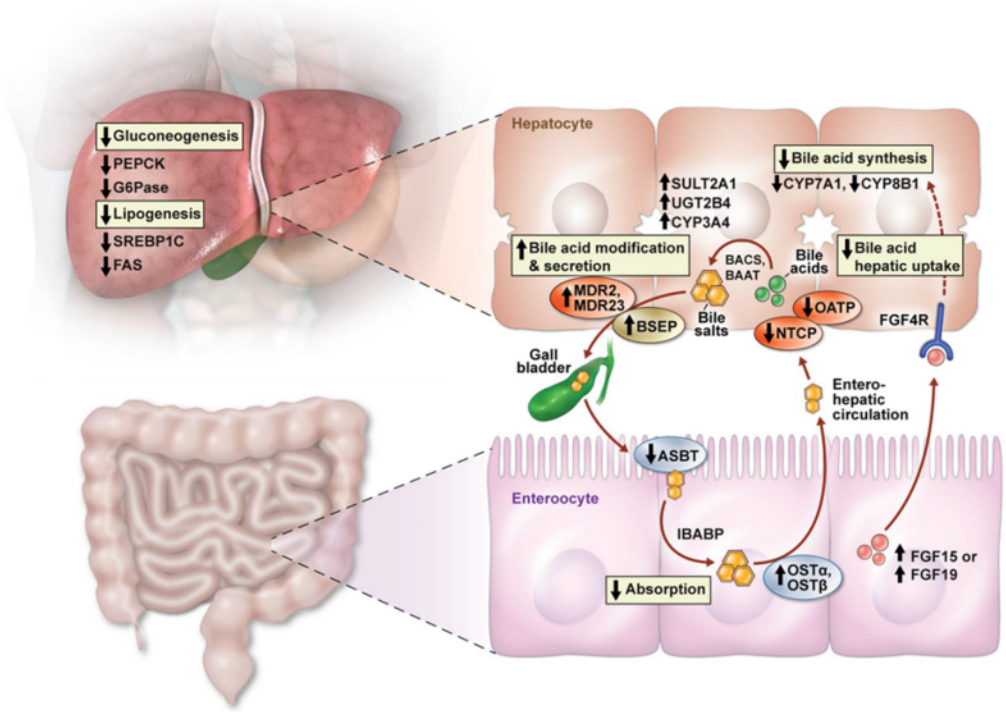
	colesevelam) for 2 weeks before the first dose of LJN452. A washout of 14 days for these agents will be allowed before first dosing. • History of extrahepatic biliary obstructive disease or complete biliary obstruction. • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception • A positive Hepatitis B surface antigen or Hepatitis C test result. • History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result.
Investigational and reference therapy	• Single oral dose of LJN452 60 µg daily for 14 days. • Single oral dose of placebo to LJN452 0 µg daily for 14 days.
Efficacy/PD assessments	• Change from baseline in stool frequency and stool form per Bristol Stool Chart.
Safety assessments	• Safety endpoints include type and frequency of adverse events, serious adverse events, and laboratory, vital signs, physical, and ECG abnormalities.
Other assessments	• PK. • Use of rescue medication. • Markers of target engagement.
Data analysis	A repeated measures analysis will be done for the two-dimensional endpoint: weekly stool frequency and the corresponding average stool form. The analysis will include fixed effects for sequence (Drug/Placebo or Placebo/Drug), Treatment (Week 1 Drug, Week 2 Drug, Week 1 Placebo, Week 2 Placebo), and period (1 or 2). The model will assume an arbitrary 2 by 2 covariance matrix for the two-dimensional endpoint (frequency, form) and a compound symmetry covariance matrix for each individual endpoint. Point estimates of the treatment effect on weekly & biweekly stool frequency and the corresponding average stool form will be reported together with 95% simultaneous confidence intervals (confidence ellipsoids).
Key words	Primary bile acid diarrhea, FXR agonist, bile acid malabsorption.

1 Introduction

1.1 Background

LJN452 is a highly potent agonist of the bile acid receptor Farnesoid X Receptor (FXR), which is expressed in liver, intestine and kidney. In the liver, FXR agonism increases expression of genes involved in canalicular and basolateral bile acid efflux and bile acid detoxifying enzymes while inhibiting basolateral bile acid uptake by hepatocytes and inhibiting bile acid synthesis (Calkin and Tontonoz 2012). FXR activation represses bile acid synthesis in the liver through induction of Small Heterodimer Partner (SHP), which is a negative regulator of Cyp7a1, the rate-limiting enzyme of the neutral bile acid biosynthetic pathway (Goodwin et al 2000). Furthermore, FXR agonists increase excretion of bile acids through the kidney, increase bile acid binding proteins in the ileum and stimulate FGF15/FGF19 expression (a key regulator of bile acid metabolism). Thus, FXR acts as a sensor of elevated bile acids and initiates homeostatic responses to control bile acid levels, a feedback mechanism that is believed to be impaired in bile acid malabsorption (Pattni et al 2012, Walters 2014).

Figure 1-1 Co-ordinated effects of FXR on metabolism



FXR regulates bile acid metabolism through multiple mechanisms in the liver and intestine. The processes regulated by FXR are shown in rectangular boxes. Genes are shown with up or down arrows to indicate the direction of regulation by FXR agonists. Arrows are used to show the flow of bile acids in the enterohepatic circulation or the movement of FGF15 (rodents) or FGF19 (human) from the enterocyte to the hepatocyte. In normal physiology, FXR detects increased levels of bile acids and responds by decreasing bile acid synthesis and bile acid uptake while increasing bile acid modification and secretion in the liver. In the intestine, FXR detects increased bile acid levels and decreases bile acid absorption and increases secretion of FGF15 or FGF19. The net result is a decrease in the overall levels of bile acids. Adapted from Calkin and Tontonoz 2012.

1.1.1 Relevant data summary

The most relevant data for the present study are summarized in the sections below. For detailed information, please refer to the Investigator's Brochure.

