STATISTICAL ANALYSIS PLAN

Study Protocol Number: H3B-6527-G000-101

Study Protocol Title: An Open-Label Multicenter Phase 1 Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of H3B-6527 in Subjects With Advanced Hepatocellular Carcinoma.

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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse event
ATC	Anatomical therapeutic class
AUC	Area under curve
$AUC_{(0\text{-}inf)}$	AUC from time point 0 extrapolated to infinity
$AUC_{(0\text{-}t)}$	AUC from time point 0 through the last measurable point
BID	Twice Daily
Cx	Cycle x
CI	Confidence interval
CL/F	Apparent Total Body Clearance Following Oral Administration
C_{max}	Maximum Observed Plasma Concentration
CRF	Case report form
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse event
DLT	Dose limiting toxicities
DME	Dose modifying events
DOR	Duration of response
ECGs	Electrocardiograms
FAS	Full analysis set
HCC	Hepatocellular carcinoma
ICC	Intrahepatic cholangiocarcinoma
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCI	National Cancer Institute
ORR	Objective response rate
OS	Overall survival
OTV	Off-treatment visit
PG	Pharmacogenetic

Abbreviation	Term
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic
PT	Preferred term
Q1 and Q3	The first and the third quartiles
QD	Once daily
QTc	Corrected QT interval
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
R_{acc}	Accumulation Ratio
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SI	Système International
SRC	Safety review committee
SOC	System organ class
$t_{1/2}$	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
TLG	Tables, listings, and graphs
t_{max}	Time of maximum observed plasma concentration
V_Z/F	Apparent volume of distribution during the terminal phase
WHO DD	World Health Organization Drug Dictionary

3 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned statistical analysis and reporting for Clinical Study Protocol *H3B-6527-G000-101* titled "An Open-Label, Multicenter Phase I Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of H3B-6527 in Subjects with Advanced Hepatocellular Carcinoma".

This SAP amendment is based on SAP Amendment 0.1 dated on 08 Nov 2017 and the protocol Amendment 09 dated on 30 Sep 2020. In the event of future amendments to the protocol, this SAP amendment will be modified to account for changes relevant to the statistical analysis.

3.1 Study Objectives

3.1.1 Primary Objectives

The primary objectives are to:

- Determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of H3B-6527 in subjects with advanced hepatocellular carcinoma (HCC).
- Assess the safety and tolerability of H3B-6527 as a single agent administered orally.

3.1.2 Secondary Objectives

The secondary objectives are to:

- Evaluate the pharmacokinetic (PK) profile of H3B-6527.
- Evaluate the preliminary antitumor activity of H3B-6527 at the RP2D and schedule in subjects with advanced HCC, who are FGF19-positive, as determined by the Sponsor-designated laboratory.

3.1.3 Exploratory Objectives

The exploratory objectives are to:

- Explore biomarkers and their correlation with safety and efficacy endpoints.
- Assess the pharmacodynamic effects of H3B-6527 on FGF19, Ki67, pERK, bile acids and CYP7A1 and other FGFR4-related biomarkers in blood and tumor samples.
- Explore the relationship between PK and pharmacodynamics.
- Exposure to H3B-6527 in tumor samples may be assessed.
- Explore the metabolite profile of H3B-6527 in plasma and urine.

