CONFIDENTIAL

IDN-6556 (Emricasan)

IDN-6556-07 STATISTICAL ANALYSIS PLAN (VERSION 2.0 FINAL)

Protocol Title	A Multicenter, Double-Blind, Randomized Trial of IDN-6556 in Subjects Who had Hepatitis C Virus (HCV) Reinfection and Liver Fibrosis or Cirrhosis following Orthotopic Liver Transplantation for Chronic HCV Infection and Who Subsequently Achieved a Sustained Virologic Response Following anti-HCV Therapy
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ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical classification
BID	Bis in die, twice daily
BMI	Body mass index
CI	Confidence interval
DILI	Drug-induced liver injury
DMC	Data monitoring committee
EAER	Exposure adjusted adverse event rate
ELF	Enhanced Liver Fibrosis Score
ECG	Electrocardiogram
eCRF	Electronic case report form
eDISH	Evaluation of drug-induced serious hepatotoxicity
ES	Enrolled Set
FAS	Full analysis set
HCV	Hepatitis C virus
IQR	Interquartile range
IWRS	Interactive web randomization system
LSMeans	Least-square means
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
ms	Milliseconds
PD	Pharmacodynamics
PK	Pharmacokinetics
PPS	Per-protocol Set
QTcB	QTc Bazett's correction
QTcF	QTc Fridericia correction
SAE	Serious adverse event
SAP	Statistical analysis plan
SMA	Smooth Muscle Actin
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
SVR	Sustained virologic response
TE	Treatment effect
TEAE	Treatment-emergent adverse event
ULN	Upper limit of the normal range

1 INTRODUCTION

Clinical protocol IDN-6556-07 describes the collection and analysis of clinical study data to evaluate the use of emricasan (IDN-6556) in subjects who had HCV reinfection and liver fibrosis or cirrhosis following orthotopic liver transplantation for chronic HCV infection and who subsequently achieved a sustained virologic response (SVR) following anti-HCV therapy. This document provides details of the statistical analyses to be performed. All decisions regarding handling of data for reporting results will be determined prior to database lock and will be described in the relevant sections of this statistical analysis plan (SAP).

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this clinical trial is to assess the effect of oral emricasan on fibrosis or cirrhosis using the Ishak Fibrosis Score, in subjects with HCV reinfection and liver fibrosis or cirrhosis following orthotopic liver transplantation for chronic HCV who subsequently achieved SVR following anti-HCV therapy.

2.2 SECONDARY OBJECTIVES

The secondary objectives of this clinical trial are:

- To determine the effects of oral emricasan on necro-inflammatory sub-score of the modified Histological Activity Index
- To determine the effects of oral emricasan on markers of mechanism of action and inflammation
- To assess the safety and tolerability of oral emricasan in subject's status post orthotopic liver transplantation.

3 STUDY DETAILS

3.1 STUDY DESIGN

This is a double-blind, randomized, multicenter study involving subjects with chronic HCV who underwent liver transplantation; developed HCV-related liver fibrosis or cirrhosis; achieved SVR following anti-HCV therapy; and still show demonstrable fibrosis or cirrhosis on liver biopsy. Upon successful screening, subjects are randomized to receive 25 mg BID of emricasan or placebo in a 2:1 ratio.

The subjects are stratified based on the stage of fibrosis or cirrhosis at Baseline:

- Ishak F2
- Ishak F3-F5
- Ishak F6

The duration of each subject's participation will be approximately 26.5 months and will consist of:

- Screening period of up to 6 weeks
- Double-blind treatment period of 24 months
- A follow-up visit 4 weeks after completion of treatment

The schedule of events is provided in Appendix 1 of the protocol.

3.2 STUDY POPULATION

Approximately 60 subjects who underwent orthotopic liver transplantation for chronic HCV, developed HCV-related liver fibrosis or cirrhosis, achieved a SVR with anti-viral treatment, and still have demonstrable fibrosis or cirrhosis on liver histology will be enrolled. Up to 15 subjects with an Ishak score of F6 can be enrolled.

3.3 RANDOMIZATION

The assignment to emricasan or placebo will be performed randomly in a 2:1 ratio to emricasan 25 mg BID or matching placebo BID. Approximately 60 subjects will be enrolled in this trial with 40 assigned to emricasan and 20 assigned to placebo. Randomization will be stratified based on baseline Ishak Fibrosis Score: F2, F3-F5, or F6.

The randomization schedule will be generated using a validated randomization program and verified for accuracy using strict quality control procedures. Randomization numbers and study drug assignment will be centrally coordinated through the study's Interactive Web Randomization System (IWRS).

3.4 BLINDING

This clinical trial is a double-blind study through the final study visit. The final randomization codes for each subject completing the trial will be provided after all subjects complete their final visit and database lock occurs.

Investigators will be able to unblind individual subjects through the IWRS when it is medically imperative to know whether a specific subject is receiving emricasan or placebo, such as in the occurrence of an adverse event (AE) that the Investigator feels cannot be adequately treated

without knowing the identity of the study drug. In the event of an individual subject being unblinded when medically imperative, the individual subject will have their study drug stopped sometime prior to unblinding. Every effort must be made to contact the Medical Monitor to discuss the case before breaking the blind, or if in an emergency, as soon as possible thereafter (no later than 24 hours after emergency unblinding) to inform the Medical Monitor that unblinding was performed but without disclosing the actual study drug assignment. The investigator should make arrangements to ensure that access to the secure internet site (i.e., individual user name and password) is maintained in strict confidence to prevent a compromise of subject blinding by non-study or unauthorized individuals.