1.2 Study purpose

The purpose of this study is to determine whether LJN452 improves the symptoms of bile acid diarrhea and to assess its safety and tolerability profile in patients with primary bile acid diarrhea (pBAD) to guide decision-making regarding further clinical development in this indication.

2 Study objectives

2.1 Primary objective(s)

Primary objective(s)	*Endpoints related to primary objective(s)*
• To determine the safety and tolerability of LJN452 in patients with primary bile acid diarrhea.	• Safety endpoints include type and frequency of adverse events, serious adverse events, and laboratory, vital signs, physical, and ECG abnormalities.
• To assess the effect of LJN452 on clinical symptoms experienced by patients with primary bile acid diarrhea.	• Changes from baseline in stool frequency and in stool form per Bristol Stool Chart.

2.2 Secondary objective(s)

Secondary objective(s)	*Endpoints related to secondary objective(s)*
• To assess the pharmacokinetics of LJN452 in pBAD patients.	• Tmax, Cmax and AUCtau of LJN452.
• To assess the effect of LJN452 on use of rescue medications during the study period.	• Use and type of rescue medications.

3 Investigational plan

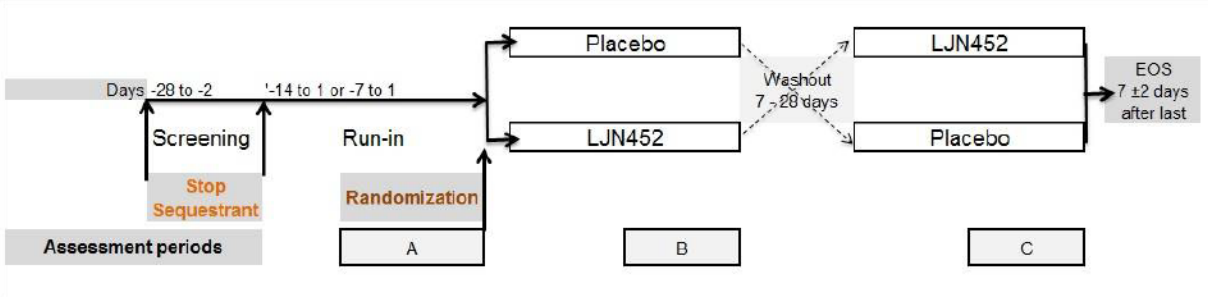
3.1 Study design

This is a multi-center, double blind (patient and investigator blind, sponsor open label), randomized placebo controlled, crossover study to assess safety, tolerability and efficacy of LJN452 in patients with primary bile acid diarrhea (pBAD). In this study approximately 30 patients will be enrolled to have 24 completers.

This is a non-confirmatory trial.

Each patient will undergo a screening period (28 days), run-in period (washing out previous treatment effect) (up to 14 days), 2 treatment periods (14 days each), washout period (at least 7 up to 28 days) between the treatment periods and end of study.

Figure 3-1 Study design schematic



Patients will be assessed for eligibility to enter the study at the screening visit.

Each patient will perform following visits

Screening visit: Day -28 to -2

During the screening period all patients will undergo screening assessment, which may be completed over multiple visits as per the patient's convenience. The screening results will be valid for 28 days, if any patient is beyond the screening validity, the patient can be re-screened. Results for all screening assessment must be available before the baseline/Day 1 pre-dose assessment.

If the eligibility is confirmed patients will be asked to discontinue their sequestrants. Patients will be handed over patient diary to record their daily stool type and frequency using Bristol Stool Chart and use of rescue medication (loperamide intake). The patient diary is expected to be used by patients' throughout the study duration.

Rescue medication will be loperamide only and patients will be instructed to take 2 mg dose only after passage of 4 stools of Bristol Stool Scale Type 6 (Fluffy pieces with ragged edges, a mushy stool) or Type 7 (Watery, no solid pieces, entirely liquid). This dose may be repeated only after 4 hours have elapsed or passage of 4 further stools of Type 6 or 7 (whichever occurs first). A total of no more than 16mg of loperamide may be taken in a 24 hour period. No BA sequestrants should be used by the patients during this study.

Run-in period (Day -7 to -1 or Day -14 to -1)

Patients who have not used bile acid sequestrants for pBAD in the previous week at the time of screening will be evaluated for inclusion/exclusion criteria during the screening visit, and if found eligible will enter a 1 week run in period (Day -7 to -1) prior to the double blind randomized treatment phase.

Eligible patients who are treated with bile acid sequestrants (at least one dose during the previous two weeks) will be asked to stop their medication and enter the 2 weeks run-in period (Day -14 to -1) of the study. Patients will be allowed to take rescue medication (loperamide), which will be recorded as concomitant medication.

Patients will continue to use patient diary to record stool type and frequency along with use of rescue medication.

Results for all screening assessment must be available before the baseline/Day 1 pre-dose assessment. Screening and run-in visits may be combined for logistic reasons.

After the run-in period, patients will enter the double blind randomized treatment phase.

There will not be a separate baseline visit, but pre-dose assessment on Day 1 will be considered as baseline assessment.

Treatment Periods (Day 1-14):

On Day 1, patient will handover stool sample collected before dosing as pre-dose stool sample. Pre-dose PK, PD and biomarker samples will be collected before dosing.

In treatment period 1 on Day 1 patients will receive either 60 µg LJN452 or placebo orally once daily for 14 days in a 1:1 ratio. Pharmacokinetic (PK), pharmacodynamic (PD) and safety samples will be collected on Day 1 for up to 8 hours post dose and on Day 2 pre-dose, which corresponds to 24 h after Day 1 dosing. Some PK and PD sample time points on Day 1 and Day 2 can be optional, see Assessment Schedule.

Patients will be handed over trial medication, to be administered at home enough to cover dosing for 14 days in each period. Throughout the 14 days of the treatment period, patients will be directed to take study drug at home with water in the morning in a fasting state, 2 hours prior to the first meal of the day, preferably at the same time of the day.

Following dosing, patients will return to clinic for PK, PD, BM and safety assessment at various time points as described in the Assessment Schedule.

