Protocol

A multicentric, open-label, non-randomized study to evaluate the pharmacokinetic, safety and tolerability of ITF2357 given as an oral single 50 mg dose in participants with chronic hepatic impairment relative to matched participants with normal hepatic function.

NCT number: NCT06736223

Unique protocol ID: ITF/2357/60

Version Date: 24 March 2025

ITALFARMACO SpA

with its registered office at
Viale Fulvio Testi 330, 20126 Milano (MI), Italy
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Via dei Lavoratori 54, 20092 Cinisello Balsamo (MI), Italy

Clinical Trial Protocol No. ITF/2357/60

European Union Clinical Trial Number: 2024-513577-43-00

IND Number: 126598

A multicentric, open-label, non-randomized study to evaluate the pharmacokinetic, safety and tolerability of ITF2357 given as an oral single 50 mg dose in participants with chronic hepatic impairment relative to matched participants with normal hepatic function.

Investigational Medicinal Product Code:	ITF2357
Trial Phase:	Phase I
Coordinating Principal Investigator:	**Sponsor:**
[redacted]	[redacted]
Biotrial	Italfarmaco SpA
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France	Italy
Version: 2.0	Date of document: 24 MAR 2025
Amendment Number: 1	Date of amended document: 07 NOV 2024

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Protocol Approval Form and Sponsor Signatories:

The protocol entitled "A multicentric, open-label, non-randomized study to evaluate the pharmacokinetic, safety and tolerability of ITF2357 given as an oral single 50 mg dose in participants with chronic hepatic impairment relative to matched participants with normal hepatic function", version 2.0 dated 24 MAR 2025 has been approved for submission to the Ethics Committee and Regulatory Authorities.

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24-Mar-2025 | 4:55 PM CE

Statistical review:

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24-Mar-2025 | 5:12 PM CE

Revised and approved by:

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Clinical R&D Director *Signature* *Date*
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Fax: [redacted]
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24-Mar-2025 | 5:14 PM CE

Principal Investigator's Approval

I, the undersigned, have examined this protocol and agree to conduct this trial according to this protocol, to comply with its requirements, subject to ethical and safety considerations, as set out in this protocol. I am aware of, and I will comply with the International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP), the Declaration of Helsinki 1964 (latest revision 2024) and all other laws and regulations on the use of investigational medicinal products.

Coordinating/Principal investigator: **Date / Signature:**

24-mars-2025 | 4:46 PM CET

[redacted]

Biotrial

[redacted]

SERIOUS ADVERSE EVENT (SAE) REPORTING

For reporting of serious adverse events, Investigators must provide all completed pages of the SAE form within 24 hours. The SAE form will be available for download in the electronic Case Report Form (as described in Section 8.4.6.), and it is to be completed manually and uploaded in a secure folder (or sent via fax as back-up method), using the contacts below:

Pharmacovigilance	Biotrial Pharmacovigilance Unit
Telephone contact	[redacted]
PV e-mail address	[redacted]

Table of Contents

Protocol Approval Form and Sponsor Signatories: 2
Principal Investigator's Approval 3
Table of Contents 5
1 PROTOCOL SUMMARY 10
1.1 Protocol Synopsis 10
1.2 Study Schema 25
1.3 Schedule of Activities (SOA) 26
2 INTRODUCTION 29
2.1 Purpose of Trial 29
2.1.1 Background 29
2.1.2 Pharmacology 29
2.1.3 Non-clinical metabolism and pharmacokinetics 29
2.1.4 Toxicology 30
2.1.5 Previous human experience 30
2.1.6 Safety and tolerability 32
2.1.7 Trial rationale 32
2.1.8 Dose rationale 33
2.2 Summary of Benefits and Risks 33
2.3 Mitigation Strategy 34
3 TRIAL OBJECTIVES AND ENDPOINTS 35
3.1 Primary/Secondary Objectives and Associated Endpoints 35
4 TRIAL DESIGN 36
4.1 Description of Study Design 36
4.2 Rationale for Trial Design 36
4.3 Access to Investigational Medicinal Product After End of Study 36
4.4 Start of Study and End of Study 37
5 STUDY POPULATION 38
5.1 Participants with HI 38
5.1.1 Inclusion Criteria for Participants with HI 38
5.1.2 Exclusion Criteria for Participants with HI 39
5.2 Matched participants with normal hepatic function 41
5.2.1 Inclusion Criteria for Matched participants with normal hepatic function 41

5.2.2 Exclusion Criteria for Matched participants with normal hepatic function 42
5.3 Lifestyle Considerations....44
5.3.1 Meals and Dietary Restrictions....44
5.3.2 Caffeine, Alcohol, Tobacco, and Other Habits....44
5.3.3 Physical Activity....44
5.4 Screen Failures....44
6 INVESTIGATIONAL MEDICINAL PRODUCTS AND CONCOMITANT THERAPY....45
6.1 Description of Investigational Medicinal Products....45
6.2 Rationale for Investigational Medicinal Products....46
6.3 Dosing and Administration....46
6.3.1 Investigational Medicinal Product Dose Modification....46
6.4 Treatment of Overdose....47
6.5 Preparation, Handling, Storage and Accountability....47
6.5.1 Preparation of Investigational Medicinal Product....47
6.5.2 Handling and Storage of Investigational Medicinal Product....47
6.5.3 Accountability of Investigational Medicinal Product....47
6.6 Participant Assignment, Randomization and Blinding....48
6.6.1 Participant Assignment....48
6.6.2 Randomization....48
6.6.3 Blinding and Unblinding....48
6.6.4 Emergency Unblinding....49
6.7 Investigational Medicinal Product Compliance....49
6.8 Concomitant Therapy....49
6.8.1 Prohibited Concomitant Therapy....49
6.8.2 Permitted Concomitant Therapy....49
6.8.3 Rescue Therapy....50
6.8.4 Other Therapy....50
7 DISCONTINUATION OF INVESTIGATIONAL MEDICINAL PRODUCTS AND PARTICIPANT WITHDRAWAL FROM TRIAL....51
7.1 Discontinuation of Investigational Medicinal Products....51
7.1.1 Criteria for Permanent Discontinuation of Investigational Medicinal Products....51
7.1.2 Temporary Discontinuation or Interruption of Investigational Medicinal Products....51

7.1.3 Rechallenge....51
7.2 Participant Withdrawal from the Trial....51
7.3 Lost to Follow-Up....51
7.4 Trial Stopping Rules....52
7.5 Replacement of participants....52
7.6 Withdrawn Participant Data Collection....53
8 TRIAL ASSESSMENTS AND PROCEDURES....54
8.1 Screening/Baseline Assessments and Procedures....54
8.2 Efficacy Assessments and Procedures....54
8.3 Safety Assessments and Procedures....54
8.3.1 Physical Examination....54
8.3.2 Vital Signs....54
8.3.3 Electrocardiograms....55
8.3.4 Clinical Laboratory Assessments....55
8.3.5 Pregnancy test and Hormone test....56
8.3.6 Special Assessments....57
8.4 Adverse Events and Serious Adverse Events....57
8.4.1 Definitions of AE and SAE....57
8.4.2 Time Period and Frequency for Collecting AE and SAE Information..57
8.4.3 Identifying AEs and SAEs....57
8.4.4 Recording of AEs and SAEs....57
8.4.5 Follow-up of AEs and SAEs....58
8.4.6 Reporting of SAEs....58
8.4.7 Regulatory Reporting Requirements for SAEs....59
8.4.8 Serious and Unexpected Adverse Reaction Reporting....61
8.5 Pregnancy and Postpartum Information....61
8.5.1 Participants Who Become Pregnant During the Trial....61
8.5.2 Participants Whose Partners Become Pregnant....61
8.6 Pharmacokinetics....62
8.6.1 Pharmacokinetic Assessment Methods and Timing....62
8.6.2 Sample handling and labelling....62
8.6.3 Sample shipment and storage....62
8.6.4 Bioanalytical method....62
8.6.5 Pharmacokinetic Criteria....62
9 STATISTICAL CONSIDERATIONS....64

9.1 Analysis Sets....64
9.2 Analyses Supporting the Objective(s)....64
9.3 Pharmacokinetics Analyses....65
9.4 Safety Analyses....65
9.5 Sample Size Determination....66
9.6 Protocol Deviations....66
10 GENERAL CONSIDERATIONS: REGULATORY, ETHICAL, AND TRIAL OVERSIGHT....67
10.1 Regulatory and Ethical Considerations....67
10.2 Committees....70
10.3 Informed Consent Process....70
10.4 Rescreening....70
10.5 Data Protection....71
10.6 Early Site Closure or Trial Termination....71
11 GENERAL CONSIDERATIONS: QUALITY ASSURANCE....72
11.1 Data Quality Assurance (QA)....72
11.2 Source Data....73
11.2.1 Data collection....73
11.2.2 Data Handling....73
11.2.3 Data coding....73
11.2.4 Data validation....74
12 APPENDIX: DRUGS WITH KNOWN RISK OF QT PROLONGATION AND TORSADE DE POINTES....75
13 APPENDIX: DRUGS KNOWN TO BE A SUBSTRATE OF CYP3A4....78
14 APPENDIX: DRUGS KNOWN TO BE A SUBSTRATE OF ORGANIC CATION TRANSPORTER 2 (OCT2) TRANSPORTER....79
15 APPENDIX: DRUGS KNOWN TO BE P-GLYCOPROTEIN (P-GP) OR BREAST CANCER-RESISTANCE PROTEIN (BCRP) INDUCERS OR INHIBITORS....80
15.1 Inhibitors/Inducers of P-gp....80
15.2 Inhibitors/Inducers of BCRP....81
16 APPENDIX: DRUGS KNOWN TO BE SUBSTRATES OF P-GP....82
17 APPENDIX: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS – DEFINITIONS, SEVERITY, AND CAUSALITY....84
17.1 Further Details and Clarifications on the AE Definition....84
17.1.1 Adverse Events....84
17.1.2 Adverse Drug Reactions....84

17.1.3 Treatment-Emergent Adverse Events and Repetitions of Adverse Events 84
17.1.4 Expected and unexpected adverse events 85
17.1.5 Adverse Event of Special Interest 85
17.2 Further Details and Clarifications on the SAE Definition 85
17.3 Severity 86
17.4 Causality 87
18 APPENDIX: DEFINITIONS AND SUPPORTING OPERATIONAL DETAILS 88
18.1 Contraception and Pregnancy 88
18.2 Testing 88
18.2.1 Definitions Related to Childbearing Potential 88
18.2.2 Contraception 88
18.2.3 Pregnancy Testing 89
18.3 Normal Ranges for Vital Signs and ECG Parameters 89
18.4 Time Windows for Procedures 89
18.5 Special Events (Overdose, Medication Error, Misuse and Abuse) 90
18.6 Country/Region-Specific Differences 90
18.7 Prior Protocol Amendments 90
18.8 Data Processing and Archiving of Documents and Data Relative to the Research 90
18.8.1 Confidentiality and Agreements 91
18.8.2 Report and Publication 91
19 APPENDIX: GLOSSARY OF TERMS 93
20 APPENDIX: REFERENCES 98

1 PROTOCOL SUMMARY

1.1 Protocol Synopsis

Name of Company:

ITALFARMACO SpA
Via dei Lavoratori, 54
20092 Cinisello Balsamo
Milano, Italy

Compound Number & Active ingredient: ITF2357 (INNM Givinostat hydrochloride Monohydrate)

Compound Name: NA

Title of Clinical Trial:

A multicentric, open-label, non-randomized study to evaluate the pharmacokinetic, safety and tolerability of ITF2357 given as an oral single 50 mg dose in participants with chronic hepatic impairment relative to matched participants with normal hepatic function.

Coordinating Principal Investigator:

Hakim Charfi, MD

Site (s) Distribution:

The study will be conducted in Europe:

- **Biotrial**, 7-9 rue Jean-Louis Bertrand, CS 34246, 35042 Rennes Cedex, France.
- **MC COMAC Medical Ltd**, with up to 2 locations: 13 Urvich, 3rd floor, Sofia, 1612, Bulgaria, and 3 Sv. Georgi Sofiyski Str., Sofia 1606, Bulgaria.

Purpose of Trial:

ITF2357 (givinostat hydrochloride monohydrate) is an orally active hydroxamic acid derivative that belongs to the pharmacological class of histone deacetylase (HDAC) inhibitors. The compound was initially developed for its anti-inflammatory properties but, in addition, it showed striking anti-tumor activity and prevented muscle degeneration in muscular dystrophies. It has been studied in 25 sponsored clinical studies, including 5 in healthy participants (up to 600 mg single dose and up to 200 mg/day for 7 days).

It is currently developed in two Muscular Dystrophies (Duchenne Muscular Dystrophy [DMD] and Becker Muscular Dystrophy [BMD]) and in a Chronic Myelo-Proliferative Neoplasm (Polycythemia Vera [PV]) at doses up to 70 mg b.i.d. in DMD and up to [redacted] in PV. Givinostat has been approved by FDA (DUVYZAT™) for the treatment of DMD in patients six years of age and older.

In humans, ITF2357 is extensively metabolized, to 4 major inactive metabolites: ITF2374 (hydroxamic acid reduction), ITF2375 (hydroxamic acid hydrolysis), and ITF2440 and ITF2563 (both from oxidative cleavage). Thus, metabolic hepatic clearance represents a significant part of the total clearance of ITF2357 and decreased metabolism of ITF2357 in patients with hepatic impairment cannot be excluded.

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20092 Cinisello Balsamo
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Compound Number & Active ingredient: ITF2357 (INNM Givinostat hydrochloride Monohydrate)

Compound Name: NA

Purpose of Trial (continued):

Moreover, during a clinical study evaluating ITF2357 potential for QTc prolongation (study ITF/2357/54), the time profile of QTc interval suggests that the prolongation could be caused by the metabolites rather than the parent compound. This is because the T_{max} for ITF2357 is around 2 hours post-dose but the largest mean QTc effect occurred around 5 hours post-dose, which is consistent with T_{max} of metabolites ITF2374 and/or ITF2375. Therefore, the exposures of the metabolites ITF2374 and ITF2375 are investigated along with the parent compound in subjects with liver impairment.

The binding of ITF2357 in human plasma was 95.9 ± 1.3% and independent of plasma concentrations. Similarly, ITF2374 and ITF2375 metabolites have a high plasma protein binding, 92.5% and 98.4%, respectively. While ITF2440 and ITF2563 metabolites have a low protein binding, 48.2 % and 13.3%, respectively. Blood to plasma ratio of ITF2357 was slightly above 1 in humans (human RB/P = 1.3) suggesting some partitioning in the red blood cells. Thus, free fraction of ITF2357, ITF2374 and ITF2375 may be modified in patients with hepatic impairment (HI), leading to variation in exposure.

In this context, evaluation of the effect of mild and moderate HI on the pharmacokinetics (PK) of ITF2357 and its metabolites ITF2374 and ITF2375 is deemed necessary. ITF2357 may be administered to patients with varying degrees of HI. The results of this study will be used to make recommendations for potential dosage adjustments of ITF2357 in these patients.

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Via dei Lavoratori, 54
20092 Cinisello Balsamo
Milano, Italy

Compound Number & Active ingredient: ITF2357 (INNM Givinostat hydrochloride Monohydrate)

Compound Name: NA

Primary and Secondary Objective(s)

	Objectives	Endpoints
Primary	To evaluate the effect of mild and moderate HI on the PK of ITF2357 in comparison with matched participants with normal hepatic function, after a single oral dose of 50 mg ITF2357 (*).	For ITF2357: • maximum plasma concentration observed (C_{max}) • area under the plasma concentration versus time curve calculated using the linear-log trapezoidal method from time zero to the real time t_{last} (AUC_{last}) • area under the plasma concentration versus time curve extrapolated to infinity (AUC_{0-inf}).
Secondary	To evaluate the effect of mild and moderate HI on additional PK parameters of ITF2357 in comparison with matched participants with normal hepatic function, after a single oral dose of 50 mg ITF2357.	For ITF2357: • time to reach C_{max} (t_{max}) • apparent terminal half-life ($t_{1/2}$) • apparent total plasma clearance from plasma (CL/F) • apparent volume of distribution (Vz/F).

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20092 Cinisello Balsamo
Milano, Italy

Compound Number & Active ingredient: ITF2357 (INNM Givinostat hydrochloride Monohydrate)

Compound Name: NA

Primary and Secondary Objective(s) (continued)

	Objectives	Endpoints
Secondary (continued)	To evaluate the effect of mild and moderate HI on the pharmacokinetic of the 2 metabolites of ITF2357: ITF2374 and ITF2375 in comparison with matched participants with normal hepatic function after a single oral dose of 50 mg ITF2357.	For metabolites: ITF2374 and ITF2375 • maximum plasma concentration observed (C_{max}) • area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to the real time t_{last} (AUC_{last}) • area under the plasma concentration versus time curve extrapolated to infinity (AUC_{0-inf}) • time to reach C_{max} (t_{max}) • apparent terminal half-life ($t_{1/2}$).

	To assess the effect of mild and moderate HI on the free fraction of ITF2357, and its metabolites with high protein binding ITF2374 and ITF2375 in comparison with matched participants with normal hepatic function.	For ITF2357and metabolites ITF2374 and ITF2375
		• Unbound fraction (fu)
		• Unbound area under the plasma concentration versus time curve (AUC_u)
		  • $AUC_{last,u}$
		  • $AUC_{0-inf,u}$
		• Unbound maximum plasma concentration observed ($C_{max,u}$)
		For ITF2357 only:
		• Unbound apparent total plasma clearance (CL/F_u)
		• Unbound apparent volume of distribution (Vz/F_u).

	To assess the safety and tolerability of ITF2357 given as a single oral dose of 50 mg in participants with mild and moderate HI and in matched participants with normal hepatic function.	Laboratory, electrocardiogram (ECG) parameters, vital signs and physical examination parameters, and adverse events (AEs)

(*) *Dose of the Investigational Medicinal Product (IMP) is expressed as givinostat hydrochloride monohydrate*.

Name of Company:

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Milano, Italy

Compound Number & Active ingredient: ITF2357 (INNM Givinostat hydrochloride Monohydrate)

Compound Name: NA

Overall Design:

Phase I, open-label non-randomized, single-period single-dose study, which will include:

- Participants with mild HI
- Participants with moderate HI
- Participants with normal hepatic function (control group)

Each participant will go through:

- A **screening** period from Day (D)-28 to D-2
- One 6-day/5-night **inpatient period** (from D-1 morning to D5 morning)
- Some baseline assessments will be conducted on D-1 and on D1 pre-dose
    - A single dose administration will be administered on D1
    - Discharge on D5 morning
- An **end-of-study** (EOS) evaluation to be done on D10 (±1 day) or to be organized as soon as possible in case of early withdrawal.

Details of the timing of each clinical visit and the assessments to be performed at each visit are summarized in the Schedule Of Activities (SOA).

Sample Size Rationale:

Sample size for this study was based upon empirical considerations and no sample size calculation was performed. However, 8 participants per group, is considered sufficient to provide evaluable data and is consistent with the Food and Drug Administration (FDA) recommendation in its Guidance on PK in patients with impaired hepatic function (May 2003).

Number of Participants:

The total number of participants to be enrolled in the study is 24 subjects:

- 16 hepatically impaired participants, 8 Child-Pugh class A (mild) & 8 Child-Pugh class B (moderate)
- 8 participants with normal hepatic function (control group/matched healthy participants).

Matching will be 1:1 between a moderate hepatic impairment patient and a healthy participant. To the extent possible, this control group should be like the patient's group with respect to weight (±10% of weight at screening).

If feasible and to be able to compare the groups, at least 3 males and 3 females should be included in each group (mild HI, moderate HI and healthy participants).

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Milano, Italy

Compound Number & Active ingredient: ITF2357 (INNM Givinostat hydrochloride Monohydrate)

Compound Name: NA

Number of Participants (continued):

A participant who prematurely ends the study may be replaced, to have a total of 24 evaluable PK profiles. The decision for replacement will be taken in common agreement between the Investigator and the Sponsor.