The Sponsor may access the randomization codes for individual subjects with potential suspected unexpected serious adverse reactions (SUSARs) for regulatory reporting or for the purpose of evaluating an emergent safety issue. In such an event, the Sponsor will document the rationale, circumstances, and the person or persons being informed about the unblinding.

If the blind for an individual subject is broken (by the Investigator or the Sponsor), an entry must be made in the electronic data capture system that contains the reason that the blind was broken and the name of the person contacted at the Sponsor or designee.

3.5 STUDY VISIT ASSIGNMENTS

Study visits are designated on the electronic case report forms (eCRFs) and data will be analyzed per the study visit assigned and collected. All post-baseline biopsies will be assigned and collected on the Month 12 and 24 eCRFs.

For purposes of sensitivity analyses, biopsies will also be assigned to Month 12 and Month 24 flags, respectively, based on biopsy date. Biopsies will be classified as Month 12 biopsies flag if the biopsy date is collected within ±8 weeks (i.e., ±56 study days, inclusive) from the planned Month 12 visit date relative to the Day 1 visit date (i.e., Month 12 visit date – Day 1 visit date + 1). Similarly, Month 24 biopsies flag will designate those biopsies at Month 24 that are within ±8 weeks (i.e., ±56 study days, inclusive) from the planned Month 24 visit date relative to the Day 1 visit date (i.e., Month 24 visit date – Day 1 visit date + 1).

4 PLANNED SIZE DETERMINATION

This study will be conducted at multiple centers at which approximately 60 subjects will be enrolled and treated in a 2:1 ratio with emricasan or placebo, respectively. The sample size determination for this study is based on the Phase 2b screening methodology presented in Fleming and Richardson (2004).

The base case for the placebo response rate of 30% was assumed and obtained from George, et al (2009), where it stated that 29% of patients showed a response in fibrosis from a mean of 1.6 years following HCV-SVR.

Treatment duration for all subjects is expected to be two years. The primary analysis of this Phase 2 "screening" study is formally based on a three-category decision guideline. The decision guideline for this study is based on whether the difference in the proportions of subjects who show a response (i.e., improvement or no change) per their Ishak Fibrosis Score at 24 months for emricasan compared to placebo is less than 5%, is from 5% up to 15%, or is more than 15%. Specifically, the outcome of the study will determine one of the following three course of action:

1. If the difference in response rates between emricasan and placebo (i.e., emricasan response rate – placebo response rate) is less than 5%, then emricasan regimen is not plausibly more efficacious than placebo; hence, emricasan or its utility in this indication will be reconsidered.
2. If the difference in response rates between emricasan and placebo is from 5% up to 15%, then emricasan is plausibly more efficacious than placebo in this indication if secondary analyses of biomarkers suggest utility of emricasan or a positive safety profile is observed; hence, emricasan could be evaluated in a subsequent Phase 3 clinical study.
3. If the difference in response rates between emricasan and placebo is more than 15%, then emricasan could be evaluated in a subsequent Phase 3 study.

These categories should not be interpreted as providing strict decision rules but rather as guidelines that will be factored into a broader scientific assessment of the benefit to risk profile for emricasan in this indication. This broader assessment will include consideration of secondary efficacy analyses, safety profile, and relevant information external to this study.

The operating characteristics for this three-category decision guideline are shown in Table 1.

Table 1. Operating Characteristics for Three-Category Decision Guideline

Probability of Obtaining an Estimated Treatment Effect (Emricasan – Placebo)			
True Treatment Effect (TE)	**≤5%**	**5%≤ TE <15%**	**≥15%**
0	67%	22%	11%
5	52%	26%	22%
10	36%	27%	37%
15	23%	24%	53%
20	13%	19%	68%
25	7%	13%	80%
30	3%	8%	89%

Note: Based on 100,000 simulations.

5 STUDY ENDPOINTS

5.1 PRIMARY EFFICACY ENDPOINT

The Ishak Fibrosis Score will be determined by liver biopsy as scored by the central histopathologist. The Ishak Fibrosis Score classification is defined as:

- 0 = No fibrosis (F0);
- 1 = Fibrous expansion of some portal areas, with or without short fibrous septa (F1);
- 2 = Fibrous expansion of most portal areas, with or without short fibrous septa (F2);
- 3 = Fibrous expansion of most portal areas, with occasional portal to portal bridging (F3);
- 4 = Fibrous expansion of portal areas, with marked bridging (F4);
- 5 = Marked bridging with occasional nodules (F5);
- 6 = cirrhosis probable or definite (F6).