The patients will return to the clinic for a series of PK, PD and biomarker sample collections on Day 12.

After 2 weeks of treatment with LJN452 or placebo, patients will undergo a washout of at least 7 days, up to a maximum of 28 days. At the end of washout period, patients will return to the study site for period 2 of the study. Period 2 will be identical to period 1 except that the treatments will be crossed over.

Patient diary will be used to capture stool frequency, consistency and rescue medication. Intake of loperamide will be allowed, but will be recorded in the concomitant medication section of the CRF.

Study Completion visit:

The patients will return to the site 7 days' ±2 days after the last dose to undergo the study completion evaluations. Following completion of all assessments, the patients will be discharged from the study. If for any reason the patient is withdrawn from the study, the patient will return to the site 7 days after the last dose to undergo the study completion evaluations. Following completion of all assessments, the subject will be discharged from the study. Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis) adverse event and serious adverse event monitoring.

3.2 Rationale of study design

This randomized, multi-center, double blind (patient and investigator blind, sponsor open label), placebo-controlled, cross-over study is designed to assess safety, tolerability and efficacy of LJN452 at 60 µg relative to placebo in patients with pBAD, as assessed by a reduction in stool frequency and stool type score after 2 weeks of double-blind treatment.

A cross-over design reduces variability as the treatment comparison can be done within patient.

Randomization will be maintained at 1:1 ratio over the entire study in order to avoid any sequence bias.

Multiple sites will be used to enroll patient in this study due to the underl ying prevalence of diagnosed pBAD. It is know that differences in criteria exist in the diagnosis of pBAD in different regions.

In order to maintain the scientific integrity of the study, investigators and patients will remain blinded regarding the allocation of active or placebo. The clinical trial team will be unblinded throughout the dosing phase to allow analysis of safety and PK/PD data.

3.4 Rationale for choice of comparator

There is no FXR agonist approved drug for treatment of bile acid diarrhea, thus placebo will be used as a comparator in this study.

3.6 Risks and benefits

No more than a transient direct benefit of LJN452 treatment to patients with pBAD is anticipated in the short term study.

A maximum of 438 mL of blood is planned to be collected over a period of 8 weeks from each patient as part of the study. Additional samples needed for monitoring of any safety findings would be in addition to this. This is not considered to be a risk for this population.

There may be unknown risks of LJN452 which may be serious and unforeseen.

The overall risk to patients with pBAD in this study is expected to be low and will be minimized by adherence to the inclusion/exclusion criteria, avoidance of prohibited concomitant medications, close clinical monitoring including on-line PK assessments, safety reviews and study stopping rules.

The overall risk/benefit assessment of LJN452 is supportive of the conduct of this study in patients with pBAD.

4 Population

The study population will be comprised of patients with primary bile acid diarrhea.

A total of approximately 30 patients will be enrolled in the study and randomized, with at least 24 patients expected to complete the study.

The investigator must ensure that all patients being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator to ensure that the study population will be representative of all eligible patients.

Patient selection is to be established by checking through all eligibility criteria at screening. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from **any** entry criterion excludes a patient from enrollment into the study.

Replacement patients will be enrolled to replace patients who discontinue the study for reasons other than safety.

4.1 Inclusion criteria

1. Written informed consent must be obtained before any assessment is performed.
2. A history of diarrheal symptoms for at least 3 months prior to dosing
   - Average stool frequency of at least 3 per day when off therapy.

   AND
   - Average stool form of >5 on Bristol Stool Chart.
3. Previous laboratory or radiological confirmation within the last 5 years of bile acid malabsorption with either:
   - Evidence of fecal bile acid loss of ≥2,000 µmol per 48 hours.

   OR
   - 7 day ^{75}Selenium homocholic acid taurine (^{75}SeHCAT) retention of <10%.
4. Age ≥ 18 years

6. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

4.2 Exclusion criteria

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2. Patients with other diagnoses leading to diarrhea, including colorectal neoplasia, ulcerative colitis, Crohn's disease, celiac disease, chronic pancreatitis, drug-induced diarrhea or active infection

   AND

   Patients who have not been investigated by standard clinical assessments to exclude these disorders.
3. Treatment with bile acid sequestrants (colestyramine, colestipol, colesevelam) for 2 weeks before the first dose of LJN452. A washout of 14 days for these agents will be allowed before first dosing.
4. Use of drugs or agents of the classes within 1 week prior to dosing or planned use during the study period:
   - Agents that alter GI transit except loperamide, including strong opioids, narcotics, anticholinergics.
   - Any medication that could interfere with the interpretation of the study (thyroxine replacement is a permissible exception).
5. History of extrahepatic biliary obstructive disease or complete biliary obstruction.

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- Evidence of urinary obstruction or difficulty in voiding at screening.

8. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
9. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or treated cervical intraepithelial neoplasia), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
10. Sexually active males must use a condom during intercourse while taking drug and for 5 days after stopping LJN452 and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
11. Significant mental and physical illness other than pBAD which has not resolved within two (2) weeks prior to initial dosing.
12. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 5 days after stopping of LJN452. Highly effective contraception methods include:
    - Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.
    - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

    In case of use of oral contraception, women should be stable on the same pill for a minimum of 3 months before taking investigational drug.
13. A positive Hepatitis B surface antigen or Hepatitis C test result.
14. History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result.
15. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Restrictions for Study Subjects

During recruitment, screening/informed consent review, and treatment day 1 visit, the patients must be informed and reminded of the restrictions.

5.1 Contraception requirements

Please refer to exclusion criteria (Section 4) for details of contraception requirements for the study.

5.2 Prohibited treatment

No medication or herbal remedies likely to have an impact on LJN452 metabolism will be allowed from the first dosing until end of study evaluations have been conducted.

Administration of acetaminophen (no more than 1000 mg in a single dose and no more than 4000 mg per day) is acceptable, but must be documented.

A full list of prohibited medications will be provided in the SOM.

5.3 Dietary restrictions and smoking

- Patient must avoid high fat foods during the study and adhere to a diet that is similar across both periods of the cross-over design.