3.2 Overall Study Design and Plan

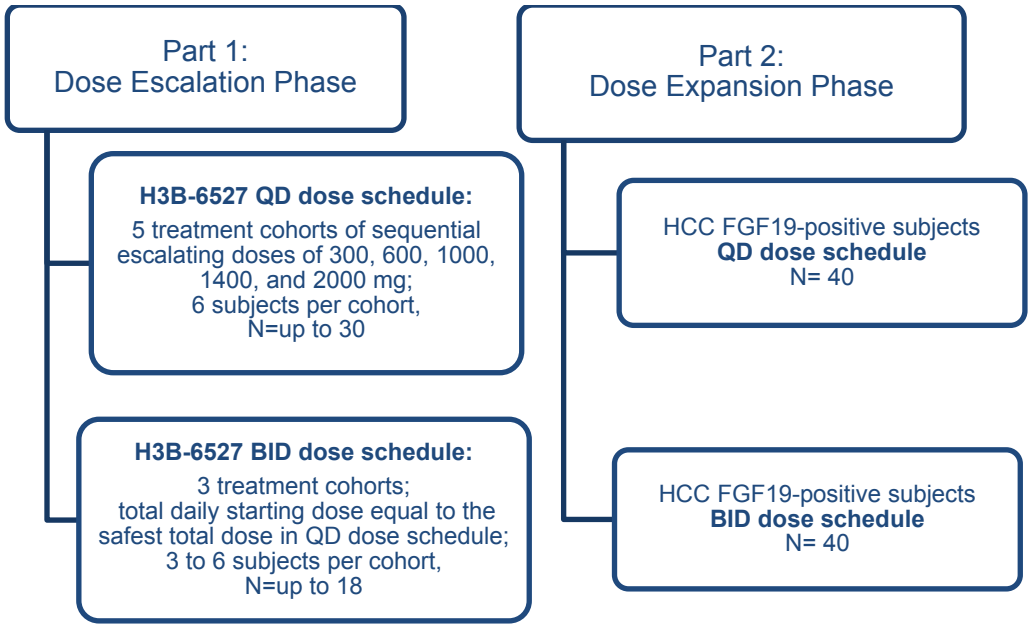
3.2.1 Study Design

This is an open-label, multicenter, Phase 1 study that will be conducted in 2 parts, a Dose Escalation phase (Part 1) and a Dose Expansion phase (Part 2). Dose escalation will follow a standard 3+3 cohort design until the MTD/RP2D is determined in this population. Approximately 30 to 128 subjects are planned for enrollment. H3B-6527 will be administered by mouth in 21-day cycles without break to examine both QD (once daily) and BID (twice daily) dose schedules.

During both parts of the study, subjects will be administered the study drug with food based on the Healthy Volunteers Food-Effect study (Study H3B 6527-A001-001: A Randomized Phase 1 Food-Effect Study of H3B-6527 in Healthy Subjects).

This study makes provision for exploring a BID schedule of H3B-6527; the criteria to evaluate a BID schedule will be based on an integrated evaluation of safety, tolerability, clinical benefit, PK, and pharmacodynamic data, for all QD dose levels tested. In this case, a new cohort of 3 subjects will be enrolled and treated with a BID dose. The initial total daily dose given BID will be equal to a total daily dose that has been well tolerated as a QD dose (dose limiting toxicities (DLT) rate <33% in a cohort of 3-6 subjects).

Figure 1: Overall Study Design



3.2.2 Dose Escalation (Part 1)

The objective of the Dose Escalation phase is to determine the MTD and/or RP2D of H3B-6527 in subjects with advanced HCC. Intrahepatic cholangiocarcinoma (ICC) subjects were also enrolled from protocol Amendement 5 to Amendment 7.

For dose-escalation purposes, toxicities assigned as DLTs during the first cycle will be assessed. After 3-6 subjects in a cohort have completed Cycle 1 (C1), all available safety data will be reviewed by the Safety Review Committee (SRC) consisting of Sponsor personnel and investigators and the decision to proceed to the next dose cohort will be made jointly. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Once a subject has completed C3 at the initially assigned dose schedule and dose level (QD or BID), intrapatient dose escalation will be allowed.

H3B-6527 will be tested in sequential escalating dose cohorts (n=3 to 6) at the dose levels listed in the Table 1.

Table 1 Dose Cohorts in H3B-6527 Dose Escalation Phase

Dose level	Initial No. of Subjects	H3B-6527 Total Daily Dose
-1	3	150 mg
1[a]	3	300 mg
2	3	600 mg
3	3	1000 mg
4	3	1400 mg
5	3	2000 mg

These total daily (dose levels may be evaluated in QD or BID) dose schedules, including intermediate levels, differing MTDs by sub-population (e.g., disease indication or ethnicity), and in expansion of an existing dose level up to 12 evaluable subjects following discussion between the Sponsor and the investigators, if supported by evolving safety, tolerability, PK, and pharmacodynamic data.

a: Planned starting dose level in QD schedule.

Subjects will be assigned to a dose level in the order of study entry. Initially, 3 subjects will be enrolled at the starting dose level. If 2 of the 3 subjects experience a DLT then the dose level -1 (150 mg) will be explored. If 1 of the 3 subjects experiences a DLT then the dose will be expanded to 6 subjects. If ≥2 of 6 subjects in the starting dose cohort experience a DLT during the first cycle, then the dose level -1 (150 mg) will be explored.

Dose escalation to the next higher dose may proceed if no DLT is observed in C1 among the first 3 subjects accrued to a cohort. If 1 of 3 subjects in the cohort experienced a DLT, up to a total of 6 subjects will be enrolled. If 2 or more of the 3-6 subjects in a cohort experience a

DLT, dose-escalation will cease, and additional subjects will be treated at a lower dose level. Dose escalation will continue until a dose level where 2 or more of 6 subjects experience a DLT.

To be evaluable for a DLT, subjects must have completed safety assessments through predose on C1 Day 1 and must have received at least 17 of 21 (80%) study days within C1, unless due to a DLT. Subjects who discontinue from the study for reasons other than DLT before completing C1 are to be replaced.