Determination of hepatic impairment:

Subjects with hepatic impairment will be categorized using the Child-Pugh score for hepatic impairment, as follows, during the screening period:

- Class A (mild): Child-Pugh score 5 to 6 points
- Class B (moderate): Child-Pugh score 7 to 9 points.

Duration of Treatment for each participant:

The duration of each participant's treatment is described in the Overall Design section.

For further information, refer to Study Schema in Section 1.2.

Duration of Trial Participation for each participant:

The duration of study participation by participant will be of 38 days maximum, including:

Details of the timing of each clinical visit and the assessments to be performed at each visit are summarized in the Schedule Of Activities (SOA).

For further information, refer to Study Schema in Section 1.2.

Treatment, dose and mode of administration:

The Investigational Medicinal Product (IMP) ITF2357 will be administered as a single oral dose and in fasting conditions, after an overnight fast of at least 10 hours.

Treatment / Pharmaceutical form / Dose Strength	Dose	Mode of administration
ITF2357, oral suspension at concentration of 10 mg/mL	50 mg*	5 mL orally

**Dose of the IMP is expressed as givinostat hydrochloride monohydrate.*

Inclusion Criteria for Participants with HI

To be eligible to participate in this trial, an individual must meet all the following criteria:

1. Male or female participants, between 18 and 75 years of age, inclusive
2. Body weight between 60.0 and 110.0 kg, inclusive if male, and between 50.0 and 100.0 kg, inclusive if female, body mass index (BMI) between 18.00 and 34.99 kg/m^2, inclusive
3. Stable chronic liver disease assessed by medical history, physical examination, laboratory values
4. Vital signs after 10 minutes resting in supine position within the following range [or if out of range, considered not clinically significant (NCS) by the Investigator]:

   95 mmHg < systolic blood pressure (SBP) < 180 mmHg
   45 mmHg < diastolic blood pressure (DBP) < 100 mmHg
   40 bpm < heart rate (HR) < 100 bpm
5. 12-lead ECG without clinically significant abnormality, in the judgment of the Investigator; in no circumstances should participants be enrolled with corrected QT according to Fridericia (QTcF) > 450 ms
6. Any confirmed clinically relevant abnormal laboratory test that, on Investigator's judgement, is inconsistent with the subject's status as a patient with hepatic impairment. However, renal function should be assessed using the estimated glomerular filtration rate (eGFR) calculated by the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula and should be strictly above 60 mL/min/1.73m².
7. Female participants who are not pregnant or nursing at Screening and Day −1, or who are not planning to become pregnant during study period and until 90 days after the IMP administration.
8. Female participants of non-childbearing potential, defined as one of the following:
   a. At least 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., appropriate age) and follicle-stimulating hormone (FSH) in the range for menopausal female confirmed by blood test according to current local standards at screening.
   b. Those with history of hysterectomy or surgical removal of both ovaries or bilateral tubal ligation performed at least 90 days prior to Screening.
9. Female participant of childbearing potential and male participant (if sexually active with a woman of childbearing potential and not sterile) and his partner must agree to use an adequate and highly effective method of contraception (according to Clinical Trials Coordination Group [CTCG] recommendations) during the study and for at least 90 days after the study drug administration for women and for men. Such methods include:
   a. combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation oral, intravaginal or transdermal.
   b. progestogen-only hormonal contraception associated with inhibition of ovulation oral, injectable or implantable
   c. intrauterine device (IUD)
   d. intrauterine hormone-releasing system (IUS)
   e. bilateral tubal occlusion
   f. vasectomized partner
   g. sexual abstinence (when in line with the preferred and usual subject's lifestyle).

   Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception.
10. Having given written informed consent prior to any procedure related to the study.
11. Covered by a health insurance system where applicable, and/or in compliance with the recommendations of the national laws in force relating to biomedical research.

Name of Company: ITALFARMACO SpA Via dei Lavoratori, 54 20092 Cinisello Balsamo Milano, Italy
Compound Number & Active ingredient: ITF2357 (INNM Givinostat hydrochloride Monohydrate)
Compound Name: NA
Inclusion Criteria for Participants with HI (continued) 12. Not under any administrative or legal supervision 13. For moderate HI cohort: Child-Pugh total score ranging from 7 to 9, inclusive. 14. For mild HI cohort: Child-Pugh total score ranging from 5 to 6, inclusive. 15. Male participants must agree not to donate sperm from inclusion up to 3 months after ITF2357 dosing.

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Milano, Italy

Compound Number & Active ingredient: ITF2357 (INNM Givinostat hydrochloride Monohydrate)

Compound Name: NA

Exclusion Criteria for Participants with HI

An individual who meets any of the following criteria will be excluded from participating in this trial:

1. Uncontrolled clinically relevant cardiovascular, pulmonary, gastrointestinal, metabolic, hematological, neurological, osteomuscular, articular, psychiatric, systemic, ocular, gynecological (if female), or infectious disease, or signs of acute illness
2. Hepatocarcinoma
3. Acute hepatitis
4. Hepatic encephalopathy grade 2, 3, and 4
5. Blood donation within 2 months before inclusion
6. Symptomatic postural hypotension, whatever the decrease in blood pressure, or asymptomatic postural hypotension defined as a decrease in SBP $\geq$ 30 mmHg within 3 minutes when changing from supine to standing position
7. Presence or history of drug hypersensitivity, or allergic disease, except seasonal rhinitis, diagnosed and treated by a physician
8. History or presence of regular use of recreational drugs or alcohol abuse (alcohol consumption more than 40 g per day on a regular basis) within 2 years before inclusion
9. Smoking more than 15 cigarettes or equivalent per day, unable to refrain from smoking over 5 cigarettes per day from D-1 and throughout the entire institutionalization (i.e., up to D5)
10. Excessive consumption of beverages with xanthine bases (more than 4 cups or glasses per day)
11. If female, pregnancy [defined as positive β-human choriogonadotropin (β-HCG) blood test] or breast-feeding
12. Any significant change in chronic treatment medication within 14 days before inclusion
13. Consumption of PgP or BCRP potent inducers or inhibitors that could impact the PK of the investigational product within 14 days before inclusion or within 5 times the elimination half-life or pharmacodynamic (PD) half-life of the medication before inclusion.

    Note: If any of those drugs is planned to be administered in any of the potential participants, it needs to be postponed for at least until the EOS visit is completed.
14. Any vaccination, including COVID-19 within 2 weeks before inclusion.
15. Any participant who, in the judgment of the Investigator, is likely to be noncompliant during the study, or unable to cooperate because of a language problem or poor mental development

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Compound Number & Active ingredient: ITF2357 (INNM Givinostat hydrochloride Monohydrate)

Compound Name: NA

Exclusion Criteria for Participants with HI (continued)

16. Any participant in the exclusion period of a previous study according to applicable regulations
17. Any participant who cannot be contacted
18. Any participant who is the Investigator or any co-Investigator, research assistant, pharmacist, study coordinator, or other staff thereof, directly involved in conducting the study
19. Positive result on any of the following tests: anti-human immunodeficiency virus 1 and 2 antibodies (anti-HIV1 and anti HIV2 Ab)
20. Positive results on urine drug screen (amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates) unless this result is secondary to a documented medical prescription (only for benzodiazepines and cannabinoids)
21. Positive alcohol breath test
22. Any consumption of citrus fruits (grapefruit, Seville orange, etc.) or their juices within 5 days before inclusion
23. Medications that prolong the QTc Interval (refer to the list provided in the Appendix 12) within 14 days before inclusion or within 7 times the elimination half-life before inclusion.

    Note: If any of those drugs is planned to be administered in any of the potential participants, it needs to be postponed for at least until the last ECG at EOS is completed.
24. Have a risk factor of QT prolongation (as for example electrolyte imbalances) or a personal or a family history of prolonged QT interval syndrome or Torsade de Pointes, or family history of sudden death.

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Compound Name: NA

Matched participants with normal hepatic function

Inclusion Criteria for Matched participants with normal hepatic function

To be eligible to participate in this trial, an individual must meet all the following criteria:

1. Male or female participants, between 18 and 75 years of age, inclusive
2. Body weight within 10% of the mean body weight of the participants with HI to be matched, and BMI between 18.00 and 34.99 kg/m^2, inclusive
3. Certified as healthy by a comprehensive clinical assessment (detailed medical history and complete physical examination)
4. Vital signs after 10 minutes resting in the supine position within the following range (or if out of range, considered NCS by the Investigator):

   95 mmHg < SBP < 140 mmHg

   45 mmHg < DBP < 90 mmHg

   40 bpm < HR < 100 bpm
5. 12-lead ECG without clinically significant abnormality, in the judgment of the Investigator; in no circumstances should participants be enrolled with QTcF > 450 ms
6. Laboratory parameters within the normal range, unless the Investigator considers an abnormality to be clinically irrelevant for healthy participants, except in the case of platelets, white blood cells and hemoglobin below lower limit of normal (LLN). However, creatinine clearance, alkaline phosphatase, hepatic enzymes (aspartate aminotransferase, alanine aminotransferase), total bilirubin (unless the participant has documented Gilbert's syndrome, with a maximum bilirubin level lower than 3 x upper limit of normal (ULN), and any parameter for which there is an explicit stopping rule should not exceed the upper laboratory range; renal function should be assessed using the eGFR calculated by the 2021 CKD-EPI formula and should be strictly above 60 mL/min/1.73m².

Name of Company:

ITALFARMACO SpA
Via dei Lavoratori, 54
20092 Cinisello Balsamo
Milano, Italy

Compound Number & Active ingredient: ITF2357 (INNM Givinostat hydrochloride Monohydrate)

Compound Name: NA

Inclusion Criteria for Matched participants with normal hepatic function (continued)

7. Female participants who are not pregnant or nursing at Screening and Day −1, or who are not planning to become pregnant during study period and until 90 days after the IMP administration
8. Female participants of non-childbearing potential, defined as one of the following:
    a. At least 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., appropriate age) and follicle-stimulating hormone (FSH) in the range for menopausal female confirmed by blood test according to current local standards at screening.
    b. Those with history of hysterectomy or surgical removal of both ovaries or bilateral tubal ligation performed at least 90 days prior to Screening.
9. Female participant of childbearing potential and male participant (if sexually active with a woman of childbearing potential and not sterile) and his partner must agree to use an adequate and highly effective method of contraception (according to CTCG recommendations) during the study and for at least 90 days after the study drug administration for women and for men. Such methods include:
    a. combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation oral, intravaginal or transdermal.
    b. progestogen-only hormonal contraception associated with inhibition of ovulation oral, injectable or implantable
    c. intrauterine device (IUD)
    d. intrauterine hormone-releasing system (IUS)
    e. bilateral tubal occlusion
    f. vasectomized partner
    g. sexual abstinence (when in line with the preferred and usual subject's lifestyle).

    Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM are not acceptable methods of contraception.
10. Having given written informed consent prior to any procedure related to the study
11. Covered by a health insurance system where applicable, and/or in compliance with the recommendations of the national laws in force relating to biomedical research.
12. Not under any administrative or legal supervision
13. Male participants must agree not to donate sperm from inclusion up to 3 months after ITF2357 dosing.

Name of Company:

ITALFARMACO SpA
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20092 Cinisello Balsamo
Milano, Italy

Compound Number & Active ingredient: ITF2357 (INNM Givinostat hydrochloride Monohydrate)

Compound Name: NA

Exclusion Criteria for Matched participants with normal hepatic function

An individual who meets any of the following criteria will be excluded from participating in this trial:

1. Any history or presence of clinically relevant cardiovascular, pulmonary, gastrointestinal, hepatic, renal, metabolic, hematological, neurological, osteomuscular, articular, psychiatric, systemic, ocular, gynecological (if female), or infectious disease, or signs of acute illness
2. Frequent headaches and/or migraine, recurrent nausea and/or vomiting (more than twice a month)
3. Blood donation within 2 months before inclusion
4. Symptomatic postural hypotension, irrespective of the decrease in blood pressure, or asymptomatic postural hypotension defined as a decrease in SBP $\geq$ 20 mmHg within 3 minutes when changing from supine to standing position.
5. Presence or history of drug hypersensitivity, or allergic disease diagnosed and treated by a physician, except seasonal rhinitis
6. History or presence of regular use of recreational drugs or alcohol abuse (alcohol consumption more than 40 g per day on a regular basis) within 2 years before inclusion
7. Smoking more than 5 cigarettes or equivalent per day, unable to stop smoking from D-1 and throughout the entire institutionalization (i.e., up to D5)
8. Excessive consumption of beverages containing xanthine bases (more than 4 cups or glasses per day)
9. If female, pregnancy (defined as positive β-HCG blood test), breast-feeding
10. Any medication (including PgP or BCRP inducers or inhibitors, or omeprazole) within 14 days before inclusion or within 5 times the elimination half-life or pharmacodynamic (PD) half-life of the medication (except HRT and contraception when applicable), any vaccination within the last 28 days (except COVID-19 vaccination) and any biologics (antibody or its derivatives) given within 4 months before inclusion.
11. Any vaccination, including COVID-19 within 2 weeks before inclusion.
12. Any participant who, in the judgment of the Investigator, is likely to be noncompliant during the study, or unable to cooperate because of a language problem or poor mental development
13. Any participant in the exclusion period of a previous study according to applicable regulations
14. Any participant who cannot be contacted
15. Any participant who is the Investigator or any co-Investigator, research assistant, pharmacist, study coordinator, or other staff thereof, directly involved in conducting the study

<table>
<tr><td colspan="2">Name of Company:

ITALFARMACO SpA
Via dei Lavoratori, 54
20092 Cinisello Balsamo
Milano, Italy</td></tr>
<tr><td colspan="2">Compound Number & Active ingredient: ITF2357 (INNM Givinostat hydrochloride Monohydrate)</td></tr>
<tr><td colspan="2">Compound Name: NA</td></tr>
<tr><td colspan="2">Exclusion Criteria for Matched participants with normal hepatic function (continued)

16. Positive result on any of the following tests: hepatitis B surface antigen (HBs Ag), anti-hepatitis B core antibodies (anti-HBc Ab), anti-hepatitis C virus (anti-HCV) antibodies, anti-HIV1 and anti HIV2 Ab
17. Positive result on urine drug screen (amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates)
18. Positive alcohol breath test
19. Any consumption of citrus (grapefruit, Seville orange, etc.) or their juices within 5 days before inclusion.
20. Have a risk factor of QT prolongation (as for example electrolyte imbalances) or a personal or a family history of prolonged QT interval syndrome or Torsade de Pointes, or family history of sudden death.</td></tr>
<tr><td colspan="2">Criteria for evaluation:</td></tr>
<tr><td><u>Pharmacokinetic Assessments</u></td><td>Blood samples will be taken at the following time-points: pre-dose (within 30 minutes before administration), then 0.5, 1, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 60, 72 hour and 96-hour post-dose.

ITF2357 and 2 of its metabolites ITF2374 and ITF2375 levels will be measured using a validated bioanalytical method (LC-MS/MS) PK parameters will be calculated using non-compartmental method.

Four additional blood samples for the assessment of the free fraction of ITF2357 and its metabolites with high protein binding, i.e., ITF2374 and ITF2375 will be collected at 2 hours (expected ITF2357 t_{max}), at 4 hours (expected ITF2375 t_{max}), at 5 hours (expected ITF2374 t_{max}) and at 12 hours (ITF2357, ITF2374 and ITF2375 C_{min} for bid regimen) post-dose.</td></tr>
<tr><td><u>Safety Assessments</u></td><td>Safety will be evaluated from:

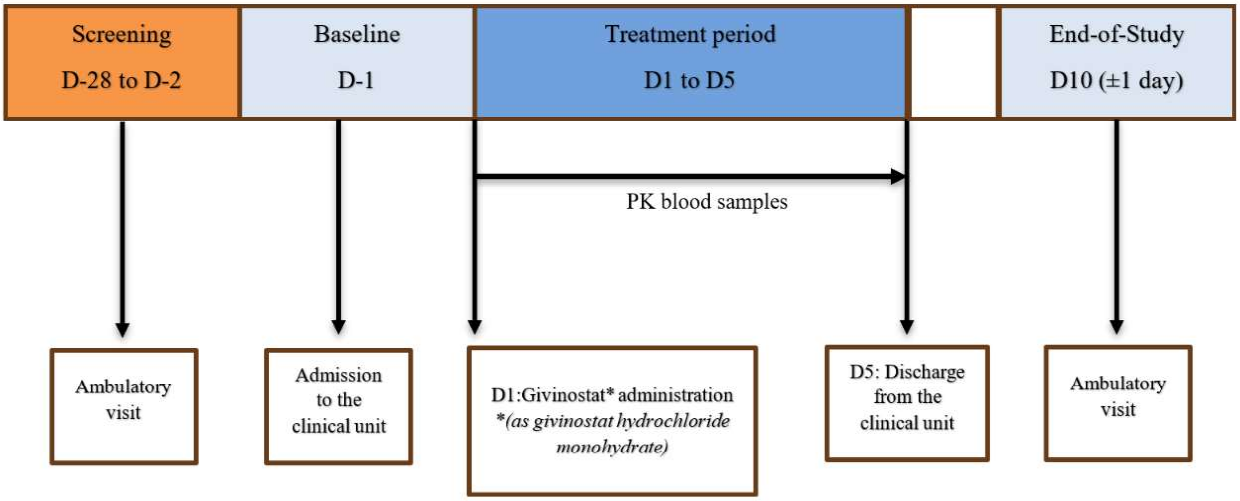
• Safety will be evaluated based on the reported adverse events, scheduled physical examinations including vital signs and digital standard 12-lead Electrocardiograms.

• Laboratory safety assessments (standard hematology, biochemistry analyses, coagulation, and urinalysis).

Adverse events (AE) will be monitored from the ICF signature throughout the study.</td></tr>
</table>

Name of Company: ITALFARMACO SpA Via dei Lavoratori, 54 20092 Cinisello Balsamo Milano, Italy	
Compound Number & Active ingredient: ITF2357 (INNM Givinostat hydrochloride Monohydrate)	
Compound Name: NA	
Statistical methods:	Statistical methods will be further outlined in the Statistical Analysis Plan (SAP) and approved by the Sponsor prior to database lock. **PK analysis:** ITF2357, and 2 of its metabolites (ITF2374 and ITF2375) PK parameters will be summarized by population group (normal and HI groups) using descriptive statistics. For log transformed C_{max}, AUC_{last} and AUC_{0-inf}, the effect of HI group on ITF2357 and its metabolites (ITF2374 and ITF2375) after a single dose of 50 mg in fasting conditions will be analyzed using a linear model with fixed terms for HI group (normal, mild and moderate) and gender and with age and body weight at baseline as covariates*. Point estimates and 90% confidence intervals (CIs) for the geometric means ratio of each HI group versus the normal control group will be provided for C_{max}, AUC_{last} and AUC_{0-inf}. Moreover, for C_{max}, AUC_{last} and AUC_{0-inf}, a point estimate and 90% CI for the geometric mean of each population group will be provided. (*) The inclusion of covariates in the model will be first assessed by the Akaike's information criterion (AIC). The model with the lowest AIC value will be selected for the final analysis. Models lack-of-fit will be assessed by residual plots. Additionally, relationships between PK parameters C_{max}, AUC_{last}, $t_{1/2}$, AUC_{0-inf}, C_{maxu}, $AUC_{last,u}$, $AUC_{inf,u}$ (for ITF2357 and metabolites ITF2374 and ITF2375), CL/F, Vz/F (for ITF2357 only) and hepatic function measures (e.g., Child-Pugh score) will be explored by graphical/regression methods as a secondary analysis. **Safety analysis:** The incidence of AEs, treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) will be tabulated and summarized by population group, primary system organ class (SOC) and preferred term (PT) (latest available MedDRA coding will be used). Descriptive summaries of raw data and changes from baseline and potentially clinically significant abnormalities (PCSA) in ECG, vital signs, and clinical laboratory values will be listed, flagged and summarized for each population group.