Fibrosis scores of F0 and F1 will be excluded from enrollment. The change from baseline in the Ishak Fibrosis Score will be derived for each subject and will be used to classify subjects into one of the three following groups:

- Improvement, defined as having a reduction from baseline of at least 1-point in the Ishak Fibrosis Score
- Stable, defined as having no change from baseline in the Ishak Fibrosis Score
- Worsening, defined as having an increase from baseline in the Ishak Fibrosis Score

Subjects will be classified as a responder or non-responder based on the above three groups and their baseline Ishak Fibrosis score. The definition of response is based on the following:

- For subjects with baseline Ishak Fibrosis Score of F2-F5, achieving either improvement or remaining stable
- For subjects with baseline Ishak Fibrosis Score of F6, achieving improvement

The response at Month 24 will be used as the primary endpoint in this study. Response rates at Month 12 using the same definitions as above will also be summarized.

5.2 SECONDARY EFFICACY ENDPOINTS

5.2.1 Ishak Modification of Knodell Histological Activity Index

The Ishak modification of Knodell histological activity index will be determined by liver biopsy. The four items and their categorizations scores include:

- interface hepatitis
  - 0 = None
  - 1 = Mild (local, few portal areas)
  - 2 = Mild/moderate (focal, most portal areas)
  - 3 = Moderate (continuous around <50% of tracts or septa)

  - 4 = Severe (continuous around >50% of tracts or septa)
- confluent necrosis
  - 0 = None
  - 1 = Focal confluent necrosis
  - 2 = Zone 3 necrosis in some areas
  - 3 = Zone 3 necrosis in most areas
  - 4 = Zone 3 necrosis + occasional portal-central bridging
  - 5 = Zone 3 necrosis + multiple portal-central bridging
  - 6 = Panacinar or multiacinar necrosis
- parenchymal injury (focal lytic necrosis, apoptosis and focal inflammation)
  - 0 = None
  - 1 = One focus or less per 10× objective
  - 2 = Two to four foci per 10× objective
  - 3 = Five to ten foci per 10× objective
  - 4 = More than ten foci per 10× objective
- portal inflammation
  - 0 = None
  - 1 = Mild, some or all portal areas
  - 2 = Moderate, some or all portal areas
  - 3 = Moderate/marked, all portal areas
  - 4 = Marked, all portal areas

The Ishak modification of Knodell histological activity index will be assessed at months 12 and 24.

5.2.2 NASH CRN Fibrosis Stage Scoring

In order to provide a potential comparison to how fibrosis improvement would be viewed in a traditional paired biopsy study in NASH, the Ishak fibrosis scores will be mapped to a comparable fibrosis stage in the NASH CRN staging system. The NASH CRN fibrosis stage classification is defined as: 0=None (F0); 1a=mild, Zone 3, perisinusoidal fibrosis (F1); 1b=moderate, Zone 3, perisinusoidal fibrosis (F1); 1c=portal/periportal fibrosis only (F1); 2=perisinusoidal and portal/periportal fibrosis (F2); 3=bridging fibrosis (F3); and 4=cirrhosis (F4). To map Ishak Fibrosis Score to the NASH CRN definitions, Table 2 will be used to map the scores from Ishak to NASH CRN:

Table 2. Mapping of fibrosis staging from Ishak to NASH CRN

Ishak Fibrosis Scoring	NASH CRN Mapped Score
F0	F0
F1	F1
F2	F2
F3	F3
F4	F3
F5	F4

F6	F4

The proportion of patients who have at least a one stage improvement in the mapped fibrosis stages will be evaluated at Month 12 and Month 24.

5.2.3 Clinical Outcomes

Clinical outcomes will be documented from a blinded medical review of MedDRA coded AEs collected from the eCRF prior to database lock. Clinical outcomes will include decompensation events, re-transplantations, and all-cause mortality. Decompensations events will include variceal bleeding, hepatic encephalopathy, ascites, hepato-renal syndrome, and jaundice. The following specific MedDRA coded preferred terms to be used are:

- Liver Transplant, Kidney Transplant
- Death
- Oesophageal varices haemorrhage
- Hepatic encephalopathy
- Ascites
- Hepatorenal syndrome
- Jaundice

5.2.4 Biomarkers

The following biomarkers will be collected:

- ALT
- AST
- caspase 3/7
- cCK18/M30
- flCK18/M65
- Enhanced Liver Fibrosis (ELF) score (based on hyaluronic acid, P3NP, TIMP-1)

The change from baseline will be derived for each of these biomarkers. If any biomarker variables are not normally distributed, a log-transformation may be applied to that biomarker endpoint prior to analysis.

5.2.5 Liver Stiffness

Liver stiffness will be assessed by transient elastography (FibroScan®) performed at seven sites on a subset of the entire study population. Fibroscan® is collected at screening and Months 6, 12, 18, and 24. Only values meeting the specific success criteria (interquartile range [IQR] / median liver stiffness <30% and success rate >60%) will be summarized. The change from baseline in liver stiffness will be derived using all available data.

5.3 EXPLORATORY ENDPOINT

A morphometric assessment will be made on all biopsies collected at screening and Months 12 and 24. Effects on liver collagen and smooth muscle actin (SMA) will be assessed by

morphometric image analysis. The change from baseline in percent of liver collagen and SMA will be derived.

5.4 SAFETY ENDPOINTS

5.4.1 Treatment Compliance

Study drug dispensation information and treatment compliance data will be collected throughout the study. The number of capsules dispensed, number of capsules returned, number of missed doses and study drug interruptions data will be collected. Treatment compliance will be calculated in the database and is defined as: (the number of capsules dispensed minus the number of capsules returned) divided by the number of expected doses.