All patients will fast (i.e. no food and liquid except water) for at least 8 hours prior to administration of study drug and will continue to fast (i.e. no food and liquid except water) for at least 2 hours thereafter.

Food intake will be monitored regularly throughout the study using a patient diary and will be included in the clinical database.

Patients can drink water *ad libitum* in addition to fluid taken with meals and medication.

On PK days Day 1 and Day 12, no breakfast will be provided. Meals should be similar in caloric content and distribution for all patients on the day of dosing.

5.4 General restrictions

No strenuous physical exercise (e.g. weight training, aerobics, football) until after Study Completion evaluation.

6 Treatment

6.1 Study treatment

Details on the storage and management of study medication, randomization and instructions for prescribing and taking study treatment are outlined in Section 3 of the Site Operations Manual.

6.1.1 Investigational treatment

The investigational drug, LJN452 10 μg (0.01 mg), and matching placebo will be prepared and supplied by Novartis as single blinded packs to be dispensed by the unblinded pharmacist at the investigator site according to the randomization schedule.

6.2 Treatment arms

Patients will be assigned to the 2 treatment sequence (Drug/Placebo or Placebo/Drug) in a ratio of 1:1. The number of patients enrolled may change based on data from interim analyses.

Study treatments are defined as:

- A: Single oral dose of LJN452 60 μg daily for 14 days (administered as LJN452 6 x 10 μg capsules).
- B: Single oral dose of placebo to LJN452 0 μg daily for 14 days (administered as placebo to LJN452 6 x 0 μg capsules).

6.3 Permitted dose adjustments and interruptions of study treatment

Study drug dose adjustments by the investigator and/or interruptions other than for safety reasons are not permitted.

In case of notable adverse events, safety concerns and/or based on pharmacokinetic data review during the study, the following changes to the administered dose may be considered by the sponsor in consultation with the investigator:

- Administration of a dose below the starting dose.
- Administration of a dose higher than the starting dose not exceeding the exposure cap.

These changes must be recorded on the Dosage Administration Record CRF.

6.4 Treatment assignment

Randomization numbers will be assigned in ascending, sequential order to eligible patients (see Site Operations Manual for details). The investigator will enter the randomization number on the CRF.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. The randomization scheme for patients will be reviewed and approved by a member of the Novartis IIS Randomization Group.

6.5 Treatment blinding

This is a double blind study: Patients, investigator staff, and persons performing the assessments will remain blinded to the identity of study treatments according to the specifications provided in the Site Operations Manual.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions: Unblinded pharmacist or authorized designee at site, and the sponsor clinical trial team.

The Interim Analysis Team may communicate interim analysis results (e.g. information needed for planning/modifying another study) to relevant Novartis teams for information, consulting and/or decision purposes.

The sponsor clinical trial team will remain unblinded throughout the study.

Unblinding to the investigator and patient will only occur in the case of patient emergencies (see Section 6.6) and at the conclusion of the study or after IAs.

6.6 Emergency breaking of assigned treatment code

Emergency unblinding should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. A complete set of emergency code break cards will be provided to the investigator site(s) and a complete set will be available at Novartis. All code break cards must be retained until the end of the study and returned to Novartis. They must be stored in a secure place but be accessible in case of emergency. The investigator will receive a blinded code break card for each patient, with the details of drug treatment covered by a removable, scratch-off cover. In an emergency, the scratch-off cover can be removed to determine the treatment. The scratch-off covers are not to be removed for any reason other than an emergency. When the investigator removes the scratch-off cover he/she must note the date, time, and reason for removing it and retain this information with the case report form documentation. **The unblinded treatment code should not be recorded on the CRF.** The investigator must also immediately inform the Novartis local monitor that the code has been broken.

6.7 Treatment exposure and compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all patients treated with LJN452, as detailed in Section 8.5.

6.8 Recommended treatment of adverse events

Expression of ALP is induced by FXR activation. Hence LJN452 is expected to increase circulating levels of ALP in a dose dependent manner and this will not necessarily indicate liver injury. Elevation of ALP should be interpreted in light of other tests, such as ALT, AST, and total bilirubin levels. Please see specific stopping rules and response to abnormal lever enzyme tests.

Medication used to treat adverse events must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.9 Rescue medication

Use of rescue medication (loperamide) will be allowed and must be recorded on the patient diary/Concomitant medications/Significant non-drug therapies CRF after start of study drug.

Rescue medication will be loperamide only and patients will be instructed to take 2 mg dose only after passage of 3 stools of Bristol Stool Scale Type 6 (fluffy pieces with ragged edges, a mushy stool) or Type 7 (watery, no solid pieces, entirely liquid). This dose may be repeated only after 4 hours have elapsed or passage of 4 further stools of Type 6 or 7 (whichever occurs first). A total of no more than 16 mg of loperamide may be taken in a 24 hour period. No BA sequestrants should be used by the patients during this study.

6.10 Concomitant treatment

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/ Significant non-drug therapies section of the CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

7 Discontinuation and study completion

7.1 Discontinuation of study treatment

Patients may voluntarily discontinue study treatment for any reason at any time.

Discontinuation of study treatment will be at the discretion of the Investigator, under the following circumstances:

- Any protocol deviation that results in a significant risk to the patient's safety.
- If continuation in the study is deemed detrimental to the patient's well-being.

The appropriate personnel from the site and Novartis will assess whether study treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

Individual patient withdrawal

Patients may voluntarily discontinue study treatment for any reason at any time.

Study treatment must be discontinued and the patient withdrawn from the study if the patient withdraws consent.

The study treatment must be discontinued and the patient's withdrawal from the study should be at the investigator's discretion if the following occur:

- Pregnancy.
- Intolerable or clinically significant diarrhea.
- Hypersensitivity reaction to LJN452.

