STATISTICAL ANALYSIS PLAN

A First-in-Human, Open Label, Phase I/II Study to Evaluate the Safety, Tolerability and Pharmacokinetics of HH2710 in Patients with Advanced Tumors

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Sponsor:	**Haihe Biopharma Co., Ltd**
Protocol Number:	**HH2710-G101**
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Signature Page

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Amendment History

Version	*Date*	*Author*	*Description*
0.7	2021-06-10	Bruce Hu	
1.0	2023-05-09	Yin Huang	1. Remove phase II exploratory objective and exploratory endpoint since it was not planned currently in protocol summary and section 3 2. Update the sample size 3. Remove the "and safety analysis set" in section 8.3 4. Update the definition of TEAE in section 8.8.1 5. Remove "24 hour…" from Urinalysis in section 8.8.3 6. Add pulse in section 8.8.4 and Table 3 7. Add "The HH2710 program…" in section 7 planned analyses
2.0	2023-05-16	Yin Huang	1. Update "all-treated" to "full analysis" in section 8.2, 8.7 2. Update "Incidence Rate ≥ 5%" to "Incidence Rate ≥ 10%" in section 8.8.1 3. Add censoring rule for TTR, TTP in section 10

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Table of Abbreviations

Term or Abbreviation	Description
ATD	Accelerated Titration Designs
CRF	Case Report Form
DLT	Dose Limiting Toxicity
DoR	duration of response
ECG	Electrocardiogram
EOI	Event Of Interest
E-R	Exposure-Response
IBG	Independent Biostatistics Group
IPD	Important Protocol Deviation
ORR	Objective Response Rate
OS	overall survival
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SMC	Safety Monitoring Committee
PD	Pharmacodynamic or pharmacodynamics
PFS	progression-free survival
PK	Pharmacokinetic or Pharmacokinetics
t1/2	plasma elimination half-life
TEAE	treatment-emergent adverse event
tmax	peak time
WHODRUG	World Health Organization Drug dictionary

1. Introduction

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for study HH2710 Protocol-EN-V2.0-final dated 21Mar2022 and CRF HH2710-G101-CRF 2022-05-11. The scope of this plan includes the interim analysis, the primary analysis and final analysis that are planned and will be executed by the Biostatistics and data sciences department of Tigermed Consulting Co., Ltd.. This SAP follows the ICH Good Clinical Practice guidance including ICH E9 and other related guidelines.

2. Objectives

2.1 Primary

Phase I:

To evaluate the safety and tolerability of HH2710 administered orally in patients with advanced tumors;

To identify the Maximum Tolerated Dose (MTD) and/or Recommended Phase II dose (RP2D).

Phase II:

To evaluate efficacy of HH2710 in patients with advanced tumors with MAPK signaling pathway genetic alterations, at the recommended phase 2 dose (RP2D).

2.2 Secondary

Phase I:

To characterize the pharmacokinetic profile of HH2710 and selected metabolites when administered orally in patients with advanced tumors.

Phase II:

To evaluate the efficacy of HH2710 in advanced tumor patients with MAPK signaling pathway genetic alterations.

To evaluate the safety of HH2710.

2.3 Exploratory

Phase I:

To assess the preliminary efficacy of HH2710.

To explore the changes of the pharmacodynamics (PD) markers of HH2710.

3. Study Overview

3.1 Study Design

This is an open-label, multicenter, first-in-human Phase I/II study which is composed of a Phase I dose escalation stage, phase I dose expansion stage and a Phase II dose extension stage.

3.1.1 Phase I: Dose escalation

The accelerated titration (ATD) incorporated with Bayesian optimal interval (BOIN) design will be used to assess the safety and tolerability, and furthermore, to help find the maximum tolerated dose (MTD), and/or to establish the recommended phase 2 dose (RP2D) combined with data from other sources.

A maximum sample size is 58 patients for the dose escalation (ATD + BOIN). The total number of patients will depend upon the number of dose escalations actually needed.

Accelerated titration part:

One patient per cohort will be assigned to receive HH2710. The first three patients will take HH2710 once daily(QD) in cycle 1 day 1 for the single dose PK testing, from the second day, HH2710 will be administered orally on a continuous twice daily (BID).

The proposed dose level in accelerated titration stage is 25mg, 50mg and 100mg twice daily (BID). It may be adjusted according to the available data.

BOIN design part:

When there is an adverse event of grade≥2 occurs, the dose escalation process will shift to a BOIN design, in which at least 3 patients per treatment cohort will be assigned (ATD + BOIN design details please see Protocol Section 6.2.3)

The provisional dose levels are planned different doses (25mg, 50mg, and 100mg BID, 300mg QD, 400mg (BID/QD), 600mg (BID/QD), and 800mg (BID/QD)) (See details in Protocol Section 6.2.2). Dosing frequency and dose level may be adjusted based on available pharmacokinetic and safety data.