Definitions of DLT and MTD

The DLTs are defined as any of the toxicities listed in Table 2 occurring during C1 and judged by the investigator as related to study drug (i.e., assessed as unrelated to disease, intercurrent illness, or concomitant medications).

Table 2 Dose-Limiting Toxicity Definition

TOXICITY	CRITERIA
Hematology	• Febrile neutropenia • CTCAE Grade 4 neutropenia that does not resolve to Grade ≤2 within 7 days • CTCAE Grade 3 thrombocytopenia requiring transfusion • CTCAE Grade 3 thrombocytopenia and clinically significant bleeding • CTCAE Grade 4 thrombocytopenia • CTCAE Grade 3 anemia if transfused or if lasting for more than 7 days • CTCAE Grade 4 anemia of any duration
Gastrointestinal	• CTCAE Grade 3 nausea, vomiting and/or diarrhea lasting more than 72 hours despite the use of optimal anti-emetic/antidiarrheal treatment • CTCAE Grade 4 diarrhea and/or vomiting irrespective of prophylaxis or appropriate treatment
Renal	• CTCAE Grade ≥3 serum creatinine
Hepatic	• CTCAE Grade 3 bilirubin (>3.0 × the upper limit of normal (ULN)) and/or alanine aminotransferase (ALT) ≥10 × ULN • For subjects with a starting ALT within the normal range for the local laboratory, an elevation ALT ≥ 5 × ULN for the local laboratory • For subjects with an abnormal value ≥ ULN at baseline based on the local laboratory ranges, an ALT elevation ≥ 10 × ULN for the local laboratory
Other AEs not listed above	• Non-hematologic toxicities of CTCAE Grade ≥3 except for the following. - CTCAE Grade 3 fatigue lasting less than 1 week, - Isolated CTCAE Grade 3 elevations in biochemistry laboratory values without associated clinical symptoms that last for ≤7 days. This includes electrolyte abnormalities that respond to medical intervention. • H3B-6527-related, CTCAE Grade 2 nonhematologic toxicities that, in the opinion of the treating investigator, require a dose reduction or discontinuation of study drug, or lead to the subject's failure to complete at least 17 days of study drug administration in C1, may be deemed to be

	dose-limiting if agreed upon by participating investigators and the Sponsor.

AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase, C = Cycle, CTCAE = Common Terminology Criteria for Adverse Events, ULN = upper limit of normal.

The MTD is defined as the highest dose at which no more than 1 of 6 subjects experiences a DLT in the dose cohort. (Note that at least 6 subjects must be treated at the dose level potentially considered to be the MTD before that dose level can be considered the MTD).

The RP2D may not exceed the MTD and will be agreed upon by the SRC based on an integrated evaluation of safety, tolerability, clinical benefit, PK, and pharmacodynamic data, for all dose levels tested. Clinically significant toxicities (eg, chronic Grade 2 toxicities) or adverse events (AEs) that meet the definition of dose limiting but occurring after C1 (dose modifying events, DME) may be considered when determining the RP2D. Once the MTD/RP2D is reached, at least 6 HCC subjects must be enrolled at the RP2D (regardless of the total number of subjects enrolled at that dose level) in order to proceed with dose expansion.

3.2.3 Expansion (Part 2)

Prior to starting Part 2 of the study, the investigators and the Sponsor will use safety, efficacy, PK, and pharmacodynamic data obtained during the Dose Escalation Phase, as well as clinical judgement, to jointly determine the dose schedules to be studied.

During Part 2, the Dose Expansion phase, approximately 40 subjects per dose schedule will be enrolled to examine QD and/or BID dose schedules. Subjects enrolled into Part 2, Dose Expansion phase, must be FGF19-positive as defined by Sponsor-designated laboratory.

When both dose schedules are accruing subjects, an alternating enrollment schema into QD and BID dose schedule will be followed.

3.2.4 Subject Participation Phases

The study will be conducted in the following 4 phases: Pretreatment Phase, Treatment Phase, Extension Phase, and Follow-up Phase.

Pretreatment Phase

Pretreatment Phase will last no longer than 28 days and includes a Screening Period to obtain informed consent and establish protocol eligibility and a Baseline Period to establish disease characteristics before treatment.

Treatment Phase

Treatment phase will last for 1 treatment cycle of 21 days. Subjects who are receiving study drug at the end of the Treatment Phase will continue to receive study drug in the Extension Phase.

Extension Phase

In the Extension Phase, subjects will continue to receive the same treatment and dose they received during the Treatment Phase, provided termination criteria are not met.