1.2 Study Schema



D = Day

PK = Pharmacokinetics

1.3 Schedule of Activities (SOA)

Table 1: Overall Study SOA

Epoch	**Enrollment**		**Treatment period**					**Follow-up**
Phase	**Screening**	**Admission**	**Hospitalization**					**End-of-Study**
Day (D)	**D-28 to D-2**	**D-1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D10 (±1 day)**
Informed consent	X							
Demographic characteristics[a]	X							
Institutionalization		X						
Discharge							X	
Outpatient visit	X							X
Inclusion/exclusion criteria	X	X						
Medical/surgical history	X	X						
Child-Pugh score[b]	X[b]	X[b]						
Prior/concomitant medications	←- - - - - -	- - - - - - - - - -	- - - - -	- - - - -	- - - - -	- - - - - - -	- - - - - - -	- - - - - - - - - →
Inclusion			X					
Investigational Medicinal Product (IMP) administration								
Givinostat (*)			X					
Safety								
Physical examination	X	X					X	X
Height	X							
Body weight	X	X						X
Body temperature (oral)	X	X						X
Vital signs (§)	X	X	X				X	X

Epoch	**Enrollment**		**Treatment period**					**Follow-up**
Phase	**Screening**	**Admission**	**Hospitalization**					**End-of-Study**
Day (D)	**D-28 to D-2**	**D-1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D10 (±1 day)**
Electrocardiogram (ECG)	X	X	X				X	X
Hematology[c], biochemistry, coagulation, urinalysis	X	X		X[c]	X[c]	X[c]	X[d]	X
Serology tests	X							
Serum pregnancy test if applicable	X	X						X
Serum follicle-stimulating hormone (FSH), if applicable	X							
Urine drug screen, alcohol breath test	X	X						
Adverse event collection	←- - - - - - -	- - - - - - - - - -	- - - - - -	- - - - - -	- - - - - -	- - - - - -	- - - - - - -	- - - - - - - - - →
Pharmacokinetics (PK)								
PK samples			X	X	X	X	X	
Blood samples for ITF2357, and metabolites ITF2374 and ITF2375 free fraction			X					

a Including age (years), race and ethnicity, and gender.
b Only in Hepatic Impairment (HI) patients
c Additional samples will be taken only for hematology test.
d On D5 at hour (H)96, urinalysis may be performed within a ± 2 hour time-window.
(*) Dose of the IMP is expressed as givinostat hydrochloride monohydrate.
(§) Blood pressure (both supine and standing position at screening and D-1, supine only thereafter), pulse rate and respiratory rate.

Table 2: Period SOA

Day	**D1**													**D2**		**D3**		**D4**	**D5**
Time (hour/minute)	**-0H30**	**0H**	**0H30**	**1H**	**2H**	**2.5**	**3H**	**4H**	**5H**	**6H**	**8H**	**10H**	**12H**	**24H**	**36H**	**48H**	**60H**	**72H**	**96H**
Indicative clock time		8:00	8:30											8:00		8:00		8:00	8:00
Concomitant medications		←	-	-	-		-	-		-	-	-	-	-	-	-	-	-	→
Discharge (breakfast will be provided)																			X
Standard meals[a]										X									
IMP administration																			
Givninostat		X																	
Safety																			
Physical examination																			X
Archival blood sample	X																		
Vital signs[c]	X				X		X		X		X		X						X
ECG	X				X				X		X		X						X
Hematology, biochemistry, coagulation, urinalysis														X		X		X	X[b]
Adverse event collection		<	-	-	-		-	-		-	-	-	-	-	-	-	-	-	>
Pharmacokinetics																			
PK samples	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood samples for ITF2357, ITF2374 and ITF2375 free fraction					X			X	X				X						

a Standardized meals will be provided during the inpatient period. However, and for the dosing on Day 1, an overnight fast will be imposed, so that no food is taken within at least 10 hours before IMP administration. Participants will remain fasted for at least 2 hours after dosing, a snack at H2 post-dose, be served lunch at H4 post-dose, possible snack in the afternoon and dinner around H10 post-dose. Drinking of water will be allowed ad libitum except for 1 h before and 1 h after dosing; before and after that period, drinking water will be permitted ad libitum.

b On D5 at H96, urinalysis may be performed within a ±2 hours' time-window.

c Supine blood pressure, pulse rate and respiratory rate.

Note: when several assessments take place at the same time, the following order should be respected: ECG, vital signs, safety samples, meals, PK, drug administration. **To respect the exact timing of PK samples, ECG and vital signs will be done ahead of the scheduled time.**

2 INTRODUCTION

2.1 Purpose of Trial

2.1.1 Background

ITF2357, also known as givinostat hydrochloride monohydrate, is an orally active hydroxamic acid derivative belonging to the pharmacological class of histone deacetylase (HDAC) inhibitors. ITF2357 was initially developed for its anti-inflammatory properties, but additionally shows strong anti-tumor activities and helps to prevent muscle degeneration in muscular dystrophies.

ITF2357 is currently being developed for two Muscular Dystrophies (Duchenne Muscular Dystrophy and Becker Muscular Dystrophy, [DMD, BMD]) and in a Chronic Myelo-Proliferative Neoplasm (Polycythemia Vera [PV]) at doses up to 70 mg b.i.d. in DMD and up to [redacted] in PV. Givinostat (DUVYZAT™) has been recently approved by the FDA for the treatment of DMD in patients six years of age and older.

2.1.2 Pharmacology

In vitro, the concentrations of HDAC inhibitors required to induce cell death, especially in solid tumors, are in the micromolar or higher range; in animals, similar circulating concentrations are needed for tumor regression. An unexpected and seemingly paradoxical property of HDAC inhibition is the reduction of inflammation, particularly in models of autoimmune diseases and inflammation. This additional effect is exerted at concentrations/doses which are significantly inferior to the tumoricidal ones and is mainly due to the inhibition of pro-inflammatory cytokine gene expression (Leoni et al., 2002; Nishida et al., 2004). The above-mentioned anti-inflammatory and immune-modulating activities are the basis of the potential use of ITF2357 in several diseases, such as rheumatological disorders, Graft Versus Host Disease, and selected oncohematological conditions. Finally, the anti-inflammatory properties of ITF2357 associated with its anti-fibrotic and proregenerative activities are the basis for the development of this compound in DMD (Minetti et al. 2006; Colussi et al. 2008 & 2009; Iezzi et al. 2004; Mal et al 2001; Nebbioso et al, 2009).In addition, ITF2357 inhibits histone deacetylase (HDACi) enzyme with antitumor activity, on cells carrying the Janus Kinase 2 (JAK2)^{V617F} mutation obtained from Polycythemia Vera and essential thrombocythemia patients as well as the HEL cell line. The clonogenic activity of JAK2^{V617F} mutated cells was inhibited by low concentrations of ITF2357 (IC50: 0.001-0.01 microM), 100- to 250-fold lower than required to inhibit growth of normal or tumor cells lacking this mutation (Guerini et al. 2008).

2.1.3 Non-clinical metabolism and pharmacokinetics

The pharmacokinetic properties of ITF2357 were studied in vivo in preclinical animal species and in vitro using human and animal cells and subcellular fractions. In vivo, low absolute bioavailability is observed after oral administration in preclinical species (21% in rats, 12% in dogs and 13% in monkeys) likely due to an extensive metabolism rather than low intestinal absorption. ITF2357 is highly bound to the plasma protein in all species (95.9% in human plasma), and slightly partitioned in the red blood cells. The compound has a broad plasma and tissue distribution, including muscle tissues. ITF2357 is extensively metabolized both in vitro and in vivo in preclinical species, metabolism representing the main clearance mechanism for ITF2357. The main metabolites are identified, and no unique or disproportional metabolites were found in vitro in human incubations respect to those observed in the preclinical species. ITF2357 excretion as unmodified drug is very low in both urine and feces; its elimination is

likely dependent on metabolism followed by renal and hepatic excretion of the resulting metabolites.

2.1.4 Toxicology

Repeated-dose oral toxicity studies were carried out in 4 different animal species. In the dog the drug was given for 4 consecutive weeks, in the mouse for 13 consecutive weeks and in the rat and monkey for up to 26 and 39 weeks, respectively. The dog was not a suitable species for chronic administration, due to gastrointestinal adverse effects.

In the repeated-dose toxicity studies in rodents the following no observed adverse effect levels (NOAELs) were identified: 100 mg/kg/day in the 13-week study in the mouse; 50 mg/kg/day in the 4-week study in the rat; 10 mg/kg/day in the 13- and 26-week studies in the rat.

In the repeated-dose toxicity studies in the monkey the following NOAELs were identified: 10 mg/kg/day in the 13-week study and 12 mg/kg/day in the 39-week studies. No clear NOAEL was identified in the 4-week study.

The main adverse effects observed in repeated-dose studies in the rat and monkey were reduction in white blood cells (WBC), red blood cells (RBC), decreased bone marrow cellularity, reduced thymus weight, increased liver enzymes. These effects were usually observed at highest tested doses of ITF2357. Changes were reversible after discontinuation of treatment, or a trend to resolution was observed at the end of the recovery period.

Two repeated-dose juvenile oral toxicity studies were conducted in the rat. The toxicological profile was similar to that seen in adult animals. ITF2357 did not affect the behavioral and physical development. The identified NOAELs were 60 mg/kg/day in the 4-week study and 40/60/90 mg/kg/day in the 13-week study (administered with a titration schedule)

In the developmental and reproductive oral toxicity studies, the following NOAELs were identified: 40 mg/kg/day in the fertility and early embryonic development study in the rat, 80 mg/kg/day in the embryofetal development study in the rat and rabbit, 80 mg/kg/day in the pre- and post-natal development study in the rat. ITF2357 was positive for frameshift mutations in the bacterial reverse mutation assay (2 out of 5 strains), negative in two in vitro mammalian cell mutation assay and in two in vivo genotoxicity studies in the rat, resulting non genotoxic to mammalian organisms. ITF2357 was not mutagenic in the in vivo mutagenicity assay in the transgenic Big Blue rat.

ITF2357 showed a favorable safety profile in safety pharmacology studies.

2.1.5 Previous human experience

To date, studies have been conducted in healthy volunteers, and in patients with chronic inflammatory disease, hematological malignancies, chronic myeloproliferative disorders, and Duchenne and Becker muscular dystrophy.

A Phase II clinical dose finding study (DSC/03/2357/06) was completed in patients with moderate to severe Crohn’s disease. A second Phase II clinical study (DSC/06/2357/23) in the same indication was prematurely discontinued due to insufficient evidence of efficacy.

Two Phase II dose-finding studies (DSC/03/2357/07 and DSC/03/2357/09) with and without placebo were performed in patients with plaque psoriasis. The second study was terminated prematurely after 6 patients were withdrawn because of either inefficacy or intolerance.

An Investigator' Initiated clinical trial (DSC/06/2357/22) in auto-inflammatory syndromes was discontinued for insufficient evidence of efficacy.

A Phase II pilot study (DSC/05/2357/19) was completed in pediatric patients with active Systemic Onset Juvenile Idiopathic Arthritis with inadequate response or intolerance to standard therapy. Thereafter, a Phase II dose finding study (DSC/08/2357/36) was completed in patients with Polyarticular Course Juvenile Idiopathic

Arthritis (Poly JIA); one patient from this study was enrolled in an extension study (DSC/11/2357/42) which was discontinued for Sponsor decision.

Two Phase II studies (DSC/04/2357/10 and DSC/07/2357/29) were conducted in patients with relapsing refractory advanced multiple myeloma. The first study was aimed at evaluating the antitumor activity and identifying the maximum tolerated dose (MTD) of ITF2357 in multiple myeloma patients. In the second study a different dose schedule foreseeing the administration of a single high dose/week of ITF2357 was to be investigated. The study was prematurely discontinued for lack of recruitment. One Phase II study (DSC/05/2357/15) was completed in patients with Acute Myeloid Leukemia. Two Phase II pilot clinical trials, in diffuse large B-cell lymphoma (DSC/05/2357/17) and chronic lymphocytic leukemia, (DSC/06/2357/21), respectively, were discontinued for insufficient recruitment rate. Two Phase II pilot clinical studies (DSC/07/2357/26 and DSC/07/2357/31) were conducted in patients with advanced Hodgkin's Lymphoma: the first one, investigating safety and efficacy of ITF2357 monotherapy, was discontinued for insufficient evidence of efficacy; the second one investigating the combination of ITF2357 with mechlorethamine, was completed.

Three studies were conducted in chronic myeloproliferative neoplasms (cMPNs), as described above (DSC/07/2357/28, DSC/08/2357/38 and DSC/11/2357/45).

Two Phase II studies (DSC/07/2357/28 and DSC/08/2357/38) were conducted in patients with $JAK2^{V617F}$ positive cMPNs: the first one, a pilot study investigating safety and efficacy of ITF2357 monotherapy, was completed in patients with $JAK2^{V617F}$ positive PV, Essential Thrombocytosis and Myelofibrosis. The second one, investigating the combination of ITF2357 with hydroxyurea (HU), was completed in patients with JAK2V617F positive PV not responding to the maximum tolerated dose of HU monotherapy. A third trial, Phase Ib/II, (DSC/11/2357/45) was designed to specifically investigate the effect of higher doses of ITF2357 on JAK2V617F positive PV patients. Finally, an open-label extension study is currently ongoing, recruiting patients from all the previous mentioned trials in cMPNs and/or from the compassionate use program (DSC/11/2357/44).

A pilot Phase II study (DSC/11/2357/43) was conducted in ambulant DMD patients aged from 7 to 10 years of age with stable corticosteroid treatment for at least 6 months, evaluating possible muscular histologic effects of Givinostat. A Phase III double blind, placebo-controlled study (DSC/14/2357/48) in ambulant DMD patients from 6 years of age with stable corticosteroid treatment was completed. This study evaluated the effects of Givinostat versus placebo administered chronically over 18 months to slow disease progression in this population. A Phase III double blind, placebo-controlled study (DSC/14/2357/50) in non-ambulant DMD patients from 9 years of age with stable corticosteroid treatment is currently ongoing. Finally, an open-label long term safety and efficacy study (DSC/14/2357/51) is ongoing, recruiting patients from all the previously mentioned trials in patients suffering from DMD.

A Phase II double blind, placebo-controlled study (DSC/15/2357/53) in 51 ambulant BMD patients aged from 18 to less than 65 years of age was conducted to evaluate the micro-macroscopic effects on muscles, the safety and tolerability, and the efficacy of Givinostat.

Further detailed information can be found in the Investigator's Brochure (IB).

2.1.6 Safety and tolerability

Overall, ITF2357 was well tolerated across its development program and has demonstrated an acceptable safety profile. The most frequent treatment-emergent adverse events (TEAEs) were diarrhea, thrombocytopenia, pyrexia, and platelet count decreased. AEs were generally mild to moderate and reversible upon discontinuation of study drug. TEAEs associated with gastrointestinal (GI) events and blood disorders/investigations were dose related. No serious adverse events (SAEs) occurred throughout the study period in any of the studies with healthy volunteers.

Despite some episodes of QTc prolongation reported, no events of clinical concern were seen. In a dedicated QT/QTc (TQT) study (ITF/2357/54), after administration in single doses of 100 mg (therapeutic dose) or 300 mg (supratherapeutic dose) to healthy subjects, ITF2357 exerted a dose-dependent effect on heart rate, which was clinically relevant for the supratherapeutic dose (300 mg) only. The effect seen on 100 mg was of no clinical concern. ITF2357 caused prolongation of the QTc interval, for the supratherapeutic dose (300 mg) only. The peak effect was seen at 5 hours post-dose for both tested doses. ITF2357 did not have a clinically relevant effect on the heart rate or QRS intervals.

Further detailed information can be found in the Section 6 "Effects in Humans" of the Investigator's Brochure (IB).

2.1.7 Trial rationale

ITF2357 has been studied in 25 clinical studies in both patient populations and healthy participants (up to 600 mg single dose and up to 200 mg/day for 7 days).

In humans, ITF2357 is extensively metabolized, to 4 major inactive metabolites: ITF2374 (hydroxamic acid reduction), ITF2375 (hydroxamic acid hydrolysis), and ITF2440 and ITF2563 (both from oxidative cleavage). Thus, metabolic hepatic clearance represents a significant part of the total clearance of ITF2357 and decreased metabolism of ITF2357 in patients with hepatic impairment cannot be excluded.

Moreover, during the clinical study evaluating ITF2357 potential for QTc prolongation (study ITF/2357/54), the time profile of QTc interval suggests that the prolongation could be caused by the metabolites rather than the parent compound. This is because the T_{max} for ITF2357 is around 2 hours post-dose but the largest mean QTc effect occurred around 5 hours post-dose, which is consistent with T_{max} of metabolites ITF2374 and/or ITF2375. Therefore, the exposures of the metabolites ITF2374 and ITF2375 are investigated along with the parent compound in subjects with liver impairment.

The binding of ITF2357 in human plasma was 95.9 ± 1.3% and independent of plasma concentrations. Similarly, ITF2374 and ITF2375 metabolites have a high plasma protein binding, 92.5% and 98.4%, respectively. Thus, free fraction of ITF2357, and metabolites ITF2374 and ITF2375 may be modified in patients with hepatic impairment, leading to variation in exposure.

There have been no formal studies conducted in patients with hepatic impairment (HI) and subjects with significant hepatic diseases have been excluded from the clinical studies with ITF2357. Therefore, and as this drug may be administered to patients with varying degrees of HI, evaluation of the effect of mild and moderate HI on the pharmacokinetics (PK) of ITF2357 and its metabolites ITF2374 and ITF2375 is considered necessary.

The results of this study will be used to make recommendations for potential dosage adjustments of ITF2357 in patients with chronic hepatic impairment.

2.1.8 Dose rationale

Pharmacokinetics of ITF2357 were characterized in healthy volunteers receiving single or repeat ITF2357 doses in 5 phase I studies (including one drug-drug interaction study). In three of these studies (DM/00/2357/01, DM/00/2357/03 and ITF/2357/55), the 50 mg dose was used and reported to be safe and well tolerated in healthy subjects.

Considering that 50 mg is also in the range of doses investigated in DMD patients, both participants with HI and normal hepatic function will receive a single 50 mg dose in this study.

Even assuming a potential two-fold increase in ITF2357 exposure in patients with moderate HI, studies using the 100 mg dose (DM/00/2357/04 and ITF/2357/54) reported that this dose is also safe and well tolerated in healthy subjects.

2.2 Summary of Benefits and Risks

The participants will not benefit from taking part in this study; the data from this study will be used to make recommendations for potential dosage adjustments of ITF2357 (givinostat hydrochloride monohydrate) in patients with chronic hepatic impairment.

The inclusion and exclusion criteria have been chosen to enable a uniform study population and to minimize possible risks after a single administration of the investigational medicinal products (IMPs), including on potential drug-drug interactions.

The previous clinical experience indicates that givinostat is well tolerated at the tested doses in healthy volunteers or patients with chronic inflammatory diseases, or with DMD where dose-related platelets count reduction and diarrhea were the most frequently reported AEs.

As far as patients with onco-hematological conditions are concerned, givinostat seems to have more profound effects on bone marrow cell-lines. Overall, there has been no other major safety concern in the patient population tested.

In particular related to patients with HI:

- Patients should be carefully monitored for signs of gastrointestinal adverse events, especially diarrhea, nausea and vomiting. If necessary, supportive treatment not limited to anti-emetics, anti-diarrheal drugs and intravenous hydration should be initiated.
- Patients' hematological parameters, in particular red blood counts and platelet counts, should be carefully monitored.
- Worsening of hepatic function parameters should also be carefully monitored in these patients during the study. Coagulation factors should also be monitored although there is no expected givinostat´s effect on coagulation parameters.

Multiple doses of oral givinostat 50 mg b.i.d, for 13 days, were safe and well tolerated in a population of healthy male and female subjects in study ITF/2357/55.

The study will be carried out in centers specialized in early phase studies with experienced medical staff and adequate facilities. From admission until discharge, the participants will be confined and under constant medical monitoring. To ensure the safety of the participants, adverse events, vital signs parameters, electrocardiogram (ECG) and laboratory parameters will

be carefully monitored.

More detailed information about the known and expected risks and reasonably expected AEs may be found in the Investigator's Brochure (IB).