5.4.2 Extent of Exposure

Overall treatment exposure will be derived as the number of days from the first date of study drug administration to the last date of study drug administration (inclusive of the first and last dates of dosing), regardless of study drug interruptions. Person years of exposure will be derived as the overall exposure divided by the number of person years observed, where 1 year is equal to 365.25 days.

5.4.3 Adverse Events (AEs)

Adverse events will be collected during the study and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All events with a start date on or after the first date of study drug administration to the last study visit date are defined as treatment-emergent adverse events (TEAEs).

Adverse events classified as definitely, probably, and possibly related to study drug will be summarized together as related AEs. Adverse events classified as unlikely and not related will be summarized together as not related AEs. For summary purposes, the AE relationship will be summarized as related, not related, or unknown.

5.4.4 Liver Ultrasound

Liver ultrasounds are performed at Screening, Month 6, Month 12, Month 18, and Month 24. Ultrasound data will be reviewed for evidence of any new focal hepatic lesion as well as for any evidence of new gallbladder inflammation.

5.4.5 Liver Monitoring

Liver transaminases (ALT, AST) and total bilirubin will be monitored at each study visit during the study for any evidence of potential DILI. The following categories for ALT, AST, and total bilirubin will be derived:

- Maximum post-baseline comparison to upper limit of the normal range (ULN):
  - ALT
    - ≤ULN
    - >ULN and ≤3× ULN
    - >3× ULN and ≤5× ULN
    - >5× ULN and ≤8× ULN
    - >8× ULN

  - AST
    - ≤ULN
    - >ULN and ≤3× ULN
    - >3× ULN and ≤5× ULN
    - >5× ULN and ≤8× ULN
    - >8× ULN
  - Total bilirubin
    - ≤ULN
    - >ULN and ≤1.5× ULN
    - >1.5× ULN and ≤2× ULN
    - >2× ULN and ≤3× ULN
    - >3× ULN
- Maximum post-baseline value >2× baseline
- Maximum post-baseline value >3× baseline
- Elevated post-baseline ALT and/or AST with concurrent (i.e., same post-baseline visit) elevated total bilirubin
  - ALT >3× ULN and concurrent total bilirubin >2× ULN
  - AST >3× ULN and concurrent total bilirubin >2× ULN
  - Either ALT or AST >3× ULN and concurrent total bilirubin >2× ULN
  - Both ALT and AST >3× ULN and concurrent total bilirubin >2× ULN
- Elevated Post-baseline ALT and/or AST with elevated total bilirubin (not necessarily concurrent)
  - ALT >3× ULN and not necessarily concurrent (i.e., across all post-baseline visits) total bilirubin >2× ULN
  - AST >3× ULN and not necessarily concurrent total bilirubin >2× ULN
  - Either ALT or AST >3× ULN and not necessarily concurrent total bilirubin >2× ULN
  - Both ALT and AST >3× ULN and not necessarily concurrent total bilirubin >2× ULN

5.4.6 Laboratory Measurements

Laboratory tests include measurements across panels of hematology, coagulation, chemistry, and urinalysis. In addition, alpha-fetoprotein is measured at screening and every 6 months during the study. All specific laboratory tests are listed in detail in clinical protocol IDN-6556-07. Normal ranges, where applicable, will be provided by the central laboratory and used to identify laboratory measurements outside the normal range.

Changes from baseline will be derived for each continuous laboratory parameter. Laboratory tests with categorical results will have no derivations made.

5.4.7 Vital Signs, Weight, and Height

Vital signs include systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and temperature. Body weight and height will be collected at protocol specified visits (weight at

screening, Month 12, and Month 24, height at screening only), and body mass index (BMI) will be derived as [weight in kilograms] / [height in meters^2].

Changes from baseline in vital signs, weight, and BMI will be derived.

5.4.8 Electrocardiograms

Electrocardiogram (ECG) data to be reported includes ventricular rate, PR interval, RR interval, QRS interval, QT interval, QTc interval, QTcB interval, QTcF interval, and findings (i.e., normal or abnormal). Post-dose maximum values in QTcB and QTcF will be classified into the following categories, in milliseconds (ms):

- <450
- ≥450 to <480
- ≥480 to <500
- ≥500

Changes from baseline in PR interval, QRS interval, QT interval, QTc interval, QTcB interval, and QTcF interval will be derived at each respective visit. Changes from baseline values in QTcB and QTcF will be classified into the following categories, in ms:

- <30
- ≥30 to <60
- ≥60

5.4.9 Medications

All additional medications taken any time during the study will be recorded at each study visit. Medications will be classified into 1 of the following 3 types:

- Prior Medication: any medication stopped prior to the first date of study drug administration
- Concomitant Medication: any medication started prior to and stopped on or after the first date of study drug administration
- New Concomitant Medication: any medication started on or after the first date of study drug administration

All medications will be coded using the world health organization drug dictionary.

Immunosuppressant therapy relative to a subject's liver transplant is collected at screening and will be classified as tacrolimus, cyclosporine, or other.