In Treatment and Extension phases, subjects will discontinue study drug at the time of disease progression, development of unacceptable toxicity, withdrawal of consent or termination of the Sponsor. However, subjects may continue to receive study treatment as long as there is demonstrated clinical benefit as judged by the investigator after discussion with the Sponsor or until the end of the study. Disease progression will be determined by the investigator following relevant Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines for ICC and modified RECIST (mRECIST) for HCC. The mRECIST for this protocol harmonizes the original mRECIST criteria (Lencioni and Llovet 2010) using triphasic liver computed tomography (CT)/magnetic resonance imaging (MRI; optimized for precontrast, arterial phase, and portal venous phase) and elements of RECIST 1.1 (Eisenhauer et al., 2009).

Follow-up Phase

After the Off-treatment Visit, all subjects who discontinue study treatment, regardless of their reasons for doing so, will be followed for survival approximately every 12 weeks for up to 12 months or until 6 cycles after last patient in, death, loss to follow-up, or withdrawal of consent, whichever occurs first. Subjects who discontinue study drug without PD (progressive disease) will continue to undergo tumor assessments every 6 weeks until documented PD or another anticancer therapy is initiated.

The data cutoff for the primary analysis will occur once the last subject completes 6 cycles of investigational therapy.

The end of study is defined as when the last ongoing subject completes their off treatment visit.

The schedules of assessments are presented in Table 6 and Table 7 of the Protocol.

4 DETERMINATION OF SAMPLE SIZE

Dose Escalation Phase (Part 1)

It is anticipated that selection of the RP2D will be based on an integrated evaluation of safety, tolerability, clinical benefit, PK, and pharmacodynamic data. The total number of subjects to be enrolled is dependent upon the observed safety profile, which will determine the number of subjects per dose cohort, as well as the number of dose escalations required to achieve the MTD and/or the RP2D. For each dose schedule of QD and BID, assuming 5 dose levels for QD dose schedule and 3 dose levels for the BID dose schedule will be studied and a maximum of 6 subjects will be enrolled per dose level, then between 30 to 48 subjects may be accrued during dose escalation.

Dose Expansion Phase (Part 2)

A total of approximately 40 to 80 subjects will be enrolled in the Dose Expansion phase. Prior to starting the Dose Expansion phase, the investigators and the Sponsor will use safety, efficacy, PK, and pharmacodynamic data obtained during the Dose Escalation Phase, as well as clinical judgement, to jointly determine the dose schedules to be studied.

During Part 2, the Dose Expansion phase, a sample size of 40 evaluable subjects per dose schedule will be enrolled to examine QD and/or BID dosing of H3B-6527 based on the recommended dose determined from Part 1 (Table 3). For a reference of the precision of ORR estimates, the associated 2-sided 95% CIs for ORR up to 30% (40 subjects) are provided in Table 4.

This study makes provision for exploring a BID schedule of H3B-6527 during the Dose Expansion phase if evaluation of the PK, pharmacodynamics, or safety of H3B-6527 suggests that it may be preferable to administer H3B-6527 BID rather than QD. When both dose schedules are accruing subjects, an alternating enrollment schema into QD and BID schedule will be followed.

Table 3. Treatment Arms for Part 2, Dose Expansion

Treatment Arm	Number of Subjects
1: Subjects with advanced HCC who are FGF19-positive to receive H3B-6527 QD for 21-day cycles	40 subjects
2: Subjects with advanced HCC who are FGF19-positive to receive H3B-6527 BID for 21-day cycles	40 subjects

Table 4. 2-sided 95% CI for ORR estimate up to 30% (40 subjects)

ORR (N=40)	2-sided 95% CI
5% (2 responders in 40 subjects)	(0.006, 0.169)
7.5% (3 responders in 40 subjects)	(0.016, 0.204)
10% (4 responders in 40 subjects)	(0.028, 0.234)
12.5% (5 responders in 40 subjects)	(0.042, 0.268)
15% (6 responders in 40 subjects)	(0.057, 0.298)
17.5% (7 responders in 40 subjects)	(0.073, 0.328)
20% (8 responders in 40 subjects)	(0.091, 0.356)
22.5% (9 responders in 40 subjects)	(0.108, 0.385)
25% (10 responders in 40 subjects)	(0.127, 0.412)
27.5% (11 responders in 40 subjects)	(0.146, 0.439)
30% (12 responders in 40 subjects)	(0.166, 0.465)

Within each treatment arm, if both QD and BID dose schedules are studied, an evaluation using efficacy, safety, PK, pharmacodynamic data will be performed and the investigators and Sponsor will jointly determine if one dose schedule is better than the other.

5 STATISTICAL METHODS

All statistical analyses and summary information are to be generated according this SAP. Any deviations from this SAP will be documented in the clinical study report (CSR).