2.3 Mitigation Strategy

In the current study, eligibility criteria exclude people with comorbidities that may increase the risk for serious illnesses such as chronic cardiovascular disease, liver disease (except HI), kidney disease, respiratory system compromise, etc. In addition, the participants will be hospitalized during the study, thus safety precautions, the clinical and para-clinical examinations, and the safety rules applied in this protocol should allow a good control of the potential risks.

3 TRIAL OBJECTIVES AND ENDPOINTS

3.1 Primary/Secondary Objectives and Associated Endpoints

	Objectives	Endpoints
Primary	To evaluate the effect of mild and moderate HI on the PK of ITF2357 in comparison with matched participants with normal hepatic function, after a single oral dose of 50 mg ITF2357 (*). (*) *Dose of the Investigational Medicinal Product (IMP) is expressed as givinostat hydrochloride monohydrate.*	For ITF2357: • maximum plasma concentration observed (C_{max}) • area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to the real time t_{last} (AUC_{last}) • area under the plasma concentration versus time curve extrapolated to infinity (AUC_{0-inf})
Secondary	To evaluate the effect of mild and moderate HI on additional PK parameters of ITF2357 in comparison with matched participants with normal hepatic function, after a single oral dose of 50 mg ITF2357.	For ITF2357: • time to reach C_{max} (t_{max}) • apparent terminal half-life ($t_{1/2}$) • apparent total plasma clearance from plasma (CL/F) • apparent volume of distribution (Vz/F)
	To evaluate the effect of mild and moderate HI on the pharmacokinetic of 2 metabolites of ITF2357: ITF2374 and ITF2375 in comparison with matched participants with normal hepatic function after a single oral dose of 50 mg ITF2357.	For metabolites: ITF2374 and ITF2375 • maximum plasma concentration observed (C_{max}) • area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to the real time t_{last} (AUC_{last}) • area under the plasma concentration versus time curve extrapolated to infinity (AUC_{0-inf}) • time to reach C_{max} (t_{max}) • apparent terminal half-life ($t_{1/2}$)

	To assess the effect of mild and moderate HI on the free fraction of ITF2357, and its metabolites with high protein binding ITF2374 and ITF2375 in comparison with matched participants with normal hepatic function.	For ITF2357 and metabolites ITF2374 and ITF2375
		• Unbound fraction (fu)
		• Unbound area under the plasma concentration time curve (AUC_u)
		  ◦ $AUC_{0-last,u}$
		  ◦ $AUC_{0-inf,u}$
		• Unbound maximum plasma concentration observed ($C_{max,u}$)
		
		For ITF2357 only:
		• Unbound apparent total plasma clearance (CL/F_u)
		Unbound apparent volume of distribution (Vz/F_u)

	To assess the safety and tolerability of ITF2357 given as a single oral dose of 50 mg in participants with mild and moderate HI and in matched participants with normal hepatic function.	Laboratory, electrocardiogram parameters, vital signs and physical examination parameters, and adverse events

4 TRIAL DESIGN

4.1 Description of Study Design

This is a phase I, open-label non-randomized, single-period single dose study, to be conducted in 3 groups:

- Participants with mild HI (Child-Pugh class A)
- Participants with moderate HI (Child-Pugh class B)
- Participants with normal hepatic function, matched to participants with moderate HI based on weight, see Table 3.

It is planned that the participants with HI (both mild and moderate) will be recruited first, then the matched participants with normal hepatic function (healthy participant) will be recruited. The matching of participants will be 1:1 between a moderate hepatic impairment patient and a healthy participant, see Section 6.6.

The duration of study participation by participant will be of 38 days maximum, including:

- A **screening period** from Day (D)-28 to D-2
- One 6-day/5-night **inpatient period** (from D-1 morning to D5 morning)
    - Baseline assessments will be conducted on D-1 and D1 pre-dose
    - A single dose administration will be administered on D1
    - Discharge on D5 morning
- An **end-of-study** (EOS) evaluation to be done on D10 (±1 day), or to be organized as soon as possible in case of early withdrawal.

For a visual representation of the study design, refer to Study Schema in Section 1.2.

The study stopping rules are defined in Section 7.4.

4.2 Rationale for Trial Design

Please refer to Section 2.1.7

4.3 Access to Investigational Medicinal Product After End of Study

Not applicable.

4.4 Start of Study and End of Study

The trial start date will be defined as the date of the first act of recruitment of a potential participant.

The end of the clinical study (EOS) will be defined as the last visit of the last participant.

The duration of trial participation by participant will be approximately up to 38 days starting with the screening visit and up to the termination assessment (EOS visit).

Refer to Section 10.6, Early Site Closure or Study Termination for information on the criteria and responsibilities related to early site closure or study termination.

5 STUDY POPULATION

5.1 Participants with HI

5.1.1 Inclusion Criteria for Participants with HI

To be eligible to participate in this trial, an individual must meet all the following criteria:

1. Male or female participants, between 18 and 75 years of age, inclusive.
2. Body weight between 60.0 and 110.0 kg, inclusive if male, and between 50.0 and 100.0 kg, inclusive if female, body mass index (BMI) between 18.00 and 34.99 kg/m^2, inclusive.
3. Stable chronic liver disease assessed by medical history, physical examination, laboratory values.
4. Vital signs after 10 minutes resting in supine position within the following range [or if out of range, considered not clinically significant (NCS) by the Investigator]:

   95 mmHg < systolic blood pressure (SBP) < 180 mmHg

   45 mmHg < diastolic blood pressure (DBP) < 100 mmHg

   40 bpm < heart rate (HR) < 100 bpm.
5. 12-lead ECG without clinically significant abnormality, in the judgment of the Investigator; in no circumstances should participants be enrolled with corrected QT according to Fridericia (QTcF) > 450 ms.
6. Any confirmed clinically relevant abnormal laboratory test that, on Investigator's judgement, is inconsistent with the subject's status as a patient with hepatic impairment. However, renal function should be assessed using the estimated glomerular filtration rate (eGFR) calculated by the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula and should be strictly above 60 mL/min/1.73m².
7. Female participants who are not pregnant or nursing at Screening and Day −1, or who are not planning to become pregnant during study period and until 90 days after the IMP administration.
8. Female participants of non-childbearing potential, defined as one of the following:
   a. At least 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., appropriate age) and follicle-stimulating hormone (FSH) in the range for menopausal female confirmed by blood test according to current local standards at screening.
   b. Those with history of hysterectomy or surgical removal of both ovaries or bilateral tubal ligation performed at least 90 days prior to Screening.

9. Female participant of childbearing potential and male participant (if sexually active with a woman of childbearing potential and not sterile) and his partner must agree to use an adequate and highly effective method of contraception (according to Clinical Trials Coordination Group [CTCG] recommendations) during the study and for at least 90 days after the study drug administration for women and for men. Such methods include:

    a. combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation oral, intravaginal or transdermal.

    b. progestogen-only hormonal contraception associated with inhibition of ovulation oral, injectable or implantable

    c. intrauterine device (IUD)

    d. intrauterine hormone-releasing system (IUS)

    e. bilateral tubal occlusion

    f. vasectomized partner

    g. sexual abstinence (when in line with the preferred and usual subject's lifestyle).

    Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception.

10. Having given written informed consent prior to any procedure related to the study.

11. Covered by a health insurance system where applicable, and/or in compliance with the recommendations of the national laws in force relating to biomedical research.

12. Not under any administrative or legal supervision.

13. For moderate HI cohort: Child-Pugh total score ranging from 7 to 9, inclusive.

14. For mild HI cohort: Child-Pugh total score ranging from 5 to 6, inclusive.

15. Male participants must agree not to donate sperm from inclusion up to 3 months after ITF2357 dosing.

5.1.2 Exclusion Criteria for Participants with HI

An individual who meets any of the following criteria will be excluded from participating in this trial:

1. Uncontrolled clinically relevant cardiovascular, pulmonary, gastrointestinal, metabolic, hematological, neurological, osteomuscular, articular, psychiatric, systemic, ocular, gynecological (if female), or infectious disease, or signs of acute illness.

2. Hepatocarcinoma.

3. Acute hepatitis.

4. Hepatic encephalopathy grade 2, 3, and 4.

5. Blood donation within 2 months before inclusion.

6. Symptomatic postural hypotension, whatever the decrease in blood pressure, or asymptomatic postural hypotension defined as a decrease in SBP ≥ 30 mmHg within 3 minutes when changing from supine to standing position.

7. Presence or history of drug hypersensitivity, or allergic disease, except seasonal rhinitis, diagnosed and treated by a physician.

8. History or presence of regular use of recreational drugs or alcohol abuse (alcohol consumption more than 40 g per day on a regular basis) within 2 years before inclusion.

9. Smoking more than 15 cigarettes or equivalent per day, unable to refrain from smoking over 5 cigarettes per day from D-1 and throughout the entire institutionalization (i.e., up to D5).

10. Excessive consumption of beverages with xanthine bases (more than 4 cups or glasses per day).

11. If female, pregnancy [defined as positive β-human choriogonadotropin (β-HCG) blood test] or breast-feeding.

12. Any significant change in chronic treatment medication within 14 days before inclusion.

13. Consumption of PgP or BCRP potent inducers or inhibitors that could impact the PK of the investigational product within 14 days before inclusion or within 5 times the elimination half-life or pharmacodynamic (PD) half-life of the medication before inclusion.

    Note: If any of those drugs is planned to be administered in any of the potential participants, it needs to be postponed for at least until the EOS visit is completed.

14. Any vaccination, including COVID-19 within 2 weeks before inclusion.

15. Any participant who, in the judgment of the Investigator, is likely to be noncompliant during the study, or unable to cooperate because of a language problem or poor mental development.

16. Any participant in the exclusion period of a previous study according to applicable regulations.

17. Any participant who cannot be contacted.

18. Any participant who is the Investigator or any co-Investigator, research assistant, pharmacist, study coordinator, or other staff thereof, directly involved in conducting the study.

19. Positive result on any of the following tests: anti-human immunodeficiency virus 1 and 2 antibodies (anti-HIV1 and anti HIV2 Ab).

20. Positive results on urine drug screen (amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates) unless this result is secondary to a documented medical prescription (only for benzodiazepines and cannabinoids).

21. Positive alcohol breath test.

22. Any consumption of citrus fruits (grapefruit, Seville orange, etc.) or their juices within 5 days before inclusion.

23. Medications that prolong the QTc Interval (refer to the list provided in the Appendix 12) within 14 days before inclusion or within 7 times the elimination half-life before inclusion.

    Note: If any of those drugs is planned to be administered in any of the potential participants, it needs to be postponed for at least until the last ECG at EOS is completed.

24. Have a risk factor of QT prolongation (as for example electrolyte imbalances) or a personal or a family history of prolonged QT interval syndrome or Torsade de Pointes, or family history of sudden death.

5.2 Matched participants with normal hepatic function

5.2.1 Inclusion Criteria for Matched participants with normal hepatic function

To be eligible to participate in this trial, an individual must meet all the following criteria:

1. Male or female participants, between 18 and 75 years of age, inclusive.
2. Body weight within 10% of the mean body weight of the participants with HI to be matched, and BMI between 18.00 and 34.99 kg/m^2, inclusive.
3. Certified as healthy by a comprehensive clinical assessment (detailed medical history and complete physical examination).
4. Vital signs after 10 minutes resting in the supine position within the following range (or if out of range, considered NCS by the Investigator):

   95 mmHg < SBP < 140 mmHg

   45 mmHg < DBP < 90 mmHg

   40 bpm < HR < 100 bpm.
5. 12-lead ECG without clinically significant abnormality, in the judgment of the Investigator; in no circumstances should participants be enrolled with QTcF > 450 ms.
6. Laboratory parameters within the normal range, unless the Investigator considers an abnormality to be clinically irrelevant for healthy participants, except in the case of platelets, white blood cells and hemoglobin below lower limit of normal (LLN). However serum creatinine, alkaline phosphatase, hepatic enzymes (aspartate aminotransferase, alanine aminotransferase), total bilirubin (unless the participant has documented Gilbert's syndrome, with a maximum bilirubin level lower than 3 x upper limit of normal (ULN), and any parameter for which there is an explicit stopping rule should not exceed the upper laboratory range; renal function should be assessed using the eGFR calculated by the 2021 CKD-EPI formula and should be strictly above 60 mL/min/1.73m^2.
7. Female participants who are not pregnant or nursing at Screening and Day −1, or who are not planning to become pregnant during study period and until 90 days after the IMP administration.
8. Female participants of non-childbearing potential, defined as one of the following:

   a. At least 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., appropriate age) and follicle-stimulating hormone (FSH) in

the range for menopausal female confirmed by blood test according to current local standards at screening.

b. Those with history of hysterectomy or surgical removal of both ovaries or bilateral tubal ligation performed at least 90 days prior to Screening.

9. Female participant of childbearing potential and male participant (if sexually active with a woman of childbearing potential and not sterile) and his partner must agree to use an adequate and highly effective method of contraception (according to CTCG recommendations) during the study and for at least 90 days after the study drug administration for women and for men. Such methods include:

   a. combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation oral, intravaginal or transdermal.

   b. progestogen-only hormonal contraception associated with inhibition of ovulation oral, injectable or implantable

   c. intrauterine device (IUD)

   d. intrauterine hormone-releasing system (IUS)

   e. bilateral tubal occlusion

   f. vasectomized partner

   g. sexual abstinence (when in line with the preferred and usual subject's lifestyle).

      Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM are not acceptable methods of contraception.

10. Having given written informed consent prior to any procedure related to the study.

11. Covered by a health insurance system where applicable, and/or in compliance with the recommendations of the national laws in force relating to biomedical research.

12. Not under any administrative or legal supervision.

13. Male participants must agree not to donate sperm from inclusion up to 3 months after ITF2357 dosing.

5.2.2 Exclusion Criteria for Matched participants with normal hepatic function

An individual who meets any of the following criteria will be excluded from participating in this trial:

1. Any history or presence of clinically relevant cardiovascular, pulmonary, gastrointestinal, hepatic, renal, metabolic, hematological, neurological, osteomuscular, articular, psychiatric, systemic, ocular, gynecological (if female), or infectious disease, or signs of acute illness.

2. Frequent headaches and/or migraine, recurrent nausea and/or vomiting (more than twice a month).

3. Blood donation within 2 months before inclusion.

4. Symptomatic postural hypotension, irrespective of the decrease in blood pressure, or asymptomatic postural hypotension defined as a decrease in SBP ≥ 20 mmHg within 3 minutes when changing from supine to standing position.
5. Presence or history of drug hypersensitivity, or allergic disease diagnosed and treated by a physician, except seasonal rhinitis.
6. History or presence of regular use of recreational drugs or alcohol abuse (alcohol consumption more than 40 g per day on a regular basis) within 2 years before inclusion.
7. Smoking more than 5 cigarettes or equivalent per day, unable to stop smoking from D-1 and throughout the entire institutionalization (i.e., up to D5).
8. Excessive consumption of beverages containing xanthine bases (more than 4 cups or glasses per day).
9. If female, pregnancy (defined as positive β-HCG blood test), breast-feeding.
10. Any medication (including PgP or BCRP inducers or inhibitors, or omeprazole) within 14 days before inclusion or within 5 times the elimination half-life or pharmacodynamic (PD) half-life of the medication (except HRT and contraception when applicable), any vaccination within the last 28 days (except COVID-19 vaccination) and any biologics (antibody or its derivatives) given within 4 months before inclusion.
11. Any vaccination, including COVID-19 within 2 weeks before inclusion.
12. Any participant who, in the judgment of the Investigator, is likely to be noncompliant during the study, or unable to cooperate because of a language problem or poor mental development.
13. Any participant in the exclusion period of a previous study according to applicable regulations.
14. Any participant who cannot be contacted.
15. Any participant who is the Investigator or any co-Investigator, research assistant, pharmacist, study coordinator, or other staff thereof, directly involved in conducting the study.
16. Positive result on any of the following tests: hepatitis B surface antigen (HBs Ag), anti-hepatitis B core antibodies (anti-HBc Ab), anti-hepatitis C virus (anti-HCV) antibodies, anti-HIV1 and anti HIV2 Ab.
17. Positive result on urine drug screen (amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates).
18. Positive alcohol breath test.
19. Any consumption of citrus (grapefruit, Seville orange, etc.) or their juices within 5 days before inclusion.
20. Have a risk factor of QT prolongation (as for example electrolyte imbalances) or a personal or a family history of prolonged QT interval syndrome or Torsade de Pointes, or family history of sudden death.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Standardized meals will be provided uniformly to all participants during the inpatient period. On D-1 an evening snack may also be provided, in compliance with the definition of the fasting period duration.

For the dosing on D1, an overnight fast will be imposed, so that no food is taken within at least 10 hours before investigational medicinal product administration. Participants will remain fasted for at least 2 hours after dosing, participants could have a snack at H2 post-dose, be served lunch at H4 post-dose, possible snack in the afternoon and dinner around H10 post-dose.

Drinking of water will be allowed ad libitum except for 1 h before and 1 h after dosing; before and after that period, drinking water will be permitted ad libitum.

5.3.2 Caffeine, Alcohol, Tobacco, and Other Habits

Consumption of citrus fruits and their juices is prohibited during participation to the study, starting from 5 days prior to the IMP)- ITF2357 (givinostat hydrochloride monohydrate) administration until D5.

From D-1 and throughout the entire institutionalization (i.e., up to D5), participants will be requested to abstain from consumption of any coffee or caffeine containing beverages (e.g., tea, chocolate), alcohol, and quinine. Participants will also be instructed to abstain from smoking from admission (D-1) to the last PK time point.

5.3.3 Physical Activity

Participants will be requested to follow a stable lifestyle with no intensive physical activity for the duration of the study until the EOS visit.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently included. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Screening assessments that yield aberrant results (e.g., safety laboratory samples) may be repeated once within the screening window by the investigator based upon clinical judgement.

Retested participants should be assigned the same participant number as for the initial screening.

Individuals who do meet the criteria for participation in this study (screen failure) after a first screening visit, may be rescreened at the Investigator’s discretion. Rescreening is permitted only once per participant.

If the rescreening is performed out of the screening window allowed, then a complete rescreening visit will be performed, and a new screening number will be assigned.

6 INVESTIGATIONAL MEDICINAL PRODUCTS AND CONCOMITANT THERAPY

6.1 Description of Investigational Medicinal Products

The following IMPs will be administered:

Study Treatment Name:	**ITF2357**
Active ingredients	Givinostat hydrochloride monohydrate
Excipients	Polysorbate 20, Glycerol, Tragacanth Gum, Sodium Benzoate, Peach Flavor, Cream Flavor, Saccharin sodium, Liquid Sorbitol 70%, Tartaric Acid, Sodium Hydroxide and Purified water
Dosage formulation:	Oral suspension at the concentration of 10 mg/mL.
Unit dose strength(s)/Dosage level(s):	50 mg (5mL) *(Dose of the study drug is expressed as givinostat hydrochloride monohydrate.)*
Route of Administration	Oral
Dosing instructions:	Refer to Section 6.3
Packaging and Labelling	It is supplied in a 150 mL capacity amber polyethylene terephthalate (PET) bottle closed by means of a high-density polyethylene (HDPE) child-proof screw cap equipped with low-density polyethylene (LDPE) shutter/syringe adapter. Each bottle contains 140 mL of ITF2357 10 mg/mL oral suspension. The bottles are intended for multi-dose use and a 5 mL graduated dosing syringe is included as measuring device.
Manufacturer	[redacted]

Further details on the mode of administration are provided in Section 6.3.

Supply of the IMPs

Enough Investigational Medicinal Product will be supplied to the Investigational sites to cover the whole study. The manufacturer and/or Sponsor's representative will provide a certificate of analysis and a batch release certificate for the batch (s) of IMP used in the study. The IMP will be packaged and labelled by the Sponsor s in accordance with the protocol and applicable national laws and regulations. Additional labelling can be performed at site (s) pharmacy if required according to site SOP.

Labelling of the IMPs

The IMPs will be labelled per participant according to the European Union-Good Manufacturing Practice (EU-GMP), including its annex 13, regulation EU 536/2014 requirements art 66 and Annex VI as well as all local regulations.