Previous hepatic treatments were collected at screening. These medications will be manually reviewed and classified as anti-viral, immunotherapy, and anti-viral+immunotherapy. These medications will also be classified as interferon-based or not.

5.4.10 Physical Examination

A comprehensive physical examination will be performed and will include assessments of general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen (including liver and spleen examination), extremities, and nervous system. No derivations will be made for physical examination components results.

6 ANALYSIS POPULATIONS

The Enrolled Set (ES) is defined as the set of subjects who provide a signed informed consent form to participate in this study.

The Full Analysis Set (FAS) consists of all randomized subjects who have received at least one dose of study drug. If the administration of study drug is not certain, the subject will be allocated to the FAS. The FAS is representative of the intention-to-treat principle assigning subjects to the planned randomized study drug assignment and will be analyzed as randomized.

The Per-Protocol Set (PPS) is defined as the set of subjects included in the FAS who have no significant protocol deviations that impact the primary endpoint and who provide a Month 24 liver biopsy. The PPS will be defined during a blinded data review meeting prior to database lock based on considerations like major protocol deviations affecting the primary endpoint, inadequate study drug compliance, etc. Meeting minutes and the final deviation tracker will serve as documentation for classification of subjects into the PPS.

The Safety Analysis Set consists of all subjects who are randomized and receive at least one dose of study drug. Subjects will be analyzed on an “as treated” basis (i.e., all subjects will be analyzed by the treatment they actually received). If no errors in randomization assignments occur, then the FAS and Safety Analysis Set will be the same.

7 GENERAL STATISTICAL CONSIDERATIONS

All biopsy data analyzed by and collected from the central histopathologist will be used in the FAS for all efficacy analyses, unless stated otherwise. All biopsy data collected per local assessments will be captured in the database and will be provided in a listing by visit.

Analyses will be conducted using SASv9.3 or higher and pooled across all enrolling sites. Data will be summarized descriptively with categorical variables being summarized using number of observations and percentages; continuous variables being summarized by n, mean, median, standard deviation, minimum, and maximum, unless otherwise specified.

All disposition, demographics, and baseline summaries will be based on using the FAS, with the disposition table also being summarized using the ES. The efficacy analyses will be based on the FAS, with the primary analysis also performed on the PPS. All safety analyses will be based on the Safety Analysis Set.

All summaries by treatment group will include each of the planned two treatment groups and all subjects combined (i.e., total).

All subjects will be assigned a unique subject number, which will consist of the study site identification concatenated with the assigned subject number.

For purposes of laboratory summaries, baseline is defined as an average all values observed up to an including Day 1. For purposes of abnormality laboratory summaries and all other analyses, baseline is defined as the last observed value up to and including Day 1.

Formatting of numerical results will include the following:

- Mean values will be reported to 1 decimal place more than the data collected.
- Standard deviation values will be reported to 2 decimal places more than the data collected.
- Median, minimum, and maximum values will be reported to the same decimal place as the data collected.
- Percentages will be reported to 1 decimal place.
- Where confidence intervals (CI) are to be reported, CIs for means will be reported to the same decimal places as mean values; CIs for percentages will be reported to 1 decimal place.
- All p-values will be reported to 3 decimal places.

8 SUMMARY OF STUDY POPULATION DATA

All study population data will be provided in subject specific listings. The disposition table will be produced using the ES and FAS. All other study population data tables will be produced using the FAS.

8.1 SUBJECT DISPOSITION

Subject disposition will be summarized descriptively by treatment group. The disposition summary will include results for subjects enrolled, subjects randomized, subjects treated, subjects included in each analysis population, discontinuation of study drug, reason for study drug discontinuation, study completion status, and reason for study withdrawal.

8.2 PROTOCOL DEVIATIONS

Protocol deviations will include the deviation recorded, the deviation category, and significance classification. The deviation category refers to the general aspect of the study the deviation affects. Classifications of protocol deviations will be determined by the clinical trial study team prior to database lock during a blinded data review meeting.

Protocol deviations will be summarized descriptively by treatment group. A listing of protocol deviations by unique subject number will be provided.

Reasons for screen failure will also be summarized by treatment group.

8.3 DEMOGRAPHICS

Subject demographics will be summarized descriptively by treatment group. The demographics summary will include results for subject age, age group, gender, race, and ethnic category. Age group is defined as the following categories:

- 18 - 40 years
- ≥40 - 64 years
- >64 years

8.4 BASELINE CHARACTERISTICS

Baseline characteristics include the following:

- Ishak fibrosis score
- Knodell histological activity index components (interface hepatitis, confluent necrosis, parenchymal injury, and portal inflammation)
- Liver collagen and SMA
- biomarkers (ALT, AST, caspase 3/7, cCK18/M30, and flCK18/M65)
- Laboratory Parameters (platelet count, total bilirubin, albumin, INR)
- Weight, BMI

The number and percentage of patients who are receiving either tacrolimus or cyclosporin as their immunosuppressant medication at the time or randomization, as well as the type of previous hepatic treatment received, will be included as part of the baseline characteristics.

All baseline characteristics will be summarized descriptively by treatment group. A listing of baseline characteristics will be provided by unique subject number.