Unless otherwise stated, tables, listings, and graphs (TLGs) for Dose Escalation (Part 1) will be broken down by dose cohort, for Expansion (Part 2) by QD/BID dose schedule.

5.1 Study Endpoints

5.1.1 Primary Endpoints

- Occurrence of DLTs as a function of the dose of H3B-6527 for determination of the MTD and RP2D.
- Safety/tolerability: the type and frequency of AEs, serious adverse events (SAEs) using CTCAE, Version 4.03, as well as changes in clinical laboratory values, electrocardiogram (ECG) parameters and vital sign measurements.

5.1.2 Secondary Endpoints

- PK: standard primary PK parameters including, but not limited to, the area under the plasma concentration-time curve from 0 through last measurable point (AUC_{0-t}), maximum observed plasma concentration (C_{max}) and time of maximum observed plasma concentration (t_{max}).
- Preliminary antitumor activity: Response will be determined by the investigator using mRECIST/RECIST 1.1. The following endpoints will be determined:
  - Objective response rate (ORR), defined as the proportion of subjects achieving a best overall confirmed response of partial or complete response (partial response [PR] + complete response [CR]) from first dose date until disease progression/recurrence.
  - Duration of response (DOR), defined as the time from the date of first documented CR/PR until the first documentation of disease progression as determined by the investigator or death, whichever comes first. If a subject had no record of disease progression or did not die before the data cut-off date, then the subject will be censored at the last available tumor assessment.
  - Progression free survival (PFS), defined as the time from first dose date to the date of the first documentation of disease progression as determined by the investigator or death, whichever occurs first.

- Overall survival (OS), defined as the time from first dose date to the date of death.
- Time to response, defined as the time from first dose date to the date of first documented CR/PR.

5.1.3 Exploratory Endpoints

- Correlation of biomarker expression levels with antitumor activity and safety.
- Expression levels of biomarkers in blood and tumor samples.
- Correlation of biomarker expression levels with H3B-6527 exposure in plasma.
- H3B-6527 levels in tumor tissue may be assessed.
- H3B-6527 metabolites in plasma and urine.

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

Full Analysis Set (FAS) will include all subjects who received at least 1 dose of study drug. This will be the primary analysis set for demographic and baseline characteristics. Efficacy analysis will be based on FAS for HCC subjects only.

Safety Analysis Set will include all subjects who received at least 1 dose of study drug. This will be the analysis set for all safety evaluations except DLT results.

DLT Analysis Set will include all subjects in Dose Escalation phase (Part 1) who are evaluable for a DLT. To be evaluable for a DLT, subjects must have completed safety assessments through predose on C2 Day 1 and must have received at least 17 of 21 (approximately 80%) study days within C1, unless due to a DLT. This will be the analysis set for analyzing DLT results only.

PK Analysis Set will include all subjects who have received at least 1 dose of study drug and have at least 1 evaluable plasma concentration.

Pharmacodynamics Analysis Set will include all subjects who have received at least 1 dose of study drug and have evaluable pharmacodynamic data.

PK/Pharmacodynamics Analysis Set will consist of all subjects in the Safety Analysis Set that also have evaluable plasma PK and pharmacodynamic pretreatment assessment and at least 1 post treatment assessment.

Response Evaluable Set will consist of those HCC subjects who have received at least 1 dose of study drug and have measurable disease at baseline and at least 1 post-baseline evaluation.

The number (percentage) of subjects enrolled in the study and included in each analysis set will be summarized.

A listing of subjects included in each analysis set will be provided.

5.2.2 Subject Disposition

The number (percentage) of subjects who screened for participation, discontinued study drug and discontinued from the study will be summarized, along with the primary reason for screening failure and/or discontinuation.

Listings of all subjects screened for participation, discontinued study drug and discontinued from the study, including primary reasons for screening failure and/or discontinuation will be provided.

5.2.3 Protocol Deviations

All major protocol deviations will be determined prior to database lock and will be agreed upon by a review of individual subject data. The summary table and listing of major protocol deviations will be provided using data in the clinical database.

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the FAS will be summarized using descriptive statistics. They include:

- age (years) and age group (<65 years, >=65 years)
- sex (male, female)
- race (White, Black or African American, Asian [Japanese, Chinese, Other Asian], American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and Other)
- ethnicity (Hispanic or Latino, not Hispanic or Latino)
- height (cm)
- weight (kg)
- ECOG performance status.

The number (percentage) of subjects of previous anti-cancer medications, previous radiotherapy and tumor diagnosis assessed in the baseline for the FAS will be summarized, respectively.

Listings of demographics, tumor diagnosis, Child-Pugh classification, previous anti-cancer medications and previous radiotherapy will be provided.