The IMPs will be bearing the following information on the labels amongst others:

- Sponsor's name and address
- Description (name/code of the drug, formulation, dosage etc.)
- Batch and/or code number
- Study code
- Treatment number
- Investigator's name
- Statement "For clinical trial use only"
- Storage conditions
- Expiry date or Retest date

The Investigator, or designee, will only dispense IMPs to participants included in this trial. Each participant will only be given the IMP carrying their number. The dispensing for each participant will be documented in the participant's case report form (CRF).

6.2 Rationale for Investigational Medicinal Products

Rationale for IMP is detailed in the Introduction in Section 2.

6.3 Dosing and Administration

The IMP will be administered only to participants included in this study following the procedures set out in the present clinical study protocol and described in the study-specific pharmacy manual.

Participants will be administered the IMP, after an overnight fast of at least 10 hours, orally as suspension at the dose of 50 mg (5mL), using a 5 mL graduated dosing syringe.

The day of IMP administration (D1), participants will be requested not to drink water 1-hour before and 1-hour after IMP administration. Participants will stay seated for 10 minutes after administration. After this period, they will stay in a semi-recumbent position for the next 4 hours. No food should be allowed for at least 2 hours after administration, please refer to Section 5.3.1.

Water supply will be at least 1500 mL for each 24 hours.

6.3.1 Investigational Medicinal Product Dose Modification

No dose modification is foreseen in this study.

Information on stopping IMP administration for individual participants due to safety/other reasons is detailed in Section 7.

6.4 Treatment of Overdose

Overdose is defined as the unintentional administration of a quantity of the study treatment given per administration or per day that is above the maximum recommended dose according to the protocol for the study treatment. This also considers cumulative effects due to overdose.

No cases of overdose have been reported with the IMP. No specific antidote exists. Thus, and in case of suspected or reported overdose, treatment of any clinical signs will be symptomatic.

For Overdose reporting please refer to Section 17.2.

6.5 Preparation, Handling, Storage and Accountability

The complete instructions will be detailed in the study-specific pharmacy manual.

6.5.1 Preparation of Investigational Medicinal Product

The complete instructions will be detailed in the study-specific pharmacy manual.

6.5.2 Handling and Storage of Investigational Medicinal Product

The shelf life of IMP oral suspension 10 mg/mL – 140 mL/bottle is 48 months under refrigerated storage conditions (5°C ± 3°C). Further instructions on storage conditions will be detailed in the study-specific pharmacy manual.

IMP containers must be kept in a secure and locked storage area with limited access, and with temperature control and monitoring. Once the container is firstly opened, the suspension can be administered for a maximum of 30 days.

The pharmacist at the Investigational sites will be responsible for the correct storage and handling of the IMPs.

Deviations from the storage requirements, including any actions taken, must be documented.

6.5.3 Accountability of Investigational Medicinal Product

The Investigator or their designee must maintain a complete and current dispensing and inventory record. The Investigator or their designee is accountable for all IMPs supplied by the Sponsor. The dispenser uses this information to maintain an accurate and complete dispensing and inventory record. The designated copies of the completed dispensing and inventory record will be provided to the Sponsor.

Regulatory agencies require accounting of the disposition of all investigational drugs received by each clinical investigational site. Information on IMP disposition required by law consists of the date received, date administered, quantity administered, and the participant to whom the drug was administered.

All unused, partially used and empty IMPs will be left in their individual containers and returned in their original container to the Sponsor, after the Monitor has performed accountability. Retention samples are maintained by the Sponsor.

Upon completion or termination of the study, a sample of all study supplies will be retained at the trial site according to applicable regulations. Once the retention period has elapsed, any remaining unused drug will be returned to Sponsor in the original containers, or destroyed, as directed in writing by Sponsor.

IMPs and if applicable supplies are shipped to the investigational site as needed. Drug accounting will be reviewed by the site Monitor during routine monitoring visits.

At the completion or termination of the study, a final drug accountability review and reconciliation must be completed, and any discrepancies must be investigated, and their resolution documented.

All full, partially full, and empty study treatment containers must be returned by each site pharmacy to the Sponsor or be destroyed at each site after the Monitor has performed final accountability and after Sponsor approval, using the appropriate agreed form.

6.6 Participant Assignment, Randomization and Blinding

6.6.1 Participant Assignment

Participants meeting the study eligibility criteria will be included in the study.

It is planned that the participants with HI will be recruited first, then the matched participants will be recruited. The matching of participants will be 1:1 between a moderate hepatic impairment patient and a healthy participant, as described in Table 3.

Table 3: Matching participants

	Participants with moderate HI	**Matched participants w/normal hepatic function**
Weight	Calculate the average weight of participants with HI	Each matched participant should weigh within 10% of the average weight of participants with HI

HI: hepatic impairment

In terms of gender and to be able to compare the group if feasible, at least 3 males and 3 females should be included in each group (mild HI, moderate HI and healthy participants).

The participants will be assigned a participant number in chronological order according to the investigational site's standard procedures within each population group:

Group	**ID number**	**Replacement ID number**
Participants with mild HI	0101 to 0108	5101 to 5108
Participants with moderate HI	0201 to 0208	5201 to 5208
Healthy participants (normal hepatic function)	0301 to 0308	5301 to 5308

ID: Identification Number; HI: hepatic impairment

6.6.2 Randomization

No randomization will be performed, as all participants will receive the same single dose treatment.

6.6.3 Blinding and Unblinding

Not applicable since this is an open-label study.

6.6.4 Emergency Unblinding

Not applicable as this is an open-label trial.

6.7 Investigational Medicinal Product Compliance

The IMP will be administered in the Investigational clinical unit under direct supervision of the Investigator or their designee.

After administration of the IMP, a mouth check will be performed to verify that the participant has swallowed the dose. The IMP administration information will be recorded in the electronic (e)CRF.

The definition of overdose is provided in Sections 6.4. and 18.5. The definition of medication errors, abuse and misuse are provided in Section 18.5. Overdoses, medication errors, abuse or misuse will be collected as part of IMP dosing information and/or as a protocol violation, as required.

6.8 Concomitant Therapy

6.8.1 Prohibited Concomitant Therapy

For matched healthy participants, concomitant treatment (except HRT for postmenopausal women and oral contraception for WOCBP) is not permitted throughout the study unless absolutely required for treatment of AEs.

For participants with HI, it is not permitted to use the following drugs:

- Drugs that Prolong the QTc Interval

  Concomitant use of ITF2357 with other product(s) with a known potential to prolong the QTc interval should be avoided.

  ITF2357 causes QTc interval prolongation. Therefore, concomitant administration of ITF2357 with other products that prolong the QTc interval may result in a greater increase in the QTc interval and adverse reactions associated with QTc interval prolongation, including Torsade de pointes, other serious arrythmias, and sudden death.

  Refer to Appendix 12 for the list of these prohibited drugs.

- P-glycoprotein (P-gp) or breast cancer-resistance protein (BCRP) potent inducers or inhibitors.

  P-gp and BCRP inducers and inhibitors may alter the pharmacokinetics of ITF2357. Therefore, concomitant use of ITF2357 with these products must be avoided.

  Refer to Appendix 15 for the list of these prohibited drugs.

6.8.2 Permitted Concomitant Therapy

For participants with HI, necessary concomitant treatments will be authorized following the Investigator's decision, considering known and potential PD and PK interactions with ITF2357. There are certain drugs that might be influenced by ITF2357, such as cytochrome P450 3A4 (CYP344) and Organic Cation Transporter 2 (OCT2) sensitive substates. Thus, they should be used with caution.

- CYP3A4 Sensitive substrates

  ITF2357 is a weak intestinal CYP3A4 inhibitor and when administered in combination with oral CYP3A4 sensitive substrates for which a small change in substrate plasma concentration may lead to serious toxicities, this needs to be closely monitored. See Appendix 13 that lists the permitted drugs known to be CYP3A4 sensitive substrate. The CYP3A4 sensitive substrates that are also known to prolong QTc interval (refer to Appendixes 12 and 13) are not permitted.

- OCT2 Sensitive Substrates

  ITF2357 is a weak inhibitor of the renal uptake transporter OCT2 and when administered in combination with drugs that are known as a sensitive substrate of the OCT2 transporter for which a small change in substrate plasma concentration may lead to serious toxicities, this needs to be closely monitored. See Appendix 14 that includes the permitted drugs known to be sensitive substrates of OCT2. The OCT2 sensitive substrates that are also known to prolong QTc interval (refer to Appendixes 12 and 14) are not permitted.

- Drugs known to be substrates of P-gp

  The potential of ITF2357 to inhibit the intestinal transporter protein P-gp cannot be excluded. Medicinal products administered orally that are known to be sensitive substrate of the P-gp transporter for which a small change in plasma concentration may lead to serious toxicities should be used with caution with ITF2357. A list of P-gp sensitive substrates is provided in Appendix 16.

Administration of ibuprofen is accepted in treatment of AE, as an alternative to paracetamol.

In general, for any participant, if the use of any concomitant treatment becomes necessary (e.g., the treatment of an adverse event), the treatment must be recorded on the eCRF, including the reason for treatment, generic name of the drug, dosage, route, and date and time of administration. If treatment is administered, a joint decision between the Sponsor and the Investigator will be taken to determine whether the participant can continue the clinical trial or if replacement is needed.

6.8.3 Rescue Therapy

None, refer to Section 6.4 for the treatment of IMP overdose.

6.8.4 Other Therapy

None.

7 DISCONTINUATION OF INVESTIGATIONAL MEDICINAL PRODUCTS AND PARTICIPANT WITHDRAWAL FROM TRIAL

7.1 Discontinuation of Investigational Medicinal Products

Not applicable as this is a single-dose study.

7.1.1 Criteria for Permanent Discontinuation of Investigational Medicinal Products

The trial stopping rules are defined in Section 7.4.

7.1.2 Temporary Discontinuation or Interruption of Investigational Medicinal Products

Refer to the Schedule of Activities (SOAs) in Section 1.3 for data to be collected, for follow up and for any further evaluations that need to be completed.

7.1.3 Rechallenge

Rechallenge is not allowed.

7.2 Participant Withdrawal from the Trial

Any participant may be withdrawn from the study at the discretion of the Investigator. The participant is also free to terminate his/her participation at any time. However, if the participant has been dosed with the IMP, it is recommended to ask the participant to remain in contact with the Investigational site, and the investigational sites should make every effort to convince the participant to return for a safety follow-up visit. An end-of-study (EOS) visit will then be organized.

The Investigator will also undertake to obtain more detailed information about any participant lost to follow-up. Participants withdrawn from the study must not be re-included.

The replacement of participants is described in Section 7.5.

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if they fail to return to the schedule EOS visit and are unable to be contacted by the study site.

The following actions must be taken if a participant is to be considered lost to follow-up:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the trial.
- In cases in which the participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

7.4 Trial Stopping Rules

Stopping rules will apply to this trial. They may lead to a final end of dosing or a temporary halt, depending on the timepoint when the stopping rule is met during the study. After a stop, the study can be restarted with a substantial amendment. Any submitted substantial amendment (if required to restart the study) should include a rationale for the proposed dosing and for the continuation of the trial and details of any adjustments to the protocol, including additional safety monitoring, if applicable.

The stopping rules are, at the study level:

- A serious adverse drug event (SAE) at least possibly related to the IMP administration in one participant.
- 'Severe' non-serious adverse events at least, possibly related to the IMP administration in two participants independent of whether they are within the same system organ class (SOC) or not.
- Any AE assessed as related to the IMP that would lead to undue risk if dosing with the IMP continued, in the judgement of the Investigator.
- New information or other evaluation regarding the safety of the trial drug that indicates a significant change in the known risk/benefit profile of the investigational trial drugs, such that the risk is no longer acceptable for participants participating in the trial,
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary trial objectives, or that compromises participant safety,

Should any stopping rule be met, the Sponsor will be informed and a joint decision of how to proceed will be made. If it is decided that the trial is continued after a temporary hold, the trial will continue upon agreement by the correspondent regulatory authorities.

7.5 Replacement of participants

If replacement of participants is necessary to have a total of 24 evaluable PK profiles, the replacement participants will have to follow the rules for participants matching described in Table 3. The replacement participants will be assigned to the same population group (mild HI, moderate HI or normal hepatic function) as the participant they are replacing (see Section 6.6.1 for participant replacement numbering).

Participants may be replaced if any of the following occurs:

- Vomiting within the first 4 hours after administration
- Less than 80% of the required PK samples are collected within 24 hours after administration
- PK samples are missing at timepoints that do not allow adequate characterization of the main PK parameters for ITF2357, ITF2374 and ITF2375
- Major protocol deviation(s).

In case of moderate or severe AE causing the participant to withdraw, a joint decision between the Sponsor and the Investigator will be taken on the appropriateness of replacing the participant or not.

7.6 Withdrawn Participant Data Collection

The Principal Investigator (PI) and/or other Investigator involved in the study will document on the termination page of the eCRF and in the participant's medical records the primary reason for the participant's withdrawal as follows:

- If applicable, "Lost to follow-up" (see Section 7.3). Intensive efforts should be made to locate and recall participants who are lost to follow-up if possible and, at a minimum, to determine their health status;
- AE: an AE form must be completed;
- Protocol non-compliance;
- Consent withdrawn;
- Lost to follow-up
- Study terminated by Sponsor
- Other: if none of the above-mentioned reasons are applicable, then the reason will be specified.

All withdrawals will be reported to the Sponsor.

For all withdrawals, the End-of-Study visit will be scheduled as soon as possible after the IMP administration and will document the progress of their condition. In every case, the eCRF must be filled in up to the last visit performed.

8 TRIAL ASSESSMENTS AND PROCEDURES

8.1 Screening/Baseline Assessments and Procedures

The detailed information is provided in Section 1.3, Schedule of Activities (SOA).

It is recommended that when vital signs, ECG, and blood samples are scheduled at the same time as the IMP administration and/or a meal, they should be done prior to IMP intake and/or the meal.

Whenever measurements of vital signs, ECG, and blood samples for PK and safety coincide, the following order will be respected: ECG, vital signs, safety, meals, and then PK samples. To respect the exact timing of PK samples, ECG and vital signs will be done ahead of the scheduled time.

8.2 Efficacy Assessments and Procedures

Not applicable.

8.3 Safety Assessments and Procedures

8.3.1 Physical Examination

The timing of the complete physical examinations, body weight and height is provided in Section 1.3, Schedule of Activities (SOA).

The physical examinations will be performed by the Investigator or their representatives.

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, dermatological and neurological, musculoskeletal in addition to head, eyes, ears, nose, throat, neck and lymph nodes systems. Height and weight will also be measured and recorded. The physical examination will NOT include pelvic, or rectal examinations. Further examination of other body systems may be performed in case of evocative symptoms at the Investigator's discretion. Investigators should pay special attention to clinical signs related to previous serious illnesses.

Any abnormality identified at Screening should be recorded as Medical History.

8.3.2 Vital Signs

The timing of the vital signs assessments is provided in Section 1.3, Schedule of Activities (SOA).

Parameters

- Measured parameters: Body temperature (oral), supine systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate (PR), and respiratory rate (RR).

Method of assessment

Qualified staff members will perform blood pressure (BP) measurements. If possible, BP measurements will be taken from the same arm (opposite the arm that is used for blood sample collection) by an automated BP monitor using the oscillometric method (e.g., Dinamap®). If there is a clinically important change in BP from the previous recording, measurements will be repeated immediately to confirm the change.

BP and PR will be measured using an automatic device for each participant, after at least 5 minutes at rest in the supine position.

BP will be also measured within 3 minutes when changing from supine to standing position at screening and D-1.

8.3.3 Electrocardiograms

The timing of the ECG recording is provided in Section 1.3, Schedule of Activities (SOA).

Parameters

- Measured parameters: HR, PR interval, QRS duration, QRS axis, QT interval;
- Derived parameters: two corrections of the QT interval will be investigated: Fridericia's correction (QTcF) and Bazett's correction (QTcB).
- Observations and comments on the quality of the trace if needed, on normality or abnormality.

Method of assessment

The measurements will consist of 12-lead digital ECGs.

Participants must rest in the supine position for at least 10 minutes before the ECG recording is started. The ECG may be recorded after the period of rest required and before the measurements of supine blood pressure and pulse. A qualified physician will review the ECGs promptly and any clinically important finding will be recorded on the appropriate CRF. The Investigator is responsible for providing the interpretation of all ECGs.

If an ECG demonstrates a prolonged QTcF interval >450 msec, 2 additional ECGs (with 5 minutes between recordings) will be obtained. The average QTcF values of the 3 ECGs (triplicates) will be calculated.

8.3.4 Clinical Laboratory Assessments

The timing of the clinical laboratory assessments is provided in Section 1.3, Schedule of Activities (SOA).

Safety Parameters

The following parameters will be determined:

- **Hematology:**

Haemoglobin, hematocrit, erythrocytes, platelets, leucocytes and absolute count for basophils, eosinophils, lymphocytes, monocytes, and neutrophils.

- **Blood chemistry:**

Sodium, potassium, chloride, calcium, urea, creatinine, albumin, glucose, total proteins, triglycerides, total cholesterol, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), creatinine phosphokinase (CPK), alkaline phosphatase, and total bilirubin.

- **Coagulation:**

Prothrombin (PT) and Prothrombin International Normalized Ratio [INR] and activated partial thromboplastin time (aPTT).

- **Serology**

Blood tests will be carried out to test for the presence of hepatitis B surface antigen (HBs Ag), anti-hepatitis B core antibodies (anti-HBc Ab), anti-hepatitis C virus (anti-HCV) antibodies, anti-HIV1 and anti-HIV2 Ab.

- **Urinalysis**

Dipstick determination of pH, protein, glucose, leukocytes, nitrites, ketones, blood will be performed. Microscopic analysis may be performed in case of abnormalities.

Qualitative: A dipstick is to be performed on a freshly voided specimen for qualitative detection using a reagent strip.

Quantitative: A quantitative measurement for erythrocytes, and leukocyte count will be required in case the urine sample test is positive for any of the above parameters by urine dipstick (e.g., to confirm any positive dipstick parameter by a quantitative measurement).

- **Others**
  - Alcohol breath test
  - Urine drug screen to test for the presence of amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates.

Method of assessment

Samples of blood and urine will be collected at the visits summarized in Section 2. Blood samples will be collected in fasted conditions. Urine collection may be performed anytime in the morning, except on D5 at H96, the urinalysis may be performed within a ±2 hours' time-window.

For all clinically significant abnormal parameter test values identified after investigational product administration, testing will be repeated until the values return to normal or baseline. If the parameter values do not return to normal or baseline within a reasonable period, the etiology should be identified, and the Sponsor notified.

Blood safety determinations

Laboratory tests will be performed by local laboratories.

8.3.5 Pregnancy test and Hormone test

For women of childbearing potential only, serum pregnancy tests (β-HCG) will be performed at screening, D-1 and EOS.

The level of follicle-stimulating hormone (FSH) will be performed at screening only in post-menopausal women without HRT.

8.3.6 Special Assessments

In case of a new COVID-19 pandemic, exceptional measures such as adjustments in study visits may be considered, if in the overall best interest of the participants. Some of the adjustments may include:

- SARS-CoV-2 viral RNA test
- Use of alternative facility for assessments (e.g., local laboratory)
- Replacement of a study visit with alternative methods for assessments (such as phone contacts or virtual visits to assess safety)
- Postponement of a study visit or of individual assessments
- Temporary suspension of sample collection

This assessment will be fully documented, and any deviations to the protocol will be recorded in accordance with the CRO's standard procedure.

8.4 Adverse Events and Serious Adverse Events

8.4.1 Definitions of AE and SAE

The definitions of an AE or SAE can be found in Appendix 17: Adverse Events and Serious Adverse Events – definitions, severity, and causality.

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up all AEs/SAEs, with special attention to the ones that are serious, considered related to the trial treatment or the trial, or that caused the participant to discontinue the IMP (see Section 7).

8.4.2 Time Period and Frequency for Collecting AE and SAE Information

All AEs, including SAEs, occurring within the period of observation for the clinical trial must be recorded.