8.5 TRANSPLANT AND HCV HISTORY

Transplant and HCV history will be summarized by treatment group. The transplant history summary will include:

- Number of years since transplant
- Liver donor age
- HCV positive donor Liver
  - Yes
  - No
- Source of transplant
  - Living
  - Cadaveric
- Immunosuppression regimen
  - Tacrolimus
  - Cyclosporine
  - Other
- Time since SVR (calculated as 12 weeks post end of previous hepatic treatment date treatment date)
- Previous HCV treatment post-transplant
  - Treatment Type
    - Antiviral
    - Immunotherapy
    - Antiviral+Immunotherapy
  - Interferon Based Treatment
    - Yes
    - No

9 EFFICACY ANALYSES

All primary, secondary, and exploratory endpoints will be summarized descriptively by treatment group at each study visit, using the FAS. Also, a sensitivity analysis for the primary endpoint will be produced using the PPS. The individual components of the primary endpoint will also be summarized descriptively by treatment group at each study visit.

All efficacy endpoints will be provided in listings by unique subject number and visit.

9.1 PRIMARY EFFICACY ANALYSIS

All screening and post-baseline biopsy data collected will be used in the primary analysis, irrespective of the defined protocol visit window. Classification of the Ishak fibrosis score will be summarized descriptively by treatment group at baseline, Month 12, and Month 24. Response at Months 12 and 24 will be summarized descriptively by treatment group, along with exact (Clopper-Pearson) 95% confidence intervals (CIs). The risk difference between groups will also be provided with its 95% CI.

For the primary efficacy analysis based on the Month 24 biopsy, subjects with a missing Month 24 biopsy will have their Ishak fibrosis score imputed. Imputation of missing Ishak fibrosis scores will be conducted using multiple imputation (MI). Results will be imputed based on age, gender, baseline Ishak fibrosis score, and the Month 12 Ishak fibrosis score. Imputations will be based on at least 5 imputed datasets, depending on the percent of missing observations and will be documented in the clinical study report. Within each imputed dataset, the change from baseline at Month 24 will be derived to allow categorization into response or no response as defined in Section 5.1.

Study success will be determined per the criteria described in Section 0. This primary analysis will be conducted using the FAS.

The following sensitivity analyses will be provided for the primary efficacy endpoint, using different methods for the handling of missing liver biopsy results at Month 24:

- All FAS observed post-baseline biopsies
- All FAS observed post-baseline at Month 24 (within the sensitivity analysis visit window, per Section 3.5)
- FAS with missing M24 biopsy imputed to ‘No’ response
- Per-protocol

Response rates at Month 12 will be summarized using the FAS in the same manner as the response rates at Month 24 (i.e., using MI). Subjects with a missing Month 12 liver biopsy will have their Month 12 Ishak fibrosis score imputed based on age, gender, and baseline Ishak fibrosis score.

9.2 SECONDARY EFFICACY ANALYSES

All secondary analyses will be conducted using the FAS. All secondary endpoints based on the Months 12 and 24 liver biopsies will include data as collected (per Section 3.5). All secondary endpoints will be summarized using observed cases.

No multiplicity adjustments will be made for the analysis of secondary endpoints.

9.2.1 Secondary Efficacy Analysis: Testing the Difference in Response Rates Stratified by Baseline Ishak Fibrosis Score

Testing of differences in response rates will be conducted using a Cochran-Mantel-Haenszel test. For each of the analyses described in Section 9.1 above, the testing will be stratified separately by each of the following:

- Baseline Ishak fibrosis score strata (F2, F3-F5, F6)
- Baseline Ishak fibrosis score grouping A (F2-F3, F4-F6)
- Baseline Ishak fibrosis score (F2-F6)

9.2.2 Secondary Efficacy Analysis: Change from Baseline in Ishak Fibrosis Score

Changes from baseline for the Ishak fibrosis score will also be summarized descriptively by treatment group using a shift table.

9.2.3 Secondary Efficacy Analysis: Ishak Modification of Knodell Histological Activity Index

The four components of the Knodell Histological Activity Index (interface hepatitis, confluent necrosis, parenchymal injury, and portal inflammation) will each be summarized descriptively by treatment group in two formats. The first format is descriptively summarizing each category by treatment group and visit. The second format is descriptively summarizing the shift in categories between baseline and Months 12 and 24, separately, by treatment group.

9.2.4 Secondary Efficacy Analysis: Clinical Outcomes

Each clinical outcome and type of decompensation event will be summarized descriptively by treatment group. This descriptive summary will summarize subjects and events across the entire study period (i.e., all post-baseline data collected up through Month 24). This summary will also be provided for all post-baseline data collected through Month 12.

9.2.5 Secondary Efficacy Analysis: Biomarkers

Biomarker endpoints will be summarized descriptively at each visit by treatment group. Change from baseline values for each biomarker at each post-baseline visit will be summarized descriptively by treatment group. If log-transformations are applied to any of the biomarker endpoints, the geometric mean, coefficient of variation, and percent relative change will also be included in the descriptive statistics.

9.2.6 Secondary Efficacy Analysis: Fibrosis Improvement: NASH CRN

The primary efficacy analysis will be repeated using the mapping from the Ishak Fibrosis Scoring System to evaluate the proportion of subjects who have at least at one-point improvement in fibrosis based on the mapping to this scoring system at Month 12 and Month 24.