When 800mg QD escalation cohort and 600mg QD expansion cohort suspended due to safety concerns, 300mg QD dose level has been added to explore before or while proceeding with further dose escalation. In addition, an alternative BID dosing regimen starting from 200mg is also reinitiated to better understand the safety, tolerability and PK of HH2710 in dose escalation stage.

After the escalation is completed, select the MTD based on the isotonic regression as specified in [1]. Specifically, select the MTD for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate. If there are ties, select the higher dose level when the isotonic estimate is lower than the target toxicity rate and select the lower dose level when the isotonic estimate is greater than or equal to the target toxicity rate.

Dose expansion stage:

An additional 15 patients per cohort may be included in order to further evaluate the safety, pharmacokinetics and anti-tumor activities among biomarker-selected patients. One or more dose levels may be expanded based on the available data. Patients enrolled could have different tumor types but must be confirmed with specific MAPK pathway genetic alteration (the same requirement as in phase II). The total number of patients will depend upon the number of dose expansions necessary.

3.1.2 Phase II Dose extension:

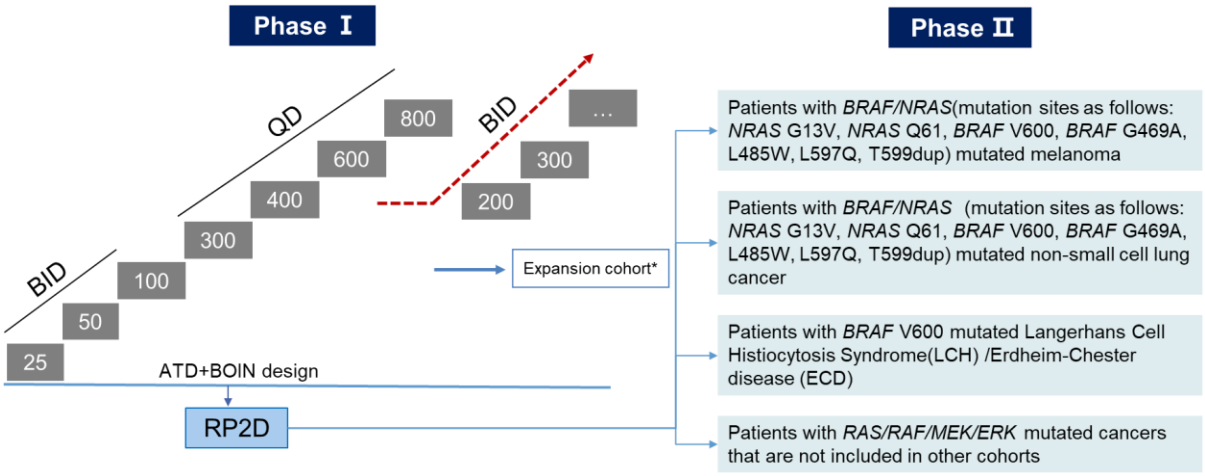
This is an open-label, multicenter, dose extension stage at RP2D to explore the response of patients with particular tumor types harboring MAPK genetic alteration. A maximum of 108 patients will be enrolled.

Patients enrolled will be divided into four cohorts once RP2D is defined and each of them focuses on specific tumors with specific genetic alteration, which NGS (next generation sequencing) will be used to detect, described as follows:

- **Cohort 1**: Patients with *BRAF/NRAS* (mutation sites as follows: *NRAS* G13V, *NRAS* Q61, *BRAF* V600, *BRAF* G469A, L485W, L597Q, T599dup) mutated melanoma;
- **Cohort 2**: Patients with *BRAF/NRAS* (mutation sites as follows: *NRAS* G13V, *NRAS* Q61, *BRAF* V600, *BRAF* G469A, L485W, L597Q, T599dup) mutated non-small cell lung cancer;
- **Cohort 3**: Patients with *BRAF* V600 mutated Langerhans Cell Histiocytosis Syndrome (LCH)/ Erdheim-Chester disease (ECD);
- **Cohort 4:** Patients with RAS/RAF/MEK/ERK mutated tumors that are not included in other cohorts.

The overall study design is described in the following study flow chart.

Figure 1 Study Flow Chart



3.2 Sample Size

Phase I Dose Escalation Stage:

The planned maximum sample size in Phase I dose escalation stage (ATD + BOIN) is 58 including up to 40 subjects for ATD + QD dose escalation cohorts (Part A) and up to 18 subjects for the additional BID dose escalation cohorts (Part B). During the ATD, one-patient per cohort is required for dose escalation. Once the BOIN design starts, cohorts of 3 patients will be used for dose escalation and the maximum number of patients for each dose level should not exceed 15 patients and 12 patients for BOIN design Part A and Part B, respectively.