The period of observation for the collection of AEs extends from the time when the participant gives informed consent until the end-of-trial visit. For all participants, this period will be extended to follow-up on all on-going AEs after the end of the treatment period, until all AEs are finally resolved or it is medically justifiable to stop further follow-up (e.g., a chronic condition has been reached).

8.4.3 Identifying AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence (e.g., "tell me the sequence of events as you perceived them", how would you describe the event?", etc.).

8.4.4 Recording of AEs and SAEs

AEs must be documented as soon and as completely as possible on the "Adverse Events" pages in the CRF. Follow-up information must be entered as soon as available.

The following will also be specified:

- Duration, severity, relationship with IMP and action taken with IMP.
- Other actions (none, medication required, tests required)
- Outcome and date of outcome according to the following definitions:
  - Recovered/resolved
  - Recovering/resolving
  - Not recovered/not resolved
  - Recovered/resolved with sequelae
  - Fatal
  - Unknown
- Seriousness: yes or no, further details are provided in Section 17.2.

AEs that occur during the trial should be treated by established standards of care that will protect the life and health of the participants. If such treatment constitutes a deviation from the protocol, the participants should be withdrawn from the trial and the reason must be documented in the CRF.

Further details on assessing severity and causality of AEs and SAEs are in Appendices 17.3 and 17.4.

8.4.5 Follow-up of AEs and SAEs

There is no time limit on the collection of SAEs that are considered related to IMP. If the Investigator detects an SAE in a study participant after the end of the period of observation, and considers the event possibly related to prior trial treatment or procedures, he or she must immediately inform the Sponsor's Representative(¤) to determine how the SAE should be documented and reported.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, returns to baseline values (if a baseline value is available), until the event is otherwise explained, or the participant is lost to follow-up.

8.4.6 Reporting of SAEs

All SAEs declared during the conduct of the study will be reported to the Biotrial safety unit within 24 hours of discovery by the Investigator by using Biotrial's SAE report form. The form will be available for downloading in the eCRF, and it is to be completed manually and uploaded in a secure folder (or sent via fax as back-up method) using the contacts below:

Biotrial Pharmacovigilance Unit

Phone: [redacted]

Phone: [redacted]

Fax: [redacted]

e-mail: [redacted]

For the SAEs that are reported after the end of the trial and after database lock, the investigators must immediately inform the Sponsor:

Italfarmaco S.p.A.

Global Pharmacovgilance

Via dei Lavoratori, 54

20092 Cinisello Balsamo (MI), Italy

Fax: [redacted]

Fax (back-up): [redacted]

Mobile [redacted]

e-mail: [redacted]

8.4.7 Regulatory Reporting Requirements for SAEs

General

SAEs must be immediately reported and no later than 24 hours of the Investigator becoming aware of the event to the Sponsor or its designated representative using the agreed SAE report form. In particular, if the SAE is fatal or life-threatening, the Sponsor or its designated representative must be notified immediately, irrespective of the extent of AE information available.

The minimum requirements for SAE reporting are: one SAE (the diagnosis or symptoms), one identifiable coded subject, one identifiable reporter, one suspect IMP, and the causality assessment.
Serious adverse event reports must be made whether or not the Investigator considers the event to be related to the investigational drug.

This timeframe also applies to additional (follow-up) information that becomes available on previously forwarded SAE reports. The Sponsor or its designated representative will then follow expedited reporting procedures according to local and international regulations as appropriate.

The Investigator is obligated to pursue and provide information to the Sponsor or its designated representative on all SAEs in accordance with the timeframes for reporting as specified above. In addition, an Investigator may be requested by the Sponsor or its designated representative to obtain specific additional follow-up information in an expedited fashion. In general, this will include a detailed description of the SAE (e.g., the diagnosis or symptoms, start date and end date of the SAE or duration, seriousness, severity, causality assessment of the investigator, actions taken with the suspect drug, etc.) to allow for a complete medical assessment of the case and an independent determination of the possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses, must be provided. In the case of death of a subject, a summary of available autopsy findings (with anonymized data), if available, must be submitted as soon as possible to Biotrial safety unit as described in Section 8.4.6.

All SAEs will be followed up until event resolution or stabilization (for chronic events), if possible, even when a subject is withdrawn from treatment. For chronic events that do not fully

resolve until years later, the outcome should be reported as 'resolved with sequelae' as soon as the event has stabilized.

Follow-up information for the SAE should be actively sought and submitted as the information becomes available, as reported in Sections 8.4.5 and 8.4.6. If the Investigator or their designee detects an SAE in the subject after the follow-up visit and considers the event to be related to the IMP or trial procedures, the Investigator should contact the Sponsor or its designated representative to determine how the SAE should be documented and reported.

The Sponsor (or Biotrial on Sponsor behalf) will comply with all relevant regulatory requirements relating to safety reporting to the regulatory authority, independent ethics committee (IEC), and investigators.

All SAEs will be reported immediately, using the SAE form, by the Investigator or their designee, to the Biotrial PV contact, see Section 8.4.6, who will then report to the health authorities as applicable as per the reporting requirements, to the IEC and to other sites.

Also, the Sponsor (or Biotrial on Sponsor behalf) will report suspected unexpected serious adverse reactions (SUSARs) under the same Sponsor / same IMP from other trials to the health authorities. The occurrence of any such SUSARs will be reported to the Eudravigilance database according to European Regulation (EU) No 536/2014.

Further details on the safety reporting, including Biotrial and Sponsor roles and responsibilities, will be detailed in the trial specific safety management plan.

In addition, according to parts V and VI of French Competent Authorities document entitled "Avis aux promoteurs - Essais Cliniques des Médicaments relevant du Règlement Européen N° 536/2014", for the phase 1 of the present trial (clinical trial conducted in France with administration of an IMP to healthy participants), the Sponsor must immediately notify to ANSM at the following address: declarationsusars@ansm.sante.fr:

- All SUSARs
- All expected serious adverse reactions
- All SAEs.

New Safety Medical Fact

An SAE may also be a new safety medical fact.

In case of a new safety medical fact (see definition in appendix, Section 17.1.4), the Sponsor will:

- Proceed to all medical and safety measures necessary for the protection of on-going volunteers,
- Interrupt the administration of the treatments to all volunteers,
- Inform without delay the French National Agency for Medicines and Health Products (ANSM) about the new safety medical fact, at the following email address: vig-essaiscliniques@ansm.sante.fr with the following subject: New fact/ Healthy volunteers/ trial number/ DCI (dénomination commune internationale) or substance code and including:
    - European Union (EU) CT N°,
    - Title of the trial protocol,

- Protocol code number,
- Summary of the new fact and urgent safety measures implemented, if necessary,

- Inform without delay the director of the Agence Régionale de Santé (ARS) at the following email address: ars35-alerte@ars.sante.fr
- Inform without delay the independent ethics committee via the Clinical Trial Information System (CTIS) portal,
- Inform the on-going volunteers about the new available information, and request for their consent before restarting the trial,
- Contact if appropriate the previously dosed volunteers in order to inform them of the new safety medical fact and/or verify that they have no safety concerns.

Any follow-up information regarding the new safety medical fact will be reported to the Sponsor's SAE contacts and regulatory authorities within 8 days, and details regarding the urgent safety measures set up will be sent within 15 days to the regulatory authorities.

8.4.8 Serious and Unexpected Adverse Reaction Reporting

Details on Serious and Unexpected Adverse Reaction reporting are provided in Appendices 17.1.2 and 17.1.4.

8.5 Pregnancy and Postpartum Information

8.5.1 Participants Who Become Pregnant During the Trial

If a participant enrolled in this study becomes pregnant, follow-up procedures are initiated by the Investigator using the study´s standard pregnancy form. Pregnancy form should be reported by the Investigator to Biotrial PV within 24 hours from the awareness. As for the SAE, the pregnancy form will be available for download in the eCRF, and it is to be completed manually and uploaded in a secure folder (or sent via fax as back-up method), as described in Section 8.4.6. The course/outcome of the pregnancy and development of the child need to be recorded as close as possible prior to the closure of the study. The new-born child, however, is followed up until twelve months after the estimated delivery date.

While pregnancy itself is generally not considered to be an AE or SAE (unless an influence e.g., by an interaction is reasonably imputed), any pregnancy complication, any elective termination of a pregnancy for medical reasons and any malformation of the new-born child will be recorded as an AE or SAE.

A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as a result of a post-trial pregnancy which is considered reasonably related to the IMP by the Investigator will be reported to the Sponsor.

8.5.2 Participants Whose Partners Become Pregnant

The participant will be asked to report to the Investigator any pregnancy through the dedicated pregnancy form from their female partner after IMP dosing. The information will be entered into the participant's eCRF.

8.6 Pharmacokinetics

8.6.1 Pharmacokinetic Assessment Methods and Timing

Blood sampling for plasma determinations of ITF2357 and its metabolites (approximately 4mL per sample) will be drawn by direct venipuncture or via an intravenous catheter, at the following time-points: pre-dose (within 30 minutes before administration), then 0.5, 1, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 60, 72 hours and 96 hours post-dose.

Four additional blood samples for the assessment of the free fraction of ITF2357 and its metabolites with high protein binding, i.e., ITF2374 and ITF2375 will be collected at 2 hours (expected ITF2357 t_{max}), at 4 hours (expected ITF2375 t_{max}), at 5 hours (expected ITF2374 t_{max}) and at 12 hours (ITF2357, ITF2374 and ITF2375 C_{min} for bid regimen) post-dose.

Full instructions for collection, processing, labelling, storage and shipment of samples are provided in the study-specific laboratory manual. Detailed method of assay will be described in Bioanalytical Report.

When a sampling time is close to mealtime, the sample will be collected before the meal.

8.6.2 Sample handling and labelling

Instructions and examples of labelling will be provided in the study-specific laboratory manual.

8.6.3 Sample shipment and storage

The samples will be shipped in a container filled with enough dry ice to ensure that the samples are kept frozen.

Trial samples will be shipped to the bioanalytical laboratory on dry ice, as separate shipments for the primary and back-up samples. For further instructions, please refer to the study-specific laboratory manual.

8.6.4 Bioanalytical method

Plasma concentrations of IMP and its metabolites will be evaluated using a validated method. Total ITF2357, ITF2374 and ITF2375 will be extracted using an automated liquid-liquid extraction and analyzed by HPLC-MS/MS. The extent of protein binding of ITF2357, ITF2374 and ITF2375 in human plasma will be determined using the Rapid Equilibrium Dialysis technique combined with HPLC-MS/MS analysis.

Further details will be provided in the Bioanalytical Report.

8.6.5 Pharmacokinetic Criteria

The pharmacokinetic parameters will be determined using Phoenix® Winnonlin® version 8.4 or higher (Certara USA, Inc., Princeton, NJ).

The following blood pharmacokinetic parameters will be calculated for parent and its metabolites, by standard non-compartmental methods for those participants with sufficient plasma concentration data:

- C_{max}: Maximum plasma concentration,
- t_{max}: time to reach maximum plasma concentration,

- AUC_{last}: Area under the plasma concentration-time curve from time zero to the last quantifiable concentration
- $AUC_{0\text{-}inf}$: Area under the plasma concentration-time curve from time zero to time of infinity,
  calculated as follows: $AUC_{0\text{-}inf} = AUC_{0\text{-}t} + C_t / \lambda z$
  With Ct last quantifiable concentration at time t
  λz: apparent terminal elimination rate constant
  The different areas under the concentration-time curve (AUC) will be calculated using the linear-log trapezoidal method (also called linear up-log down) method).
- $t_{1/2}$: terminal elimination half-life calculated as follows: $t_{1/2} = Ln(2)/\lambda z$.

The following blood PK parameters will be calculated only for the parent:

- CL/F: Apparent total body clearance calculated as follows
  $CL/F = Dose / AUC_{0\text{-}inf}$.
- Vz/F: Apparent volume of distribution calculated as follows
  $Vz/F = CL/F / \lambda z$

Unbound PK parameters will be calculated only for parent and metabolites with high protein binding (ITF2374 and ITF2375):

- f_u: Unbound fraction.
- $C_{max,u}$: Unbound maximum plasma concentration,
- AUC_{lastu}: Unbound area under the plasma concentration time curve from time zero to the last quantifiable concentration
- AUC_{infu}: Unbound area under the plasma concentration time curve extrapolated to infinity

Only for ITF2357:

- CL/F_u: Unbound apparent total body clearance
- Vz/F_u: Unbound apparent volume of distribution

The list of parameters could be adjusted if needed during the analysis.

9 STATISTICAL CONSIDERATIONS

9.1 Analysis Sets

The analysis will be conducted on all participant data at the time the end of study.

The Enrolled Set will be defined as all participants having signed their informed consent.

The Treated Set will be defined as all included participants having taken at least one dose of IMP.

The PK set will be defined as all treated participants with available PK plasma time-concentration data.

The PK-evaluable set is a subset of the PK population who have adequate dosing and plasma concentration-time data for estimation of PK parameters.

The study pharmacokineticist will be responsible for determining if adequate concentration data are available and in addition, the final analysis set will be validated during the study data review meeting.

The number of participants included in each study population (Treated Set, PK set and PK-evaluable set) will be provided by population group (normal and HI groups) and on overall participants. All exclusions from any analysis populations will be fully documented in the clinical study report.

9.2 Analyses Supporting the Objective(s)

The statistical analyses will be performed by the Biostatistics Unit of Biotrial Biometrics using SAS® software version 9.4 or higher release (SAS Institute Inc., Cary, NC, USA).

Descriptive statistics will be supplied according to the nature of the criteria:

- Quantitative variable: sample size, arithmetic mean, standard deviation (SD), standard error of the mean (SEM), minimum, median and maximum, and quartiles if necessary [with geometric mean, arithmetic and geometric coefficients of variation (CV) for PK parameters].
- Qualitative variable: sample size, absolute and relative frequencies per class.

All listings will be presented by population group and participant.

No interim analysis is planned.

Statistical methods will be further outlined in the Study-Specific Statistical Analysis Plan (SAP) and approved by the Sponsor prior to database lock.

Management of missing data and values below/above a limit of detection/quantification will be detailed in the SAP.

For all parameters and for participants with retest values, the last reliable value will be used for the measurement time before the IMP administration and the first reliable value will be used for the measurement time after the IMP administration.

The participants' demographic characteristics and baseline characteristics will be summarized by population group and overall and listed. Tables by population group and overall, with the number of participants having at least one medical or surgical history and a corresponding listing will be prepared. Tables by population group and overall, with number of participants having at least one previous treatment will be prepared. The same table will be prepared for concomitant treatments. Details of drug dosing and meals will be listed.

9.3 Pharmacokinetics Analyses

The analysis will be performed on the PK Set.

PK parameters will be calculated by a non-compartmental analysis using Phoenix 8.41 (Certara^{TM}) or updated version for participants with sufficient plasma concentration data for the IMP and its metabolites.

Plasma concentrations for ITF2357 and 2 of its metabolites ITF2374 and ITF2375 levels will be summarized over time and corresponding listings will be prepared.

Time profile plots will be prepared on linear and log-linear coordinates for each participant, as well as arithmetic mean (±SEM) for ITF2374 and its metabolites separately, with all population groups on the same graph.

PK parameters for ITF2357 and its metabolites will be summarized by population group and corresponding listings will be prepared.

For ITF2357 and its metabolites, scatter plots will be generated for main PK parameters by population group.

Hepatic impairment effect

For log transformed C_{max}, AUC_{last} and $AUC_{0\text{-}inf}$, the effect of HI group on ITF2357and its metabolites (ITF2374 andITF2375) after a single dose of 50 mg in fasting conditions will be analyzed using a linear model with fixed terms for HI group (normal, mild and moderate) and gender and with age and body weight at baseline as covariates*. Point estimates and 90% confidence intervals (CIs) for the geometric means ratio of each HI group versus the normal control group will be provided for C_{max}, AUC_{last} and $AUC_{0\text{-}inf}$. Moreover, for C_{max}, AUC_{last} and $AUC_{0\text{-}inf}$, a point estimate and 90% CI for the geometric mean of each population group will be provided.

(*) The inclusion of covariates in the model will be first assessed by the Akaike's information criterion (AIC). The model with the lowest AIC value will be selected for the final analysis. Models lack-of-fit will be assessed by residual plots.

Secondary analysis on hepatic impairment effect

Additionally, relationships between PK parameters C_{max}, AUC_{last}, $t_{1/2}$, $AUC_{0\text{-}inf}$, C_{maxu}, $AUClast_u$, $AUCinf_u$ (for ITF2357 and metabolites ITF2374 and ITF2375), CL/F, Vz,F (for ITF2357 only) and hepatic function measures (e.g., Child-Pugh score) will be explored by graphical/regression methods as a secondary analysis.

9.4 Safety Analyses

Analysis of safety parameters will be performed on the Treated Set.

Safety data will be summarized by population group using descriptive statistics (number of

participants, mean, median, standard deviation, minimum, and maximum) for continuous variables and using frequency and percentages for discrete variables.

Adverse events

AEs will be summarized overall and by system organ class and preferred term in tables with:

- The number of subjects with at least one AE and the number of adverse events by group and overall,
- The number of subjects with at least one treatment-emergent AE and the number of treatment-emergent AEs by group.

Analyses considering intensity and drug relationship to treatment will be also carried out.

All AEs will be listed as well as TEAEs and AEs leading to death and other serious and significant AEs (SAEs or AEs) leading to study withdraw.

Laboratory variables, vital signs and electrocardiograms

Potentially clinically significant abnormalities in ECG, vital signs and clinical laboratory will be provided. ECG, vital signs, and clinical laboratory data will be summarized descriptively over time by population group.

9.5 Sample Size Determination

Sample size for this study was based upon empirical considerations and no sample size calculation was performed. Eight participants with mild HI, eight participants with moderate HI and eight control participants with normal hepatic function, who will be matched with the moderate HI patients based on the weight. This sample size is consistent with the sample size recommended in the FDA Guidance on pharmacokinetics in patients with impaired hepatic function, for study design including more than one group of participants with hepatic impairment (FDA reference).

9.6 Protocol Deviations

Details on the procedures followed for detecting, reviewing, and reporting deviations from the protocol are provided in the trial Protocol Deviations Assessment Plan (PDAP).

Critical and major protocol deviations will be listed in the safety population.

10 GENERAL CONSIDERATIONS: REGULATORY, ETHICAL, AND TRIAL OVERSIGHT

10.1 Regulatory and Ethical Considerations

This trial will be conducted in accordance with the protocol and with the following:

- The most recent recommendations of the World Medical Association (WMA).
- The International Council of Harmonization (ICH) recommendations: Good Clinical Practice [E6 (R2)], (CPMP/ICH/135/95), 2016.
- The clinical research guidelines established by the basic principles defined by the FDA regulations and guidelines for biomedical research on human subjects (21 CFR).
- The decree of 26th April 2006 (n°2006-477) relative to biomedical research and French law n°2002-303 of 4th March 2002 regarding participant's rights.
- French law n°78-17 of 6th January 1978 relative to Data processing, Data files and individual liberties, modified by law n°2016-41 of 26 JAN 2016, ruling n°2016-800 of 16 JUN 2016 and updated by deliberation n°2016-262.
- European directive 2005/28/CE dated 8 April 2005 (GCP) translated in French law by the Decision of 24 Nov 2006 setting the GCP for biomedical research on drugs for human use.
- Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons regarding the processing of personal data and on the free movement of such data.
- Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.
- Applicable regulations in France and Bulgaria for interventional clinical trials with IMPs.

Obligations of the Sponsor and Contracting to Contract Research Organization (CRO)

Sponsor will:

- Assure that the CRO to which they delegate their tasks is fully qualified and that the trial location and the logistical means are adapted to and available for his requirements.
- Contract an insurance policy for the present project.
- Supply the Investigator with the following:
  - an up-to-date investigator’s Brochure,
  - information on the investigational medical product (IMP),
  - the exclusion period during which the person cannot participate in another trial,
- Supply the IMP and the documentation, take charge of supplementary costs for specific apparatuses and supplies and of general running costs incurred for the trial,

- Immediately forward to the Investigator any information that is liable to have direct consequences on the trial.
- Immediately examine with the Investigator any serious adverse event and take the required steps to guarantee the security of the trial participants.