9.2.7 Secondary Efficacy Analysis: Liver Stiffness

Liver stiffness will be summarized descriptively at each visit collected by treatment group. Change from baseline values in liver stiffness at each post-baseline visit will also be summarized descriptively by treatment group.

9.3 EXPLORATORY EFFICACY ANALYSES

The percent collagen and percent SMA from morphometric analysis will be summarized descriptively at Month 12 and Month 24 by treatment group. Change from baseline values in percent collagen and SMA will be summarized descriptively by treatment group and overall.

9.4 EXAMINATION OF SUBGROUPS FOR EFFICACY ENDPOINTS

The primary endpoint will be summarized descriptively using observed cases by treatment group for the following subgroups:

- Gender (Female, Male)
- Time since transplant (≤median, >median)
- Time since SVR (≤median, >median)
- Baseline Ishak fibrosis score strata (F2, F3-F5, F6)
- Baseline Ishak fibrosis score grouping A (F2-F3, F4-F6)
- Baseline Ishak fibrosis score grouping B (F2-F3, F3-F4, F5-F6)
- Baseline Ishak fibrosis score (F2, F3, F4, F5, F6)
- Investigative site

No statistical hypothesis testing will be conducted for these subgroup analyses.

10 PHARMACOKINETIC (PK) ANALYSES

All concentration levels and collection times for emricasan and its metabolites from the Month 1 visit will be provided in a listing. Population PK concentrations will be provided in a listing by visit.

10.1 EMRICASAN, METABOLITES, AND IMMUNOSUPPRESSION PK PROFILES

Blood samples will be collected at the Month 1 visit for generation of PK profiles for emricasan (IDN-6556), three metabolites (IDN-8741, IDN-6556-6, and IDN-6556-9), and four immunosuppressants (cyclosporine, everolimus, mycophenolate, and tacrolimus). The concentration levels will be used to derive the PK parameters that will be included in the PK analysis. Theses analyses will be conducted outside the scope of this SAP with a separate PK report being generated for inclusion in the clinical study report as an appendix.

10.2 POPULATION PK ANALYSIS

Blood samples will be collected for population PK assessment. A population analysis of time versus emricasan plasma concentration data will be performed using the nonlinear mixed effects modeling approach. The software NONMEM (UCSF, California, USA) will be used to derive the population mean and variance values for specific PK parameters. Additionally, a relationship between PK parameters (or dose) and efficacy, as well as AEs, will be investigated.

In the PK (and pharmacodynamics, PD) analysis, several covariates will be tested and incorporated into the structural model if shown to significantly improve the model's ability to describe the data. The final PK/PD model for emricasan will be obtained from this "full" model using only the covariate relationships that are thought to result in clinically significant alterations in drug PK and/or PD. This model will include data from this study and also from previously conducted emricasan studies.

Results from these population PK/PD models will be provided in a separate report and all analyses are outside the scope of this SAP.

11 SAFETY ANALYSES

All safety endpoints will be provided in listings by unique subject number and visit. All Safety related tables will be produced using the Safety Set.

11.1 DOSING AND EXTENT OF EXPOSURE

Study drug capsule counts will be summarized descriptively by treatment group and visit. Treatment compliance and extent of treatment exposure endpoints (i.e., days and person years of exposure) will be summarized descriptively by treatment group.

11.2 ADVERSE EVENTS

The incidence of TEAEs will be summarized descriptively by treatment group for the following:

- system organ class (SOC) and preferred term
- SOC, preferred term, and severity
- SOC and preferred term for TEAEs classified as related to study drug
- SOC and preferred term for events having incidence of ≥5% in any treatment group
- SOC and preferred term for subjects with study discontinuation due to the AE
- SOC and preferred term for subjects with study drug interruption due to the AE
- preferred term (alphabetical and highest incidence in all emricasan dose groups)

Missing values for severity, relationship to study drug, action taken with study drug, treatment required, and/or outcome will be summarized as unknown.

The incidence of SAEs for each SAE will be summarized descriptively by treatment group and overall for the following:

- SOC and preferred term
- SOC, preferred term, and severity
- SOC and preferred term for SAEs classified as related to study drug
- preferred term (alphabetical and highest incidence in all emricasan dose groups)

Subject listings by unique subject number and visit will be provided for the listings below:

- All AEs
- Subjects who discontinued from the study
- Subjects who had a study drug interruption
- Subjects with SAEs
- Subjects who died

11.3 LIVER ULTRASOUND

Incidence of abnormal findings and number of events from the liver ultrasound will be summarized by treatment group. This summary will also include the incidence and events

considered to be clinically significant. The list of abnormal events, as determined by a blinded medical review prior to database lock, will also be provided.

11.4 POTENTIAL LIVER INJURY

Subject incidence of the categorizations for ALT, AST, and total bilirubin as described in Section 5.4.5 will be summarized descriptively by treatment group and visit. An evaluation of drug-induced serious hepatotoxicity (eDISH) plot of all subjects coded by treatment group will be provided, which displays the ALT or AST value (on a log 10 scale) versus the total bilirubin value (on a log 10 scale). The eDISH plot will be produced with concurrent results for ALT, AST, and bilirubin by visit and an additional plot that displays the maximum post-baseline values of ALT, AST and total bilirubin (both on a log 10 scale).