Medical history

The number (percentage) of subjects reporting a history of any medical condition will be summarized for the FAS. The medical history and current medical condition at baseline will be summarized as appropriate. Reported medical conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA), version 19.0 or later.

A listing of medical and surgical history will be provided.

5.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded on the case report form (CRF) will be coded using the World Health Organization Drug Dictionary (WHO DD) 2016 or current. The number (percent) of subjects who have taken prior and concomitant medications will be summarized on the FAS by Anatomical Therapeutic Chemical (ATC) Classification and WHO DD preferred term. Prior medications will be defined as medications that stopped prior to the first dose of study drug. Concomitant medications will be defined as medications that started after the date of the first dose of study drug up to 30 days after the subject's last dose.

All medications will be presented in subject data listings.

5.2.6 Treatment Compliance

Subjects with treatment related protocol deviations will be summarized.

5.3 Data Analysis General Considerations

5.3.1 Pooling of Centers

Subjects from all centers will be pooled for all analyses.

5.3.2 Adjustments for Covariates

Not applicable.

5.3.3 Multiple Comparisons/Multiplicity

Not applicable.

5.3.4 Examination of Subgroups

No formal subgroup analyses are planned. Exploratory subgroup analyses may be performed as needed.

5.3.5 Handling of Missing Data, Drop-outs, and Outliers

In general, missing or incomplete data, including dates, will be treated as missing or incomplete and no data imputation will be applied. Data that are potentially spurious or erroneous will be queried and examined during the review of the study data.

For efficacy data summarized for the FAS for HCC subjects, subjects who start trial therapy and drop out prior to any tumor response assessment for any reason will be considered as nonresponders and will be included in the denominator when calculating the response rate.

Some numerical laboratory data may contain a "<" or ">" or letters, the numerical value will be used for calculation and analysis in tables and figures and the complete character records in listings.

5.4 Efficacy Analyses

Efficacy analyses will be based on the FAS for HCC subjects only and/or Response Evaluable Set.

5.4.1 Analysis of Efficacy Endpoints Based on Tumor Response

ORR, duration of response (DOR), time to response and PFS will be analyzed on the FAS for HCC subjects and Response Evaluable Set as appropriate.

The exact 95% confidence intervals of ORR will be calculated using Clopper-Pearson method. DOR and time to response will be for subjects who have achieved a best response of CR or PR only. Censoring rules for PFS will follow the FDA guidance and are specified in Table 5. PFS will be reported in both summary tables and plotted with Kaplan-Meier curve.

Table 5 Censoring Rules for PFS

No.	Situation	Date of Event (Progression/Death) or Censoring	Outcome
1	No baseline tumor assessments	Date of first dose	Censored
2	Progression documented between scheduled visits	Date of first radiologic PD assessment	Event
3	No progression	Date of last adequate radiologic assessment	Censored
4	New anticancer treatment started	Date of last adequate radiologic assessment prior to or on date of new anticancer treatment	Censored
5	Death before first PD assessment	Date of death	Event
6	Death between adequate assessment visits*	Date of death	Event
7	Death or progression after more than one missed visit/tumor assessment**	Date of last adequate radiologic assessment before missed tumor assessments	Censored

CR = complete response, PD = progressive disease, PR = partial response, SD =stable disease,

* Adequate tumor assessment is radiologic assessment of CR, PR, SD, non-CR/non-PD or PD at regular interval as defined in the protocol.

** More than one missed visit/adequate tumor assessment is defined as having either one of the following two durations being longer than 14 weeks - 1 day, which is 97 days (= ((6+1) x 2 x 7) – 1) for subjects on the every 6 week tumor assessment schedule:

a. Duration between two consecutive tumor assessments

b. Duration between the last adequate tumor assessment and death or PD

The priority of the censoring rules is as follows,

1. If the subject had PD or death, the following sequence will be applied:

- If a subject did not have a baseline tumor assessment (No. 1), the subject will be censored on the date of first dose.
- If the subject died within 97 days (14 weeks -1 day) following first dose and did not receive a new anticancer treatment, it will be counted as PFS event at the date of death.

- If a subject had new anticancer treatment before PD or death (No. 4), the subject will be censored on the date of the last adequate tumor assessment prior to or on the date of new anticancer treatment.
- If a subject missed two or more tumor assessments before PD or death (No. 7), the subject will be censored on the date of the last adequate tumor assessment before PD or death. Note that if a subject is censored by both this criterion and the anticancer treatment criterion, the earliest censoring date will be used.
- Otherwise, if a subject had an event (No. 2, No. 5, or No. 6), the earliest event date will be used.