- An increase in aminotransferase enzymes (ALT or AST) of greater than 3 x ULN AND EITHER symptoms such as anorexia, fatigue, right upper quadrant abdominal pain or tenderness, fever, rash and/or eosinophilia OR elevation of serum TBL to greater than 2 x ULN OR INR>1.5.
- Medically significant (>8 x ULN) ALT or AST elevation.
- An AE with a CTCAE rating of Grade 3 or higher regardless of drug causality, unless it is caused by elevation of ALT (as above) or an accident that could not reasonably be attributable to the drug.
- An AE with a CTCAE rating of Grade 2 or higher considered to be due to study drug, unless it is caused by elevation of ALT (as above).
- An elevation of ALP or GGT of >2.5 x ULN considered to be due to study drug or >5 × ULN regardless of drug causality.

Patients who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 7.3). Where possible, they should return for follow up assessments. If they fail to return for assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact them as specified in Section 7.2.1.

7.2 Study completion and post-study treatment

Each patient will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them. Study completion is defined as when the last patient completes their End of Study visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

At a minimum, patients will be contacted for safety evaluations during the 30 days following the Study Completion visit, including a final post-study safety contact at the 30-day point. Documentation of attempts to contact the patient should be recorded in the source documentation.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care. All patients who complete the study will return to their standard of care after the end of study visit.

7.2.1 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

7.3 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a patient does not want to participate in the study anymore **and** does not want any further visits or assessments **and** does not want any further study related contact **and** does not allow analysis of already obtained biologic material.

If a patient withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information. Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

7.4 Study Stopping rules

The study will be placed on hold and may be stopped or amended based on full review of all available clinical safety data and discussion with the Investigator if any of the following occur:

- Two or more patients on study drug experience a similar adverse event that is a CTCAE Grade 3 or higher apart from ALT elevation (see below).
- One patient on study drug experiences any adverse event that is CTCAE Grade 4 or higher apart from ALT elevation (see below) other than an accident that is not related to study drug).
- Two or more patients with an increase in aminotransferase enzymes (ALT or AST) of greater than 3 x ULN AND EITHER symptoms such as anorexia, fatigue, right upper quadrant abdominal pain or tenderness, fever, rash and/or eosinophilia OR elevation of serum total bilirubin to greater than 2 x ULN OR INR >1.5.
- Two or more patients on study drug experience an elevation of ALP or GGT of >5 × ULN or one patient on study drug experiences an elevation of ALP or GGT of >20 × ULN.
- The Principal Investigator and the Sponsor consider that the number and/or severity of adverse events justify discontinuation of the study.
- The Sponsor unilaterally requests discontinuation of the study.

Safety reviews will be conducted jointly between medically qualified representatives of the Sponsor and Investigator and a joint decision will be made. The severity of adverse events will be graded by the study site Investigator (or his designee) based on clinical judgment and captured in the CRF AE page. This information will be used to quantify events that may lead to patient's discontinuation or stopping of the study.

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason. If a patient withdrawal occurs for any reason, the Investigator must make every effort to determine the primary reason for a patient's withdrawal from the study and record this information on the Study Completion CRF.

7.5 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, patients should be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests.

The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Procedures and assessments

Patients should be seen for all visits on the designated day, with the assessments performed as per schedule, within the allowed "visit/assessment window" specified in the Site Operations Manual.

Table 8-1 Assessment Schedule

Study Phase	Screening	Run-in	Treatment Period 1 / Washout / Period 2																EOS
Visit Numbers[1]	V1[5]	V2[5]	V3							V4	V5	V6[2]							V777
Visit Numbers			V7							V8	V9	V10							
Study Day(s)	-28 to -2	-14 to -1	1							2	7±2	12							43±2
Time (post-dose)	-	-	0h	1h	2h	4h	5h	6h	8h	0h	-	0h	1h	2h	4h	5h	6h	8h	-
Informed consent	X																		
Inclusion / Exclusion criteria	X																		
Medical history/current medical conditions	X																		
Physical examination	X		X									X							X
Demography	X																		
Hepatitis screen	X																		
HIV screen	X																		
Alcohol Test and Drug Screen	X																		
Pregnancy test	X[3]		X[4]									X[4]							X[3]
Body height	X																		
Body weight	X		X									X							X
Body temperature	X		X									X							X
Blood Pressure and Pulse Rate	X		X									X							X
ECG evaluation	X		X									X							X
Coagulation Panel[6]	X		X									X							X
Blood chemistry	X[7]		X	X[8,18]	X[8,18]	X[8,18]	X[8,18]	X[8,18]	X[8,18]	X[8,18]	X[9]	X	X[8]	X[8]	X[8]	X[8]	X[8]	X[8,18]	X
Hematology	X		X									X							X

Study Phase	Screening	Run-in	Treatment Period 1 / Washout / Period 2															EOS
Visit Numbers[1]	V1[5]	V2[5]	V3							V4	V5	V6[2]						V777
Visit Numbers			V7							V8	V9	V10						
Study Day(s)	-28 to -2	-14 to -1	1							2	7±2	12						43±2
Time (post-dose)	-	-	0h	1h	2h	4h	5h	6h	8h	0h	-	0h	1h	2h	4h	5h	6h	8h	-
Urinalysis	X		X									X							X
Drug dispensation			X																
Drug administration record[10]			X								X	X							
Stool Collection[11]			X[12]									X[12]							X
Patient diary	X	X	X									X							X
Corporate Confidential Information	X	X[19]	X									X							X
			X	X[18]	X[18]	X[18]	X[18]	X[18]	X[18]	X[18]		X	X	X	X	X	X	X[18]	
			X									X							
PK blood collection			X	X[18]	X[18]	X[18]	X[18]	X[18]	X[18]	X[18]		X	X	X	X	X	X	X[18]	
Corporate Confidential Information			X[15]																
Corporate Confidential Information												X							
Adverse events	As required																		
Serious adverse events	As required																		
Concomitant therapies	As required																		
Comments																			
Study completion information																			X