The Sponsor will contract with Biotrial to:

- Transmit to the Competent Authorities (CA) all the information concerning any new discovery concerning the conduct of the study or the IMP,
- Submit the Clinical Trial Application (CTA) via CTIS and obtain the approval for the present biomedical study.
- Inform CA of any serious adverse event as soon as he becomes aware of the fact.
- Inform CA of premature termination of the trial and indicate the reason(s).
- Send to CA within the legal time limit, any Ethics Committee decision further to extra information submitted.
- Designate the qualified people who participate in the clinical research and guarantee their training.
- Designate the appropriate people or Committees who undertake the management and the supervision of the trial, data collection, data management and statistical analysis and writing of the trial report.
- Ensure that the investigation is conducted in accordance with the protocol.
- Maintain study records and documents for at least 25 years after the end of the clinical study.

FDA opinion

As this study is a post marketing requirement from the FDA, the present protocol will be submitted to the FDA by the Sponsor for opinion before requesting regulatory approvals at the country level.

Submission to the Competent Authorities

It is the responsibility of the Sponsor to obtain the authorization to conduct the clinical trial (CT) via the Clinical Trials Information System (CTIS) portal. Sponsor has delegated CTIS submission to Biotrial. The authorization consists in a single administrative decision by the Member State concerned (scientific, regulatory and ethical assessments).

The present CT will not be initiated until authorization is received.

Protocol Amendments

Should any change to the signed final trial protocol be made, a protocol amendment will be written.

Substantial modification:

Any significant change (i.e., is likely to have an impact on the safety of the study participants or to change the interpretation of the scientific documents in support of the conduct of the CT) in the trial requires a protocol amendment for authorization. When a substantial protocol amendment is sent to the applicable Member State for authorization, the Investigator must not make any changes to the trial without approval of the Member State and the Sponsor, except when necessary to eliminate apparent immediate hazards to the participants. Should the opinion of the ethics committee be favorable, and the regulatory authority approves the above-mentioned substantial protocol amendment, the CT may continue following the amended protocol.

A protocol change intended to eliminate an apparent immediate hazard to participants may be implemented immediately, but the change must then be documented in an amendment, reported to the Member State, and submitted in the required time frame. All protocol amendments must be reviewed and approved following the same process as the original protocol.

Non-substantial amendment / modification:

Protocol amendments only due to logistical or administrative changes may be implemented immediately after agreement with the Sponsor. The amended protocol will be submitted in the CTIS for information to the Member State.

It is the responsibility of the Sponsor to determine whether a change is substantial (submission for authorization) or non-substantial (submission for information).

Notification

The Sponsor may submit different types of notification in the CTIS:

- **Trial and recruitment periods**: Allow the Sponsor to inform the Member States about different events related to the CT life cycle, such as: start, restart and end of the trial, start and restart of recruitment, temporary halt, EOS in EU/European Economic Area and global end of the trial. These types of notifications must be made within 15 days from the start of the event (article 36-38 of the CT Regulation).
- **Unexpected event**: Allows the Sponsor to inform the member state concerned (MSC) about any unexpected event that might influence the benefit-risk balance of the medicinal product, or that would lead to changes in the administration of a medicinal product or in overall conduct of a CT (e.g., a significant hazard to the volunteer population). Such notifications must be made without undue delay but no later than 15 days from the date the Sponsor became aware of the event (article 53 of the CT Regulation).
- **Urgent safety measure**: Allows the Sponsor to inform where an unexpected event is likely to seriously affect the benefit-risk balance and the urgent safety measures which have been taken to protect the participants. The Sponsor must notify the MSC of such events without undue delay but no later than 7 days from the date on which the measures were taken (article 54 of the CT Regulation).

- **Serious breach**: Allows the Sponsor to inform about a breach likely to affect to a significant degree the safety and rights of a volunteer or the reliability and robustness of the data generated in the CT. These notifications must be made without undue delay but no later than 7 days from the date on which the Sponsor became aware of the breach (article 52 of the CT Regulation).
- **Third-Country Inspectorate Inspection**: Allows the Sponsor to submit all inspection reports of third-country authorities concerning the CT (article 78 of the CT Regulation).

Regulatory requirements

In compliance with French law, approval as a site for biomedical research without direct individual therapeutic benefit was granted to François PEAUCELLE by the Minister for Health to Biotrial Rennes centre (site n°05001M).

In compliance with Bulgarian law, the COMAC sites are registered as clinical sites.

10.2 Committees

None.

10.3 Informed Consent Process

An unconditional prerequisite for a participant's participation in the trial is his/her written informed consent. The participant's written informed consent to participate in the trial must be given before any trial-related activities are carried out.

Participants will be verbally informed by an investigator of all pertinent aspects of the trial: the nature of the trial, its aim, its possible risks and restrictions, its duration and the fee that they will receive. The protocol will be explained during a meeting prior to the trial and each participant must be informed that participation in the trial is voluntary and that they may withdraw from the trial at any time. At this meeting, an information sheet will be given to each participant. The language used in doing so must be chosen so that the information can be fully and readily understood by lay persons.

The participant should carefully read before signing and dating the informed consent form. They can ask all necessary questions to the investigator. The informed consent form must be signed and personally dated by both the participant and the investigator. A copy of the signed document should be given to the participant.

The completed "participant / patient screen log" will be signed by the Investigator to attest that consent has been obtained from all participants.

Whenever important new information becomes available that may be relevant to the participant's consent, the written participant information sheet and any other written information provided to participants will be revised by the Sponsor and be submitted again to the IEC/IRB for review and favorable opinion/authorization. The agreed, revised information will be provided to each participant in the trial for signing and dating. The Investigator will explain the changes from the previous version.

10.4 Rescreening

The rescreening process is described in Section 5.4.

10.5 Data Protection

This study will be performed in accordance with the standard operating procedures of the Sponsor (or designee), GCP, the EU Clinical Trials Directive and the Code of Federal Regulations (CFR), the guidelines of the International Council for Harmonization (ICH), any applicable local regulation, and the most recent guidelines of the Declaration of Helsinki.

All personal data will be processed according to Regulation (EU) 2016/679 on General Protection of personal Data (GDPR), and as per local data protection regulations.

The Investigator must guarantee the confidentiality of the study data in the medical files by implementing security measures to prevent unauthorized access to the data and to the computer system.

10.6 Early Site Closure or Trial Termination

The Sponsor may suspend or terminate the study at any time for any reason.

If the Investigator suspends or terminates the study, the Investigator will promptly inform the Sponsor and the regulatory authorities and provide them with a detailed written explanation. The Investigator will also return all test articles, test article containers, and other study materials to the Sponsor.

Upon study completion, the Investigator will provide the sponsor and IRB/IEC with final reports and summaries as required by regulations.

11 GENERAL CONSIDERATIONS: QUALITY ASSURANCE

11.1 Data Quality Assurance (QA)

Monitoring

The investigator will allow the representative of the sponsor and the study Monitor:

- To check and to verify the site, the facilities and the material used for the study,
- To meet all members of the team involved in the study,
- To consult all the documents relevant to the study,
- To check that the CRFs have been correctly completed,
- To have direct access to source documents for comparison of data therein with the data in the CRFs,
- To check that AEs have been documented,
- To verify that the study is carried out in compliance with the protocol.

This study will be monitored according to the monitoring plan, by agreement of the investigator, the Monitor and the Sponsor.

All information dealt with during these visits will be treated as strictly confidential.

The monitor will verify the following:

- Study screen log and study status updates,
- Adequately completed eCRFs.

Audit- Inspection

The Investigator will be informed that an audit will be carried out, at the request of the sponsor, before, during or after the study.

The Investigator will be informed that the Regulatory Authorities may also carry out an inspection. In this case, the Investigator must inform the Sponsor as soon as he receives the notification of inspection.

The Investigator must allow the representatives of the Regulatory Authorities and persons responsible for the audit to:

- Inspect the site, facilities and material used for the study,
- Meet all members of his team involved in the study,
- Have direct access to study data and source documents,
- Consult all the documents relevant to the study.

Quality control and quality assurance

Written procedures describing data flow, data entry or electronic capture, data cleaning and processing, and required quality control must be utilized.

Trained site personnel must conduct data entry, or data must be transferred electronically from the device into the EDC system.

The entered/electronically transferred data will be systematically checked by CRO (Biotrial) staff, either by using error messages printed from validation programs or by manual checks carried out based on database listings. Data checks for data consistency and plausibility must be defined and implemented in the EDC system. Queries are raised and resolved electronically within the EDC system.

After the completion of the data cleaning and data review process and full resolution of the data queries, the database will be locked. Any changes to the database after that time may only be made by joint written agreement between the Clinical Pharmacologist and the investigator.

The Investigator must guarantee the confidentiality of the trial data in the medical files by implementing security measures to prevent unauthorized access to the data and to the computer system.

11.2 Source Data

11.2.1 Data collection

Electronic Data Capture (EDC) via eCRFs will be used for this trial, for each participant who received at least one administration of trial drug, and also for screen failure participants. This also applies to those subjects who fail to complete the trial. If a subject withdraws from the trial, the reason must be noted on the eCRF. Case report forms are to be completed on an ongoing basis.

Trial data will be collected by the investigator or dedicated trial personnel. Data will be collected on source documents and entered by the trial personnel into the eCRFs.

11.2.2 Data Handling

As described in Section 11.2.1, data will be recorded in an FDA CFR Part 11-compliant and local data protection regulation-compliant eCRF.

All data in the eCRF must reflect the corresponding source data. No data are to be recorded directly on the eCRFs (i.e., the eCRF is not to be considered as source data).

Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained.

The Investigator should agree to have completed source documents and eCRFs available for inspection by the clinical monitor at the time of each scheduled monitoring visit. The Investigator must sign the completed eCRF.

All the documents (including but not limited to Trial Master File, Investigator Site File, and participants medical charts) must be archived for a minimum of 25 years.

11.2.3 Data coding

Biotrial will ensure coding for adverse events, prior and concomitants medications and medical history in compliance with the Medical Dictionary for regulatory activities (MedDRA) and the World Health Organization Drug Dictionary (WHODRUG), using the most recent versions of MedDRA and WHODRUG Global.

11.2.4 Data validation

Biotrial will prepare the data validation document.

Biotrial will be responsible for data entry and their validation (according to the sponsor requirements).

Biotrial will organize a data review of the data before database locking.

12 APPENDIX: DRUGS WITH KNOWN RISK OF QT PROLONGATION AND TORSADE DE POINTES

Drug	Therapeutic class / indication
Cocaine	Anesthetics
Propofol	Anesthetics
Sevoflurane	Anesthetics
Dronedarone	Antiarrhythmic
Procainamide	Antiarrhythmic
Quinidine	Antiarrhythmic
Sotalol	Antiarrhythmic
Disopyramide	Antiarrhythmic (Class Ia)
Hydroquinidine (Dihydroquinidine)	Antiarrhythmic (Class Ia)
Flecainide	Antiarrhythmic (Class Ic)
Amiodarone	Antiarrhythmic (Class III)
Dofetilide	Antiarrhythmic (Class III)
Ibutilide	Antiarrhythmic (Class III)
Nifekalant	Antiarrhythmic (Class III)
Ciprofloxacin	Antibiotics (Fluoroquinolones)
Gatifloxacin	Antibiotics (Fluoroquinolones)
Grepafloxacin	Antibiotics (Fluoroquinolones)
Levofloxacin	Antibiotics (Fluoroquinolones)
Moxifloxacin	Antibiotics (Fluoroquinolones)
Sparfloxacin	Antibiotics (Fluoroquinolones)
Azithromycin	Antibiotics (Macrolides)
Clarithromycin	Antibiotics (Macrolides)
Erythromycin	Antibiotics (Macrolides)
Roxithromycin	Antibiotics (Macrolides)
Aclarubicin	Anticancer drug

Drug	**Therapeutic class / indication**
Anagrelide	Anticancer drug
Arsenic trioxide	Anticancer drug
Cesium Chloride	Anticancer drug
Mobocertinib	Anticancer drug
Oxaliplatin	Anticancer drug
Vandetanib	Anticancer drug
Donepezil	Anti-dementia drugs
Citalopram	Antidepressant
Escitalopram	Antidepressant
Fluconazole	Antifungals
Astemizole	Antihystaminic
Terfenadine	Antihystaminic
Chloroquine	Antiprotozoals
Halofantrine	Antiprotozoals
Hydroxychloroquine	Antiprotozoals
Meglumine antimoniate	Antiprotozoals
Pentamidine	Antiprotozoals
Chlorpromazine	Antipsychotic
Chlorprothixene	Antipsychotic
Droperidol	Antipsychotic
Haloperidol	Antipsychotic
Levomepromazine (Methotrimeprazine)	Antipsychotic
Levosulpiride	Antipsychotic
Mesoridazine	Antipsychotic
Pimozide	Antipsychotic
Sertindole	Antipsychotic
Sulpiride	Antipsychotic

Drug	Therapeutic class / indication
Sultopride	Antipsychotic
Thioridazine	Antipsychotic
Cilostazol	Antithrombotic
Bepridil	Calcium channel blockers
Terlipressin	Hormonal treatments
Probucol	Lipid modifying agents
Ibogaine	Opioid dependence
Levomethadyl acetate	Opioid dependence
Methadone	Opioid dependence
Cisapride	Propulsive
Domperidone	Propulsive
Ondansetron	Serotonin 5HT3 antagonists
Terodiline	Urologicals
Papaverine HCl (Intra-coronary)	Vasodilators

Source:

- Arizona Center for Education and Research on Therapeutics. Link to: Woosley RL, Heise CW, Gallo T, Woosley D and Romero KA, www.CredibleMeds.org, QT drugs List, [05 April 2023], AZCERT, Inc. 1457 E. Desert Garden Dr., Tucson, AZ 85718.
- Thakkar S, Li T, Liu Z, Wu L, Roberts R, Tong W. Drug-induced liver injury severity and toxicity (DILIst): binary classification of 1279 drugs by human hepatotoxicity. Drug Discov Today. 2020 Jan;25(1):201-208. doi: 10.1016/j.drudis.2019.09.022. Epub 2019 Nov 1. PMID: 31669330.

13 APPENDIX: DRUGS KNOWN TO BE A SUBSTRATE OF CYP3A4

Drug
Alfentanil (Alfenta®)
§Cyclosporine (Neoral®, Gengraf®, Sandimmune®)
Dihydroergotamine (DHE-45®, Migranal®)
Fentanyl (Duragesic®)
*Pimozide (Orap®)
*§Quinidine
Sirolimus (Rapamune®)
Tacrolimus (Prograf®)

Source: www.straighthealthcare.com/cytochrome-p450-3a4. Accessed: 28th March 2023.
For the other substrate of CYP3A4, please refer to the source.

*These drugs are also known to prolong QTc interval (see Appendix 12), and are therefore prohibited according to Section 6.8.1 (Prohibited Concomitant Therapy).

§These drugs are also known to be potent P-gp or BCRP inducers or inhibitors (see Appendix 15), and are therefore prohibited according to Section 6.8.1 (Prohibited Concomitant Therapy).

14 APPENDIX: DRUGS KNOWN TO BE A SUBSTRATE OF ORGANIC CATION TRANSPORTER 2 (OCT2) TRANSPORTER

Generic Name	**Brand Names (Partial List)**	**OCT2 interaction**
Amantadine		Substrate
Amiloride	Midamor®	Substrate
Cimetidine	Tagamet®	Substrate
Creatinine		Substrate
*Dofetilide	Tikosyn®	Substrate
Dopamine		Substrate
Famotidine	Pepcid®	Substrate
Memantine	Namenda®	Substrate
Metformin	Glucophage®	Substrate
*Oxaliplatin	Eloxatin®	Substrate
Pindolol	Visken®	Substrate
*Procainamide		Substrate
Ranitidine	Zantac®	Substrate
Trimethoprim	Bactrim®	Substrate
Varenicline	Chantix®	Substrate

Abbreviations: OCT2 transporter = Organic Cation Transporter 2.
Source: http://www.straighthealthcare.com/organic-cation-transporter-2.html. Accessed 28th March 2023.

*These drugs are also known to prolong QTc interval (see Appendix 12), and are therefore prohibited according to Section 6.8.1 (Prohibited Concomitant Therapy).

15 APPENDIX: DRUGS KNOWN TO BE P-GLYCOPROTEIN (P-GP) OR BREAST CANCER-RESISTANCE PROTEIN (BCRP) INDUCERS OR INHIBITORS

15.1 Inhibitors/Inducers of P-gp

Inhibitors
Amiodarone
Azithromycin (systemic)
Catpopril
Carvedilol
Clarithromycin
Conivaptan
Cyclosporine (systemic)
Diltiazem
Dronedarone
Erythromycin (systemic)
Itraconazole
Ketoconazole (systemic)
Lopinavir
Osimertinib
Quercetin
Quinidine
Ritonavir and ritonavir-containing coformulations
Verapamil

Inducers:
Carbamazepine
Phenytoin
Rifampin (rifampicin)
St. John's wort

Source:

- https://www.uptodate.com/contents/image?imageKey=EM/73326 consulted on 19MAR2025
- Palareti G, Poli D. The challenges and limitations of widespread direct oral anticoagulant treatment: practical suggestions for their best use. Expert Rev Cardiovasc Ther. 2016;14(2):163-76. doi: 10.1586/14779072.2016.1115344.

15.2 Inhibitors/Inducers of BCRP

BCRP inducers
Apalutamide
Dovitinib
Progesterone
Venlafaxine

BCRP inhibitors		
Afatinib	Fluvastatin	Regorafenib
Amiodarone	Fulvestrant	Rifampicin
Apixaban	Fluoconazole	Rifapentine
Aprepitant	Gefitinib	Ritonavir
Aripiprazole	Imatinib	Sildenafil
Atazanivir	Indometacin	Simvastatine
Atorvastatin	Ivacaftor	Sorafenib
Axitinib	Ivermectin	Sulfasalazine
Bexarotene	Ketoconazole	Sunitnib
Bicalutamide	Leflunomide	Tacrolimus
Bortezomib	Lopinavir	Telmisartán
Bosutinib	Loratadine	Temserolimus
Cabazitazel	Lovastatin	Teriflunomide
Carfilzomib	Masitinib	Ticagrelor
Celecoxib	Meloxicam	Tolcapone
Cisplatin	Miconazole	Toramefine
Cyclosporine	Nifedipine	Vandetanib
Dabigatran	Nilotinib	Vemurafenib
Dabrafenib	Nilvapidine	Vilorelbine
Dasatinib	Omeprazole	Vitamine D2
Daunorubicin	Osimertinib	Ziprasidone
Doxorubicin	Paclitaxel	
Erlotinib	Pazopanib	
Estradiol	Pantoprazole	
Everolimus	Pitavastatin	
Flutamide	Ponatinib	

Source:

- https://go.drugbank.com/categories/DBCAT003986 consulted on 19MAR2025
- https://go.drugbank.com/categories/DBCAT002662 consulted on 19MAR2025
- Mao Q, Unadkat JD. Role of the breast cancer resistance protein (BCRP/ABCG2) in drug transport--an update. AAPS J. 2015 Jan;17(1):65-82. doi: 10.1208/s12248-014-9668-6.
- Deng F, Sjöstedt N, Santo M, Neuvonen M, Niemi M, Kidron H. Novel inhibitors of breast cancer resistance protein (BCRP, ABCG2) among marketed drugs. Eur J Pharm Sci. 2023 Feb 1;181:106362. doi: 10.1016/j.ejps.2022.106362.