Phase I Dose Expansion Stage:

We plan to recruit 15 evaluable patients per expansion cohort in the phase I stage of the study. The enrolled patients with different cancers must have confirmation of specific MAPK pathway genetic alteration. The primary focus of the dose expansion is to further assess the safety and pharmacokinetics of HH2710. Preliminary efficacy will also be examined but serve only for an exploratory purpose.

Phase II Dose Extension Stage:

In Phase II, patients will be recruited into the following 4 cohorts at the RP2D level:

Cohort 1: Patients with BRAF/NRAS (mutation sites as follows: NRAS G13V, NRAS Q61, BRAF V600, BRAF G469A, L485W, L597Q, T599dup) mutated melanoma;

Cohort 2: Patients with BRAF/NRAS (mutation sites as follows: NRAS G13V, NRAS Q61, BRAF V600, BRAF G469A, L485W, L597Q, T599dup) mutated non-small cell lung cancer;

Cohort 3: Patients with BRAF V600 mutated Langerhans Cell Histiocytosis Syndrome (LCH)/ Erdheim-Chester disease (ECD);

Cohort 4: Patients with RAS/RAF/MEK/ERK mutated tumors that are not included in other cohorts.

Cohort 1-2 will utilize the Bayesian Optimal design for phase II trials (BOP2). The null hypothesis of the response rate is 0.05, and the alternative hypothesis is 0.16. The design controls the type I error rate at 0.1 and yields the power of 0.8201 under H1.

Table 3-1 Optimized stopping boundaries for cohort 1 and cohort 2 in Phase II

# patients treated	Stop if # responses <=
23	1
36	3

Based on Table 3-1, we will perform an interim analysis for the first 23 patients. When at least 2 patients experience CR or PR or SD(SD≥6 weeks) events, the study will continue recruiting up to 13 more patients in the second stage. When the total number of patients reaches the maximum sample size of 36, we reject the null hypothesis and conclude that the treatment is promising if the number of responses (CR or PR or SD(SD≥6 weeks)) are greater than 3; otherwise we conclude that the treatment is not promising.

We plan to recruit a maximum of 9 patients in Cohort 3. Since there are currently no sufficient data available (due to the rarity of the disease), we are unable to calculate the sample size provided for an acceptable statistical justification. However, at this stage, we think that data from 9 patients is considered to be adequate to allow a preliminary investigation of the study objectives for this cohort.

Cohort 4 will include a maximum of 27 patients. Patients included in this cohort will have different cancer types led by different genetic mutations. Thus, it is difficult to calculate sample size for this cohort based on very accurate efficacy goals (e.g. minimum ORR for the alternative hypothesis). Therefore, this cohort serves for an exploratory

purpose and the number of patients has been based on the desire to obtain adequate data whilst exposing as few patients as possible to the study procedures.

4. Study Endpoints and Covariates

4.1 Study Endpoints

Primary Endpoint

Phase I:

Safety and Tolerability: The incidence, type, and severity of adverse events (AEs) assessed according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) V5.0, physical examination findings, clinical laboratory values, vital signs and Electrocardiograms (ECGs)

The MTD, if any, and RP2D for HH2710 will be determined based on safety, tolerability, PK, preliminary efficacy, and other available data.

Phase II:

Tumor objective response rate (ORR) based on RECIST version 1.1.

Secondary Endpoints

Phase I:

Peak plasma concentration (Cmax), peak time (tmax), area under the plasma concentration-time curve from time 0 to time (t) (AUC0-t), plasma elimination half-life (t1/2), plasma clearance rate constant (λz), apparent clearance (CL/F), apparent volume of distribution (Vz/F).

Phase II:

the duration of response (DoR), progression-free survival (PFS), disease control rate (DCR), time to response (TTR), time to progression (TTP), and 1-year overall survival (OS) rate.

The incidence, type, and severity of adverse events (AEs) assessed according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) V5.0, physical examination findings, clinical laboratory values, vital signs and Electrocardiograms (ECGs).

Exploratory Endpoints

Phase I:

ORR, DoR, DCR, PFS and TTR.

Changes in PD markers of HH2710 efficacy including phosphorylation of RSK (pRSK) and total RSK.

4.2 Planned Covariates

No covariates will be accounted for in Phase I (dose-finding and dose expansion). In Phase II (cohort extension), analyses will be analyzed by subgroups of tumor types and/or genetic mutations in order to evaluate the preliminary efficacy.