[1] Visit structure given for internal programming purpose only
[2] Minimum 7 days and up to 28 days washout starting after last dose in period 1.
[3] Serum pregnancy test.
[4] Urine pregnancy test can be performed and results will be required before dosing. A positive urine pregnancy test should be confirmed with a serum pregnancy test.
[5] Visit 1 and visit 2 can be combined
[6] Panel includes Activated partial thromboplastin time (aPTT), fibrinogen (Fbg), prothrombin time (PT), international normalized ratio (INR, transformed by PT), and thrombin time (TT)
[7] Alpha fetoprotein measured in screening visit only
[8] Measure total bile acids only.
[9] LFT assessments (GGT, ALP, AST, ALT). Blood sample can be collected at home or work per investigators discretions.
[10] Patients shall be dosed till Day 14 in each period.
[11] Stool analysis may include fecal occult blood, microbiome and bile acids. Samples will be collected once on the day of assessment. All bowel movements will be recorded daily with the exact time, daily frequency and consistency (using the Bristol stool chart) in the patient diary. Diary will also capture food intake.
[12] Morning stool sample preferable collected before dosing or within 2 hours of dosing.
[13] BM plasma will be collected to assess bile acid multiplex.

8.1 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

The date of signing of informed consent (and withdrawal, if later withdrawn) should be documented in the CRF.

Novartis will provide to investigators a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or Ethics Committee approval will be obtained.

The study includes an optional scintigraphic clonic transit assessment in a US center only which requires a separate signature if the patient agrees to participate. As part of this protocol only Investigators in US will present this option to the patient. The process of obtaining consent should be exactly the same as described above for the main informed consent.

A copy of the approved version of all consent forms must be provided to the Novartis monitor after IRB/IEC approval.

8.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data will be collected on all patients.

Relevant medical history/current medical conditions data includes data until signature of informed consent. Where possible, diagnoses and not symptoms will be recorded.

Investigators have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

8.2.1 Demography

Patient demographic and baseline characteristic data to be collected on all patients include: date of birth, age, sex, race, predominant ethnicity.

8.2.2 Medical history/current medical conditions

Relevant medical history and current medical conditions will be recorded on the CRF until signature of the informed consent.

Where possible, diagnoses and not symptoms will be recorded.

Any event or change in the subject's condition or health status occurring *prior to* informed consent will be reported in the Relevant medical history / Current medical conditions section of the CRF.

8.3 Efficacy / Pharmacodynamics

Pharmacodynamic assessments are specified below, with the methods for assessment and recording specified in the Site Operations Manual. Assessments will be performed/samples collected at the timepoint(s) defined in the Assessment Schedule.

In order to better define the PD profile, the timing of the sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

8.3.1 Patient-Reported Outcome - IBS-QOL

The IBS-QOL is a self-reported quality-of-life measure specific to Irritable Bowel Syndrome (IBS) that can be used to assess the impact of IBS and its treatment. The IBS-QOL was developed using a needs based model. The IBS-QOL consists of 34 items, each with a five-point response scale.

The individual responses to the 34 items are summed and averaged for a total score and then transformed to a 0-100 scale for ease of interpretation with higher scores indicating better IBS specific quality of life. There are also eight subscale scores for the IBS-QOL (Dysphoria, Interference with Activity, Body Image, Health Worry, Food Avoidance, Social Reaction, Sexual, Relationships).

The IBS-QOL is designed to be self-administered, and takes an average of 10 minutes to complete. The IBS-QOL can be interviewer-administered if necessary.

The transformation formula used for the IBS-QOL total and scale scores is:

Score = (The sum of the items - lowest possible score/Possible raw score range)*100

8.3.2 Patient diary

Patient diary will be used to capture stool frequency, consistency and rescue medication. Intake of loperamide or equivalent will be allowed, but will be recorded in the concomitant medication section of the CRF.

8.4 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the Site Operations Manual, with the Assessment Schedule detailing when each assessment is to be performed.

8.4.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed.

Information for all physical examinations must be included in the source documentation at the study site and will not be recorded the CRF. Significant findings that are present prior to informed consent are included in the Relevant Medical History CRF. Significant findings observed after informed consent signature which meet the definition of an Adverse Event must be appropriately recorded on the Adverse Event CRF.

8.4.2 Vital signs

8.4.2.1 Blood Pressure and Pulse Rate

Vital signs include blood pressure (BP) and pulse measurements. After the patient has been supine for approximately 5 minutes systolic and diastolic BP will be measured once using a validated BP device, with an appropriately sized cuff.

The CRF should contain the BP measurements.

8.4.2.2 Body temperature

Oral body temperature will be obtained at specified times during the study.

8.4.3 Height and weight

8.4.3.1 Body height

Height in centimeters (cm) in indoor clothing, but without shoes) will be measured.

8.4.3.2 Body weight

Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured.

Body mass index (BMI) will be calculated using the following formula:

- BMI = Body weight (kg) / [Height (m)]^2

8.4.4 Laboratory evaluations

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

8.4.4.1 Hematology

Basophils, Eosinophils, Hematocrit, Hemoglobin, Lymphocytes, Monocytes, Neutrophils, Platelets, Erythrocytes, Leukocytes

8.4.4.2 Blood chemistry

Alkaline Phosphatase, Alanine Aminotransferase, Amylase, Aspartate Aminotransferase, Creatine Kinase, Gamma Glutamyl Transferase, Lactate Dehydrogenase, Triacylglycerol Lipase, Triglycerides, Urea, Albumin, Bicarbonate, Bilirubin, Blood Urea Nitrogen, Calcium, Cholesterol, Chloride, Creatinine, Glucose, Potassium, Magnesium, Phosphate, Protein, Sodium, HDL Cholesterol, LDL Cholesterol, Alpha Fetoprotein, Urate, Cholesterol/HDL-Cholesterol Ratio, Direct Bilirubin, Indirect Bilirubin, Lipids

8.4.4.3 Urinalysis

A midstream urine sample (approx. 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments. Required assessments are specified in the protocol.

Casts, Occult Blood, pH, Specific Gravity, Ketones, Glucose, Protein, Bilirubin, Nitrite, Leukocytes, Sodium/Potassium Ratio, Appearance, Color, Osmolality, Turbidity

8.4.5 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have regular urine pregnancy tests during the study. A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative.