2. If a subject did not have PD or death, the censoring date will be the earliest censoring date if the subject met multiple censoring criteria (No. 1, No. 3, No. 4, No. 7).

A listing of target lesion response, non-target lesion response, new lesion and overall response at each assessment time point will be provided. Best overall response will be identified in the listing.

5.4.2 Analysis of Overall Survival

OS will be summarized, estimated and plotting using Kaplan-Meier method on the FAS for HCC subjects. Time of death will be censored for subjects who are without death information at the time of OS analysis. Censoring rules for OS are specified in Table 6.

Table 6 Censoring Rules for Overall Survival Endpoint

Situation	Event Date or Censoring	Outcome
Death during study	Date of death	Death
Death after data cut-off	Date of data cut-off	Censored
Subject still alive at data cut-off	Date of data cut-off	Censored
Subject lost to follow-up before data cut-off	Date last known to be alive	Censored

A listing of PFS and OS will be provided.

5.5 PHARMACOKINETIC, PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKERS ANALYSES

Pharmacokinetic Analysis

Plasma concentrations of H3B-6527 will be tabulated and summarized by dose level, day, and time. H3B-6527 PK parameters will be derived from plasma concentrations by noncompartmental analysis using actual times. Minimally, the following PK parameters will be calculated: C_{max}, t_{max}, $AUC_{(0-t)}$, accumulation ratio (R_{acc}); and if data permit, area under the plasma concentration-time curve extrapolated to infinity ($AUC_{(0-inf)}$), terminal elimination half-life ($t_{1/2}$), apparent total body clearance (CL/F), and apparent volume of distribution during the terminal phase (V_z/F). More details will be described in a separate PK analysis plan.

Pharmacodynamics, Pharmacogenetics (PG) and other biomarker analyses will be performed and reported separately. Details of these analyses will be described in separate analysis plans.

5.6 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set and "as treated" basis except the evaluation of DLT and determination of the MTD. The number (percentage) of DLT will be summarized on and the determination of the MTD will be based on DLT Analysis Set in the Dose Escalation part.

Subjects who do not receive study drug for at least 17 of 21 days (80%; not necessarily consecutively) during the first cycle for reasons not considered to be a DLT by both the investigators and the Sponsor will be replaced. The subjects who are replaced will not be considered evaluable for DLT assessments.

Safety data include all AEs, SAEs, clinical laboratory tests, vital signs, ECGs, MUGA/echocardiogram, and ophthalmic examinations.

Safety parameters will be summarized using descriptive statistics (mean, standard deviation, median, Q1, Q3, and range for continuous variables; numbers and percentages for categorical measures).

The effects of H3B-6527 on cardiovascular repolarization will be evaluated via 12-lead continuous cardiac Holter monitoring around first dose administration on C1 Day 1 and Day 8 in the dose escalation part of the study only. Individual ECGs will be extracted from the Holter recordings at specified time points per ECG manual and will be evaluated by a central laboratory. QT intervals will be measured from Lead II and will be corrected for heart rate (QTc) using Fredericia's (QTcF) correction factors. The primary QTc parameter will be QTcF; secondary parameters (QTc corrected using Bazett's formula [QTcB], QT, QRS, PR, and heart rate) and wave forms (T waves) will be evaluated.

5.6.1 Extent of Exposure

The extent of exposure of study drug will be summarized for the Safety Analysis Set by number of cycles/days on treatment, duration of treatment, total dose, the number of cycles received and the number of subjects requiring dose reductions, treatment delay and treatment discontinuation due to AEs. A subject listing of study drug administration by cycle/visit will be provided.

The treatment compliance will be summarized for the Safety Analysis Set by dose intensity and received dose as percentage of planned starting dose.

Duration of treatment (days) = last dose date of study drug– first dose date of study drug+1.

Dose intensity (mg/day) = total dose received during the study / (duration of treatment in days)

Received dose as percentage of planned starting dose (%) = 100 x dose intensity (mg/day) / planned starting dose (mg/day).

Listings of study drug administration by cycle/visit and treatment exposure will be provided.

5.6.2 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using MedDRA. AEs will be coded to the MedDRA (Version 19.0 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment up to 28 days after last dose, having been absent before treatment or:

- reemerges during treatment, having been present before treatment but stopped before treatment, or
- worsens in severity during treatment relative to before treatment state, when the AE was continuous.

Only TEAEs will be included in summary tables.

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within a SOC and PT, even if the subject experienced more than one TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by highest CTCAE grade.

The number (percentage) of subjects with TEAEs, the number (percentage) of subjects with TEAEs leading to death, the number (percentage) of subjects with SAEs, and the number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT.

Also, the TEAEs will be summarized by relationship to study drug (Yes or No) and by CTCAE grade.