11.5 LABORATORY MEASUREMENTS

Hematology, chemistry, coagulation, and alpha-fetoprotein laboratory parameters will be summarized descriptively at each visit by treatment group. Where applicable, change from baseline in laboratory tests will also be summarized descriptively at each post-baseline visit by treatment group.

A shift table will be provided for descriptively summarizing the classification around the normal range of each hematology, chemistry, coagulation, and alpha-fetoprotein laboratory parameter between baseline to each of the minimum and maximum post-baseline values.

An additional shift table will be provided for descriptively summarizing the classification of urinalysis laboratory parameters between baseline and the maximum post-baseline values by treatment group and overall.

11.6 VITAL SIGNS AND WEIGHT

Vital signs, weight, and BMI will be summarized descriptively at each visit by treatment group. Change from baseline in vital signs, weight, and BMI will also be summarized descriptively at each post-baseline visit by treatment group and overall.

Abnormalities in vital signs will also be summarized descriptively by treatment group and visit.

11.7 ELECTROCARDIOGRAMS

Classifications of observed values and change from baseline values in QTcB and QTcF, as described in Section 5.4.8, will be summarized descriptively by treatment group and visit. Maximum values and maximum change from baseline values during the treatment period will also be summarized descriptively.

11.8 MEDICATIONS

Incidence of prior medications will be summarized descriptively by treatment group, anatomical therapeutic chemical classification (ATC) level, and preferred term. This summary will be included as part of the study population data summaries described in Section 5.4.9.Incidence of concomitant, new concomitant, and all concomitant medications will be summarized descriptively by treatment group, ATC level, and preferred term.

The number and percentage of subjects receiving anti-viral, immunotherapy, and immunosuppressants medications prior to the study and during the study will each be summarized by ATC classification and preferred term.

11.9 PHYSICAL EXAM

Physical examination assessments will be summarized descriptively at each visit by treatment group. Changes in physical exam status will be summarized descriptively by treatment group using shift tables.

11.10 EXAMINATION OF SUBGROUPS FOR SAFETY ENDPOINTS

Overall AEs will be summarized descriptively by treatment group for the following subgroups:

- Gender (Female, Male)
- Age (18-40, ≥40 - ≤64, >64)
- Baseline Ishak fibrosis score strata (F2, F3-F5, F6)
- Baseline Ishak fibrosis score grouping A (F2-F3, F4-F6)
- Baseline Ishak fibrosis score grouping B (F2-F3, F3-F4, F5-F6)
- Baseline Ishak fibrosis score (F2, F3, F4, F5, F6)

12 HANDLING OF MISSING DATA

The details of handling missing data for the primary endpoint are provided in Section 9.1. There will be no imputations made for any of the secondary endpoints.

13 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will review safety data from this study at 6-month periodic intervals. The DMC will review data within its general remit to oversee subject safety in the study, and provide recommendations and guidance to the Sponsor in accordance with the procedures stated in its charter.

All Investigators, responsible institutional review boards/institutional ethics committees, and applicable regulatory agencies will be informed of any decisions made by the Sponsor based on recommendations from the DMC relating to subject safety that affect the conduct of this study. The Investigators will inform the subjects of such actions, and the protocol and informed consent form will be revised, as appropriate.

14 CHANGES IN PLANNED ANALYSIS

14.1 CHANGES FROM PROTOCOL TO SAP VERSION 1.0

The primary endpoint was clarified from the protocol such that the response rate is declared as the primary endpoint to make it consistent with the sample size calculations. Response is defined per Section 5.1 of this SAP.

The primary analysis was updated to reflect the primary endpoint as defined in Section 5.1. All secondary analyses will be conducted using observed cases in the FAS.

All biopsy data collected by local assessments will be captured in the database and will not be summarized or listed.

All other details provided in this SAP are intended to provide more detail and clarity to the protocol planned analyses.

14.2 CHANGES FROM SAP VERSION 1.0 TO SAP VERSION 2.0

Clarifications were made to text throughout the SAP to help clarify further details.

A translation of the Ishak Fibrosis Score to NASH CRN Fibrosis Stage Scoring (Section 5.2.3) was added with a corresponding planned summary table.

Local biopsy assessments collected will be provided in a data listing.

Baseline was redefined for laboratory summaries as the average of all values observed up to and including Day 1.

Age group categories were updated for the baseline characteristics summary table and primary endpoint subgroup analysis.

Details regarding the transplant and HCV history, along with immunosuppressant and previous hepatic treatments, collected at screening will be summarized.

Sensitivity analyses for the primary endpoint were updated.

An additional summary table of specific concomitant medications will be produced that will include immunosuppressants, antivirals, and immunotherapies.

15 REFERENCES

Fleming T, Richardson B. *Some design issues in trials of microbicides for the prevention of HIV infection*. J Infectious Diseases 2004;190(4):666-674.

George et. al. *Clinical, virologic, histologic, and biochemical outcomes after successful HCV therapy: A 5-year follow-up of 150 patients*. Hepatology; 49(3):729-738

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