8.4.5.1 Pregnancy test

Pregnancy tests are required of all female patients regardless of reported reproductive/menopausal status. Follicle stimulating hormone will be estimated for postmenopausal females at screening only.

Serum pregnancy tests will be performed at screening and initial baseline. Urine pregnancy tests may be used at other visits. A positive urine pregnancy test should be confirmed with a serum pregnancy test.

When performed at screening and baseline, the result of this test must be received before the patient may be dosed.

8.4.6 Coagulation Panel

A blood sample will be taken to analyze the following parameters: PT, INR, APTT and TT.

8.4.7 ECG evaluation

A standard 12-lead ECG will be performed with the patient in a supine position. Interpretation of the tracing must be made by a qualified physician and documented on the ECG and in the ECG section of the CRF. Each ECG tracing should be labeled with the

- study number
- patient initials
- patient number
- date

and kept in the source documents at the study site. Clinically significant abnormalities should be recorded on the relevant medical history CRF page prior to informed consent signature and on the Adverse Events page thereafter. Clinically significant findings must be discussed with the sponsor.

The CRF will contain:

- date and time of ECG
- heart rate
- PR interval
- QT interval
- QTcF interval
- QRS duration

Original ECG tracings, appropriately signed, will be archived at study site.

8.5 Pharmacokinetics

A complete schedule of blood sampling for pharmacokinetics (including sampling time as sampling volumes) can be found in the blood log tables, while explicit details related to PK blood collection and processing, labeling, and shipment instructions, see Site Operations Manual (SOM).

All samples will be given a unique sample number (as listed in the SOM). The actual sample collection date and time will be entered on the PK blood collection page of the eCRF. Sampling problems will be noted in the Comments page of the eCRFs.

8.5.1 PK blood collection

For details on PK blood collection and processing, labeling, and shipment instructions, see laboratory manual.

The exact clock time of dosing, as well as actual sample collection date and time will be entered on the PK blood collection summary page of the CRF. Sampling problems will be noted in the relevant field of the CRF.

8.6 Other assessments

9 Safety monitoring

9.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for liver related events are included in Section 9.3.

Adverse events must be recorded on the Adverse Events CRF for patients that pass screening and enter into the study. The adverse events should be reported according to the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. the Common Toxicity Criteria (CTC) AE grade (version 4) - if CTC-AE grading does not exist for an adverse event, use:
   - 1=mild,
   - 2=moderate,
   - 3=severe
   - 4=life threatening.

CTC-AE grade 5 (death) is not used, but is collected in other CRFs (e.g. Study Completion, Death/Survival).

2. its relationship to the study treatment (no/yes), ,
3. its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
4. whether it constitutes a serious adverse event (SAE) See Section 9.2 for definition of SAE
5. action taken regarding [study] treatment(select as appropriate).

All adverse events should be treated appropriately. Treatment may include one or more of the following:

- no action taken (i.e. further observation only)
- study treatment dosage adjusted/temporarily interrupted
- study treatment permanently discontinued due to this adverse event
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged

6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or Core Data Sheet (for marketed drugs) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

The investigator should also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in bile acid malabsorption diarrhea
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug

- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- social reasons and respite care in the absence of any deterioration in the patient's general condition

- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All AEs (serious and non-serious) are captured on the CRF, SAEs also require individual reporting to DS&E as per Section 9.2.2.

9.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis within 24 hours of learning of its occurrence as described below. Any SAEs experienced after this should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (either initial or follow up information*)* is collected and recorded on the paper Serious Adverse Event Report Form. The investigator must assess the relationship to each specific component of study treatment (if study treatment consists of several drugs) complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department, notifying the Clinical Trial Leader. Contact information is listed in the Site Operations Manual.

The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the source documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

SAEs (initial and follow-up) that are recorded electronically in the Electronic Data Capture system should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing SAE. These data will automatically be submitted to Novartis Drug Safety & Epidemiology immediately after investigator signature or 24 hours after entry, whichever occurs first. Study site personnel must also inform the Clinical Trial Leader.

Follow- up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

9.3 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study:

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Table 9-1 and Table 9-2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event should be followed up by the investigator or designated personal at the trial site, as summarized below and detailed in in Table 9-2.

For the liver laboratory trigger:

- Repeating the LFT within the next week to confirm elevation.

These LFT repeats should be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory should then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event should be reported on the Liver CRF pages.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug (refer to Section 7.1, if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g. disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed should be recorded as appropriate in the CRF, including the liver event overview CRF pages.

Table 9-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
Liver laboratory triggers	3 x ULN < ALT / AST ≤ 5 x ULN 1.5 x ULN < TBL ≤2 x ULN
Liver events	ALT or AST > 5 × ULN
	ALP > 2 × ULN (in the absence of known bone pathology)
	TBL > 2 × ULN (in the absence of known Gilbert syndrome)
	ALT or AST > 3 × ULN and INR > 1.5
	Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)
	Any clinical event of jaundice (or equivalent term)
	ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	Any adverse event potentially indicative of a liver toxicity *

Table 9-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study drug immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study drug immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit

Criteria	Actions required	Follow-up monitoring
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study drug immediately • Hospitalize the patient • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study drug interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

9.4 Pregnancy reporting

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The study drug must be discontinued, though the patient may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The patient may continue all other protocol assessments. Pregnancy must be recorded on a Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on an SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

9.5 Early phase safety monitoring

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

10 Data review and database management

10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the eligibility criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the Site Operations Manual and assessment schedule and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

10.3 Database management and quality control

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

CRO working on behalf of Novartis review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to CRO working on behalf of Novartis who will make the correction to the database.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to a designated CRO.

Diary data will be entered into an electronic diary by the patient. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to a designated CRO. In case the electronic diary is not used then the patients will enter data in paper diary. These diaries will be handed over to site and site personnel will enter data in the clinical database or send them to the designated CRO to enter data in the clinical database.