To assess the MTD and DLT, the number (percentage) of subjects with DLT events in each dose level will be summarized.

All AEs will be presented in subject data listings. In addition, listings of DLTs, SAEs, AEs leading to death and AEs leading to discontinuation from study drug will be provided.

5.6.3 Laboratory Values

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative laboratory parameters, the actual value and the change from baseline to each post baseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit. Qualitative parameters will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each post-baseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both non-missing baseline and relevant post-baseline results.

The frequency of laboratory abnormalities by maximum post-baseline CTCAE grade will be tabulated by cycle and overall for selected laboratory parameters to include at least hemoglobin, white blood cell count, ANC, lymphocytes, platelet count, AST, ALT, bilirubin,

creatinine, alkaline phosphatase, and electrolytes. Shift tables will also be produced for these parameters based on the baseline CTCAE grade and maximum CTCAE grade overall and by cycle.

Listings of laboratory results will be provided.

5.6.4 Vital Signs

Descriptive statistics for vital sign parameters (i.e. systolic and diastolic blood pressure, heart rate, respiratory rate, temperature, and weight) and changes from baseline will be summarized over time.

A listing of vital sign measurements will be provided.

5.6.5 Electrocardiograms

Descriptive statistics for ECG parameters (i.e. QTcF, QTcB, QT, QRS, heart rate and waveforms) and changes from baseline will be summarized over time. Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment.

In addition, the number (percentage) of subjects with at least 1 post baseline abnormal ECG result in QTcF during the treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTc interval prolongation:

- QTc interval > 450 ms
- QTc interval > 480 ms
- QTc interval > 500 ms

Change from baseline in QTc interval:

- QT_C interval increases from baseline > 30 ms
- QT_C interval increases from baseline > 60 ms

Listings of ECG results, ECG abnormalities and Holter recordings will be provided.

5.6.6 Other Safety Analyses

ECOG performance status will be summarized by visit. Shift tables will present changes from baseline in ECOG performance status to worst post-baseline visit.

Ophthalmologic examination will be summarized for left eye and right eye by visual acuity test and central corneal thickness as continuous variables, and by funduscopic examimation and slit-lamp examination in terms of normality (normal/abnormal) and clinically significant at each visit..

Listings of ECOG, MUGA/echocardiogram, and ophthalmologic examinations will be provided.

5.7 Other Analyses

Other analyses may be conducted as appropriate.

5.8 Exploratory Analyses

Exploratory analyses may be conducted as appropriate. More details will be given in a separate analysis plan if necessary.

6 INTERIM ANALYSES

There will be interim analyses to define the MTDs and/or RP2Ds prior to initiating the Expansion phase of the study. Other interim analyses may be performed to determine if a different dosing schedule (eg, BID) or frequency (eg, 2-weeks on/1-week off) may be preferable. Database locks are not required to perform these analyses. Safety and PK summaries may be provided periodically.

7 CHANGES IN THE PLANNED ANALYSES

SAP Amendment 0.1: DLT analysis set is defined for the evaluation of DLTs.

SAP amendment 0.2: Efficacy summaries will only include HCC subjects. Efficacy listings will include both HCC and ICC subjects who were enrolled prior to Protocol Amendment 8.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

The Baseline value will be defined as the last non-missing measurement prior to the first dose of the study drug. A Baseline value doesn't have to be collected in the Baseline period.

Descriptive statistics for continuous variables will be reported using number of non-missing measurements (n), mean, standard deviation (SD), median, the first quartile (Q1), the third quartile (Q3), minimum and maximum.

Descriptive statistics for categorical variables will be summarized as number (percentage) of subjects.

P-values will be presented with 3 decimal places or "< .001", rates will be presented with 1 decimal place or 0, CIs of rates will be reported as two-sided and calculated using Clopper-Pearson method, and time-to-event variables will be estimated using Kaplan-Meier method.

Further definitions and conventions for data handling will be presented in "Programming Specifications".

9 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

10 STATISTICAL SOFTWARE

All statistical analyses will be performed using SAS 9.4, or later.

11 MOCK TABLES, LISTINGS AND GRAPHS

The shells of TLGs in the study report will be provided in a separate document which will show the content and format of TLGs in detail. Additionally, the Global Study Report Template gives the standard numbering structure for Section 14 tables, figures, and for Appendix 16.2 listings.

12 REFERENCES

1. E.A. Eisenhauer, P. Therasse, J. Bogaerts, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1), European Journal of Cancer 45 (2009) 228-247.
2. Riccardo Lencioni, MD, and Josep M. Llovet, M.D. Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma, SEMINARS IN LIVER DISEASE/VOLUME 30, NUMBER 1 2010.