16 APPENDIX: DRUGS KNOWN TO BE SUBSTRATES OF P-GP

Aldosterone	Edoxaban	Methadone	§Regorafenib
Alfentanil	Elagolix	Methylprednisolone	Relugolix
Aliskiren	Eletriptan	Mibefradil	Remogliflozin
Ambrisentan	Ensartinib	Mirabegron	Repotrectinib
Amisulpride	Entrectinib	Mitapivat	§Rifampicin
Amitriptyline	*§Erythromycin	Mitomycin	Riluzole
Amprenavir	Ethinylestradiol	Morphine	Ripretinib
§Apixaban	Etoposide	Nelfinavir	Risperidone
Apremilast	Everolimus	§Nilotinib	§Ritonavir
§Aripiprazole	Faldaprevir	Nintedanib	Rivaroxaban
Asciminib	Fentanyl	Nirmatrelvir	Saquinavir
§Atorvastatin	Fexofenadine	Nortriptyline	Saxagliptin
*§Azithromycin	Fidaxomicin	Odevixibat	Selpercatinib
Belumosudil	Finerenone	Olanzapine	Selumetinib
Belzutifan	Fosamprenavir	Olaparib	Sertraline
Bilastine	Futibatinib	Omecamtiv Mecarbil	Silodosin
Bosentan	Gefapixant	§Omeprazole	Simeprevir
Budesonide	§Gefitinib	*Ondansetron	Sirolimus
Buprenorphine	Glibenclamide	*§Osimertinib	Sitagliptin
Capmatinib	Grazoprevir	Paclitaxel	Sofosbuvir
§Carvedilol	Haloperidol	Paliperidone	§Tacrolimus
Ceritinib	Hydrocortisone	§Pantoprazole	Talinolol
Cetirizine	§Imatinib	Paroxetine	Telaprevir
*Chlorpromazine	Indinavir	Parsaclisib	§Temsirolimus
§Ciclosporin	Infigratinib	Pasireotide	Teniposide
Cimetidine	Irinotecan	§Pazopanib	Terfenadine
*Citalopram	Ispinesib	Pemigatinib	Tigecycline
Clozapine	§Itraconazole	Perospirone	Tipranavir
Cobimetinib	§Ivermectin	§Phenytoin	Tolvaptan
Colchicine	Lansoprazole	Pibrentasvir	Topotecan
Crizotinib	Lapatinib	Pimozide	Trametinib
§Dabigatran	Lenalidomide	Pixantrone	Trilaciclib
Daclatasvir	Lenvatinib	Plicamycin	Tucatinib
Dacomitinib	Levocetirizine	Pomalidomide	Umeclidinium

§Daunorubicin	Levoketoconazole	Posaconazole	Vecuronium
Desloratadine	Linagliptin	Pralsetinib	Vemurafenib
Dexamethasone	Loperamide	Prazosin	Venlafaxine
Digoxin	§Loratadine	Prednisone	Verapamil
§Diltiazem	§Lovastatin	Quetiapine	Vilanterol
Docetaxel	Lurasidone	*Quinidine	Vinblastine
*Domperidone	Lurbinectedin	*Quizartinib	Vincristine
§Doxorubicin	Maraviroc	Ranitidine	Vinorelbine
*Droperidol	Mefloquine	Ranolazine	Zavegepant

Source: https://www.who.int consulted on 19MAR2025

*These drugs are also known to prolong QTc interval (see Appendix 12), and are therefore prohibited according to Section 6.8.1 (Prohibited Concomitant Therapy).

§These drugs are also known to be potent P-gp or BCRP inducers or inhibitors (see Appendix 15), and are therefore prohibited according to Section 6.8.1 (Prohibited Concomitant Therapy).

17 APPENDIX: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS – DEFINITIONS, SEVERITY, AND CAUSALITY

17.1 Further Details and Clarifications on the AE Definition

17.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptoms, or disease temporally associated with the use of a medicinal product, whether related to the medicinal product or not.

An AE includes, but is not limited to, the following:

- Any clinically significant worsening of a pre-existing condition,
- An AE occurring from overdose of an IMP, whether accidental or intentional. Overdose is a dose greater than specified in the protocol,
- An AE occurring from abuse (e.g., use for nonclinical reasons) of an IMP,
- An AE that has been associated with the discontinuation of the use of an IMP.

Laboratory/ECG/vital signs abnormalities should not be documented as AEs unless they are considered clinically relevant, require treatment, fulfil any serious AE (SAE) criterion, or cause the participants to change the trial schedule.

In the case of laboratory/ECG abnormalities that are a sign of a medical condition, the condition should be reported as an AE and not the sign.

Events occurring in participants during a clinical trial during treatment-free periods or on treatment with placebo or a comparative medicine are also to be considered AEs.

17.1.2 Adverse Drug Reactions

An Adverse Drug Reaction (ADR) is a response to a drug that is noxious and unintended and that occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as an ADR.

All AEs for which the judgement of relationship to trial medication is “related” will be considered ADRs.

17.1.3 Treatment-Emergent Adverse Events and Repetitions of Adverse Events

A treatment-emergent AE is an AE that occurs after IMP dosing or that was present prior to dosing but becomes exacerbated between dosing during a treatment period and the end of the trial.

An AE that occurs more than once in the same participant with the same preferred term during the same treatment period is a repetition and will only be counted once. A clinically relevant

worsening of an AE (e.g., relevant change in severity, seriousness) must result in a new entry. The original entry remains unresolved and is given an end date reflecting the date of the worsening and a comment must be entered stating that the AE is continuing with a changed severity/seriousness (e.g., "continues as event name with onset date and new severity/seriousness"). The onset date of the new entry is also the date of worsening.

17.1.4 Expected and unexpected adverse events

Expected AEs with the IMP are those described in the current Investigator's brochure. An unexpected AE is an experience not previously reported in or the nature or severity of which is not consistent with the current prescribing information. Suspected Unexpected Serious Adverse Reactions (SUSARs) are unexpected SAEs having a reasonable possibility of a causal relationship with the trial drug.

17.1.5 Adverse Event of Special Interest

Not applicable.

17.2 Further Details and Clarifications on the SAE Definition

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- results in death,
- is life threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect,
- is an important medical event that requires intervention to prevent one of the above.

Additionally, a Serious Adverse Drug Reaction is a SAE that occurs after IMP administration and is considered to have any potential causal relationship with the IMP according to the Investigator or the Sponsor.

Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Life-threatening refers to immediate risk of death as the event occurred per the reporter. A life-threatening experience does not include an experience, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

Hospitalization is official admission to a hospital. Hospitalization or prolongation of hospitalization constitutes criteria for an AE to be serious; however, it is not in itself considered

as a serious adverse event (SAE). In absence of an AE, hospitalization or prolongation of hospitalization should not be reported as an SAE. This is the case in the following situations:

- The hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol.
- The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (e.g., stent removal after surgery). This should be recorded in the trial file.

In addition, hospitalization for a pre-existing condition that has not worsened does not constitute an SAE.

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

If there is any doubt about whether the information constitutes an SAE, the information is treated as an SAE.

Other Reportable Information (see Appendix 18.5): Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes:

- Overdose (*) of an investigational product as specified in this protocol with or without an AE.
- Inadvertent or accidental exposure with or without an AE.

(*) if there is an AE associated with the overdose of givinostat hydrochloride monohydrate, this will have to be reported as SAE, even if no other criteria for seriousness are met.

17.3 Severity

The maximum intensity of an AE during a day should be graded according to the most recently published Common Terminology Criteria for Adverse Events (CTCAE) see definitions below, and the grade should be recorded in detail, as indicated on the CRF. If the intensity of an AE changes over a number of days, then separate entries should be made having distinct onset dates.

- **Grade 1: mild**; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- **Grade2: moderate**; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) (*).
- **Grade 3: severe** or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (**).
- **Grade 4: life-threatening** consequences; urgent intervention indicated.
- **Grade 5: death** related to AE.

(*) Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

(**) Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

17.4 Causality

The relationship of an AE to the investigational product is a clinical decision by the Investigator based on all available information at the time of the completion of the eCRF and is graded as follows:

1. **Not related**: a reaction for which sufficient information exists to indicate that the etiology is unrelated to the IMP; the participant did not receive the trial medication or the temporal sequence of the AE onset relative to administration of the trial medication is not reasonable or the event is clearly related to other factors such as the participant's clinical state, therapeutic intervention or concomitant therapy. An assessment of "Not related" would include the existence of a clear alternative explanation, or non-plausibility.
2. **Related**: A "reasonable possibility" of a relationship conveys that there are facts, evidence and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
3. **Unknown:** An assessment "Unknown" indicates there is not a reasonable suspicion that the adverse event is associated with the use of the IMP and at the same time there is not the existence of a clear alternative explanation or non-plausibility. In this case, Investigator has to collect all possible information in order to assess the relationship with the IMP, particularly in case of Serious Adverse Events.

Factors to be considered in assessing the relationship of the adverse event to study drug include:

- The temporal sequence from IMP administration;
- The recovery on discontinuation and recurrence on reintroduction;
- The concomitant diseases;
- The evolution of the treated disease;
- The concomitant medication;
- The pharmacology and pharmacokinetics of the IMP;
- The presence of an alternative explanation.

18 APPENDIX: DEFINITIONS AND SUPPORTING OPERATIONAL DETAILS

18.1 Contraception and Pregnancy

18.2 Testing

18.2.1 Definitions Related to Childbearing Potential

Women of childbearing potential

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

The definition of childbearing potential may be adapted for alignment with local guidelines and requirements.

18.2.2 Contraception

Per ICH M3(R2), highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly.

The following are acceptable forms of highly effective methods of contraception for female participants of childbearing potential, and female partners of trial participants, of childbearing potential:

Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [a] (oral, intravaginal, or transdermal)
Progestogen-only hormonal contraception associated with inhibition of ovulation [a] (oral, injectable, or implantable)
Intrauterine device [b]
Intrauterine hormone-releasing system [b]
Bilateral tubal occlusion [b]
Vasectomized partner [b, c]
Sexual abstinence [d].

a. Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

b. Contraception methods that in the context of this guidance are considered to have low user dependency.

c. Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of child-bearing potential (trial volunteer) and that the vasectomized partner has received medical assessment of surgical success.

d. In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with

the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the volunteer.

(*) Summary adapted from "Recommendations related to contraception and pregnancy testing in clinical trials. Advisory from the Clinical Trials Coordination Group Version 1.2., 07/03/2024. (CTCG recommendations, 2024).

18.2.3 Pregnancy Testing

Refer to Section 8.3.5.

18.3 Normal Ranges for Vital Signs and ECG Parameters

Normal ranges applicable for vital signs in supine position:

Age	Parameter	Normal ranges
18-65 years	Systolic blood pressure	[90-145] mmHg
	Diastolic blood pressure	[45-90] mmHg
	Pulse rate	[40-100] beats/min
	Tympanic temperature	[36-37.5] °C
	Respiratory rate	[7 – 20] breath/min

Normal ranges applicable for ECG parameters:

Sex	Parameter	Normal ranges
Male & Female	QRS duration, aggregate	<=120 msec
	PR interval, aggregate	<=220 msec
	ECG mean heart rate	[40-100] beats/min
	QTcF interval, aggregate	<=450 msec

18.4 Time Windows for Procedures

Procedure	Time Point	Time Window
Laboratory assessments (hematology, biochemistry, urinalysis)	Inferior or equal to H2	± 15 min
	]H2-H6]	± 30 min
	]H6-H24]	± 60 min
	Superior to H24	± 120 min
12-lead ECG	[5-10[min	± 2 min
	[10-15] min	± 5 min
	]15-30] min	± 10 min
	]30 min-H2]	± 15 min
	]H2-H6]	±30 min
	]H6-H24]	± 60 min

Procedure	Time Point	Time Window
	Superior to H24	± 120 min
PK blood sampling	Pre-dose	Within 30 min before dosing
	0.5 h post dose	± 2 min
	1, 2, 2.5, 3, 4, 5, 6 h post-dose	± 5 min
	8, 10, 12, 24, 36, 48h post dose	± 10 min
	60, 72, 96 h post dose	± 30 min
Vital signs	Inferior or equal to H2	± 15 min
	]H2-H6]	± 30 min
	Superior to H24	± 120 min

18.5 Special Events (Overdose, Medication Error, Misuse and Abuse)

Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes:

Overdose of an investigational product as specified in this protocol with or without an AE.

Inadvertent or accidental exposure with or without an AE.

Overdose is a dose of trial drug greater than specified in the protocol.

Medication error refers to an unintentional error in dispensing or administration of the trial drug not in accordance with the protocol.

Misuse is defined as any situation where the trial drug is intentionally and inappropriately used not in accordance with the protocol.

Abuse is defined as the persistent or sporadic intentional excessive use of the trial drug, which is accompanied by harmful physical or psychological effects.

18.6 Country/Region-Specific Differences

Not applicable.

18.7 Prior Protocol Amendments

This protocol has not been amended.

18.8 Data Processing and Archiving of Documents and Data Relative to the Research

After the trial, the Investigator will keep all information relevant to the trial for 25 years.

18.8.1 Confidentiality and Agreements

Before starting the trial, the Investigator must confirm receipt of adequate documentation from the Sponsor to be able to decide whether or not to perform the study.

All documents and information given to the Investigator by the Sponsor with respect to the study are strictly confidential.

The Investigator and their colleagues agree to use them only with the framework of this study, in order to carry out the protocol. This agreement is binding, as long as, the confidential information has not been disclosed to the public by the Sponsor.

The Investigator may use the technical protocol to obtain the informed consent of trial participants. It must not be disclosed to other parties without the written authorization of the Sponsor.

The Investigator keeps a confidential subject identification list for the study. The Investigator must maintain source documents for each volunteer in the trial.

Data on participants collected in eCRFs during the trial will be documented in an anonymous fashion. All information in the eCRFs must be traceable to these source documents.

The contents of this protocol and any amendments and results obtained during the study should be kept confidential and not disclosed, in whole or in part to others, or used for any purpose other than reviewing or performing the trial, without written consent of the Sponsor.

The Investigator shall ensure that the study participants authorize the use and disclosure of protected health information in accordance with the EU Clinical Trials Directive and EU Law or the CFR, and in a form satisfactory to the Sponsor to allow for review and monitoring of the conduct of the trial and to allow verification of the accuracy of data by the Sponsor, its representatives, IRBs/IECs, and regulatory authorities.

The Investigator will ensure that all persons assisting in the performance of the trial preserve the confidentiality of the participant's data as set forth in the Participant Informed Consent Form and Clinical Trial Agreement. On eCRFs or any other documents and biological samples submitted to the Sponsor, the participants will not be identified by their names. Each participant will be assigned an identification number to be used on any data or laboratory samples collected by the Sponsor. Documents not for submission to the Sponsor, e.g., the signed ICFs and participants medical records, will be maintained by the Investigator and made available for review and inspection for as long as it is required by local regulations.

18.8.2 Report and Publication

Report:

The results of the trial will be reported in a Clinical Study Report. This report will be prepared by Biotrial according to existing standard operating procedures (ICH Biotrial or Sponsor's own format).

In compliance with the regulations, the final report will be communicated to the Member State within one year after the end of the trial.

The final report will also be provided to the Investigator of the trial.

The CSR will be provided as Word and PDF files. In addition, SAS® transfer files of the data will be provided electronically. All data will be presented electronic Common Technical Document (eCTD)-compliant.

Publication:

The Investigator will only use the information in the context of the trial. The information cannot be used without the Sponsor's authorization. Hence, all or part of the information should only be divulged, submitted for publication, or claimed for industrial proprietary act with the written consent of the Sponsor.

19 APPENDIX: GLOSSARY OF TERMS

ADL	Activities of daily living
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Specific Interest
AIC	Akaike's Information Criterion
ALT	Alanine Amino Transferase
a.m.	*Ante meridiem* (in the morning)
ANOVA	Analysis of Variance
ANSM	Agence Française de Sécurité Sanitaire des Produits de Santé (French Drug Agency)
aPTT	Activated Partial Thromboplastin Time
ARS	Agence Régionale de Santé
AST	Aspartate Amino Transferase
AUC	Area Under the Curve
$AUC_{0\text{-}inf}$	Area Under the Plasma Concentration time curve from time 0 to the infinity
AUC_{last}	Area Under the Plasma Concentration time curve from time 0 to the last quantifiable concentration
AUC_t	Area Under the Plasma Concentration time curve from time 0 to the time of last quantifiable concentration
AUC_u	Unbound Area Under the Plasma Concentration
BCRP	Breast Cancer Resistance Protein
b.i.d.	Twice daily
β-HCG	Beta-Human Chorionic Gonadotropin
BMD	Becker Muscular Distrophy
BMI	Body Mass Index
BP	Blood pressure
bpm	Beats per minute
BSA	Body Surface Area
CA	Competent Authorities
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CFR	Code of Federal Regulations
CL/F	Total body clearance
CL/F_u	Unbound Total body clearance

C_{max}	Maximum plasma concentration observed
$C_{max,u}$	Unbound Maximum plasma concentration observed
C_{min}	Minimal Concentration
cMPNs	Chronic Myeloproliferative Neoplasms
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CPK	Creatinine Phospho Kinase
CPP	Comité de Protection des Personnes (Independent Ethics Committee)
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Clinical Trial
CTA	Clinical Trial Application
CTCAE	Common Terminology Criteria for Adverse Events
CTCG	Clinical Trials Coordination Group
CTD	Clinical Trial Document
CTIS	Clinical Trials Information System
CV	Coefficient of variation
CYP	Cytochrome P450
CYP344	Cytochrome P450 3A4
D	Day
DBP	Diastolic Blood Pressure
DMD	Duchenne Muscular Dystrophy
DRD	Daily Recommended Dose
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
e.g.	*Exempli gratia* (for example)
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EOS	End of Study
EU	European Union
EU-GMP	European Union-Good Manufacturing Practice
FDA	Food and Drug Administration (USA)
FSH	Follicle Stimulating Hormone

fu	Unbound fraction
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
GI	Gastrointestinal
H or h	Hour
Hb	Hemoglobin
HBc	Hepatitis B core
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HDAC	Histone Deacetylase
HDPE	High-Density Polyethylene
HI	Hepatic Impairment
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HRT	Hormone Replacement Therapy
HU	Hydroxyurea
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonization
i.e.	*Id est* (that is)
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	Prothrombin International Normalized Radio
IRB	Institutional Review Board
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
JAK	Janus Kinase
kg	Kilogram
LAM	Lactational amenorrhea method
LC-MS/MS	Liquid Chromatography coupled to tandem Mass Spectrometry
LDPE	Low-Density Polyethylene
LLN	Lower Limit of Normal
λ_z	Elimination rate constant
MD	Medical Doctor

MedDRA	Medical Dictionary for Regulatory Activities
MI	Milano
mg	Milligram
mL	Milliliter
mm	Millimeter
mmHg	Millimeter of mercury
MSC	Member State Concerned
MTD	Maximum Tolerated Dose
NA	Not applicable
NCS	Non-Clinically Significant
NOAEL	No Observed Adverse Effect Level
OCT2	Organic Cation Transporter 2
PCSA	Potentially Clinically Significant Abnormality
PD	Pharmacodynamic(s)
PDAP	Protocol Deviations Assessment Plan
PET	Polyethylene Terephthalate
P-gp	P-glycoprotein
PhD	Doctor of Philosophy
PK	Pharmacokinetics
pp	Per protocol
PR	PR interval is the time from the onset of the P wave to the start of the QRS complex
PT	Prothrombin Time or Preferred Term – based on the context
PV	Pharmacovigilance or Polycythemia Vera – based on the context
QA	Quality Assurance
QRS	A combination of Q wave, R wave and S wave – QRS complex
QTc	Corrected QT
QTcF	QT corrected according to Fridericia
QTLs	Quality Tolerance Limits
RBC	Red Blood Cells
RGDP	General Personal Data Protection Regulation
s	second
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SBP	Systolic Blood Pressure
SEM	Standard error of the mean
SOA	Scheduled Of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Apparent terminal elimination half-life
TE	Treatment Emergent
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to reach C_{max}
T_{last}	Time corresponding to the last concentration above the limit of quantification, C_{last}
u	Unbound
ULN	Upper Limit of Normal
USA	United States of America
Vz/F	Apparent Volume of Distribution during the terminal elimination phase
Vz/F_u	Unbound Apparent Volume of Distribution
WBC	White Blood Cells
WHODRUG	World Health Organization Drug Dictionary
WMA	World Medical Association
WOCBP	Women of Childbearing potential

20 APPENDIX: REFERENCES

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