At the conclusion of a non-IRT study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis.

The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Global Head of Clinical Information Sciences and the Clinical Franchise Head.

DNA samples:

To maximize confidentiality, all samples and the information associated with the samples will be double-coded to prevent the exposure of the patient's information and identity. This double-coding process allows Novartis to go back and destroy the sample at the patient's request. In addition, sample information is stored in one secured database while genetic data is stored in an independent secured database.

The use of DNA to search for biomarkers of disease and drug action is exploratory. Any results from this DNA study will not be placed in the patient's medical records.

10.4 Data Monitoring Committee

A Data Monitoring Committee (DMC) has been assembled for this compound to monitor safety data. This committee is comprised of Novartis personnel not directly involved with the study and include one or more Novartis physician with expertise in the indication. The DMC will convene as outlined in the DMC Charter to review an event or combination of events that fulfil the study stopping rules defined in Section 7.4.

In addition, adverse events, including clinical laboratory data will be continuously reviewed by the Novartis Clinical trial team, including the study physician, on an ongoing basis as data become available from the Electronic Data Capture system.

10.5 Adjudication Committee

Not required.

11 Data analysis

11.1 Analysis sets

For all analysis sets, patients will be analyzed according to the study treatment(s) received.

The safety analysis set will include all patients that received any study drug.

The PK analysis set will include all patients with available PK data and no protocol deviations with relevant impact on PK data.

The PD analysis set will include all patients with available PD data and no protocol deviations with relevant impact on PD data.

11.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment sequence (drug followed by placebo or vice-versa) and patient. Summary statistics will be provided for all patients, as well as for each treatment sequence.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment sequence and patient.

11.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment sequence and patient.

11.4 Analysis of the primary variable(s)

11.4.1 Variable(s)

The primary analysis variables are: a) stool frequency, b) and stool form assessed by the Bristol stool chart.

11.4.2 Statistical model, hypothesis, and method of analysis

A repeated measures analysis will be done for the two-dimensional endpoint: weekly stool frequency and the corresponding average stool form. The analysis will include fixed effects for sequence (Drug/Placebo or Placebo/Drug), Treatment (Week 1 Drug, Week 2 Drug, Week 1 Placebo or Week 2 Placebo), and period (1 or 2). The model will assume an arbitrary 2 by 2 covariance matrix for the two-dimensional endpoint (frequency, form) and a compound symmetry covariance matrix for each individual endpoint. Point estimates of the weekly & biweekly treatment effect on stool frequency and form will be reported together with 95% simultaneous confidence intervals (confidence ellipsoids).

Baseline weekly stool frequency and the corresponding average stool form will be analyzed similarly using the method described above to assess unequal carryover effects.

11.4.3 Handling of missing values/censoring/discontinuations

Missing values will be assumed missing at random. No imputation of missing values will be done for any analyses.

11.5 Analysis of secondary and exploratory variables

The number and percentage of subjects using loperamide will be tabulated by treatment. Total weekly loperamide use (in mg) will be summarized by treatment and visit (including baseline). The stool index, calculated as [weekly stool frequency*mean stool form]+loperamide use [weekly mg*3], will also be summarized and analyzed using a linear mixed effects model including sequence, period and treatment as fixed effects and subject nested within sequence as a random effect.

11.5.2 Safety

Vital signs

All vital signs data will be listed by treatment sequence, patient, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

ECG evaluations

All ECG data will be listed by treatment sequence, patient and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment sequence, patient, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time. Baselines will be the last available measurement in each treatment period post washout and prior to dosing.

Adverse events

All information obtained on adverse events will be displayed by treatment and patient.

The number and percentage of patients with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. An adverse event starting in one period and continuing into the next period is counted only in the onset period. A patient with multiple adverse events within a body system and treatment period is only counted once towards the total of this body system and treatment.

11.5.3 Pharmacokinetics

For standard pharmacokinetic abbreviations and definitions see the list provided at the beginning of this protocol.

All patients with at least one period of evaluable pharmacokinetic (PK) parameter data will be included in the pharmacokinetic data analysis.

The following pharmacokinetic parameters and other appropriate parameters may be determined for LJN452:

AUClast, AUCtau, Cmax, Cmin, Cav,ss, Tmax, CL/F, Racc (accumulation ratio = AUCtau,ss/AUCtau,day 1) may be assessed from plasma concentration-time data.

non-compartmental method(s) with Pheonix (Version 6.3 or higher).

11.5.4 Pharmacokinetic / pharmacodynamic interactions

The relationship between PK and key PD parameters (for example, change in stool frequency) may be explored, if needed.

11.5.5 Other assessments

11.6 Sample size calculation

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11.7 Power for analysis of key secondary variables

No assessment of power for the secondary objectives has been done.

11.8 Interim analyses

Corporate Confidential Information

12 Ethical considerations

12.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, patient recruitment procedures (e.g. advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Novartis around the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

12.3 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators must apply due diligence to avoid protocol deviations. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

13.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the Health Authorities and the reviewing IRB/IEC are subsequently notified by protocol amendment.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the CTL should be informed and (serious) adverse event reporting requirements (Section 9) followed as appropriate.

14 References

Available upon request.

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Goodwin B, Jones SA, Price RR, et al. (2000) A regulatory cascade of the nuclear receptors FXR, SHP-1, and LRH-1 represses bile acid biosynthesis. Mol Cell; 517-26.

Pattni SS, Brydon WG, Dew T, et al. (2012) Fibroblast growth factor 19 and 7α-hydroxy-4-cholesten-3-one in the diagnosis of patients with possible bile acid diarrhea. Clin Transl Gastroenterol; e18.

Walters JR (2014) Bile acid diarrhoea and FGF19: new views on diagnosis, pathogenesis and therapy. Nat Rev Gastroenterol Hepatol; 426-34.

Walters JR, Johnston IM, Nolan JD, et al. (2015) The response of patients with bile acid diarrhoea to the farnesoid X receptor agonist obeticholic acid. Aliment. Pharmacol. Ther; 54-64.