5. Hypotheses and/or Estimations

Phase I:

No hypothesis for this phase since the primary endpoint are safety profile, MTD and RP2D.

Phase II for Cohort 1 and Cohort 2:

In Cohort 1 and Cohort2, the null hypothesis of the response rate is 0.02, and the alternative hypothesis is 0.16. The design controls the type I error rate at 0.1 and yields the power of 0.8201 under H1.

We will perform an interim analysis for the first 23 patients. When at least 2 patients experience CR or PR or SD (SD≥6 weeks) events, the study will continue recruiting up to 13 more patients in the second stage. When the total number of patients reaches the maximum sample size of 36, we reject the null hypothesis and conclude that the treatment is promising if the number of responses (CR or PR or SD(SD≥6 weeks)) are greater than 3; otherwise we conclude that the treatment is not promising.

No hypothesis for cohort 3 and cohort 4 of phase II since both cohorts are served as preliminary investigation or exploratory purpose.

6. Analysis Sets

6.1 Full Analysis Set (FAS)

The Full Analysis Set includes all patients who have received at least one dose of study medication. This set will be used for efficacy analysis.

6.2 Safety Analysis Set (SAS)

The Safety Analysis Set (SAS) includes all patients who receive at least one dose of study medication. This set will be used for safety analysis.

6.3 Pharmacokinetic Analysis Set (PKS)

The pharmacokinetic analysis set (PKS) consists of all patients who receive at least 1 dose of study drug and have sufficient, valid PK samples to estimate key parameters for at least 1 of the days of sampling.

6.4 Pharmacodynamics analysis set (PDS)

The pharmacodynamics analysis set (PDS) consists of all patients set who receive at least 1 dose of study drug and have sufficient, valid PD samples to estimate key parameters for at least 1 of the days of sampling.

6.5 Subgroup Analyses

Subgroup analyses will be performed to explore the consistency of the treatment effect when the sample sizes allows for meaningful interpretation. The following subgroup may be used to examine efficacy:

Sex (female vs. male)

Age (<65 vs ≥65)

Race

Tumor type

Genetic mutation

7. Planned Analyses

The HH2710 program is stopped and this study is terminated ahead of time with a limited number of subjects treated than planned. As the result, many planned analyses will have insufficient data to render the planned analyses feasibly, meaningful or interpretable. Therefore, many of the planned analyses described in this SAP may not be conducted, depending on data availability or maturity, and purpose of the analysis.

7.1 Interim Analysis and Early Stopping Guidelines

There are three planned interim analyses during the study. One is performed for the determination of RP2D when Phase I completes. The other two are conducted for futility evaluation for the first 23 patients in each of cohort 1 and cohort 2 when they have recruited and completed the assessments in Phase II. Additional or administrative interim analyses may be conducted as necessary by the sponsor for safety/efficacy monitoring while the study is ongoing.

A Safety Monitoring Committee (SMC) will be used to evaluate safety as well as preliminary efficacy during the study. In Phase I, safety data will be reviewed by the committee after a minimum of 3 patients have been enrolled into each dose level and received treatment. Once the dose escalation stage completes, the committee will review safety data as well as data from other sources (e.g. efficacy, PK/PD) to determine the RP2D for Phase II.

In Phase II, the efficacy review will be conducted for cohort 1 and cohort 2 by the committee when each cohort has recruited and completed the assessments for the first 23 patients. For safety, the committee will review the data when every 6 or 12 patients have recruited and received treatments in all cohorts. Following the data review, the committee will decide as to whether the cohort may continue, whether amendment(s) to the protocol should be implemented, or whether the study should be stopped.

Members of the committee will be internal and external to the sponsor, which can include employees of the Sponsor and study investigators.

7.2 Primary Analysis

The primary analyses in Phase I focuses on safety endpoints for HH2710 administered alone in patients with the advanced and/or refractory tumors. The RP2D will be determined based upon the observed DLTs and information from other sources (e.g pharmacokinetics) as described in the protocol.

In Phase II, the primary analyses will investigate the preliminary efficacy of the ORR and other endpoints including DoR, DCR, TTR, TTP, PFS and 1-year OS rate, and by tumor

type and by genetic mutation if warranted. The RP2D might be adjusted based on the phase II data.

8. Statistical Methods of Analysis

8.1 General Principles

TFLs will be displayed by treatment groups, which are the dose levels for phase I study and cohort levels for phase II study. If necessary, the same dose level may be combined and analyzed across phase I and II studies.

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, standard deviation (SD), median, minimum value (min), and maximum value (max). The number of subjects (n) will represent the number with non-missing data on the continuous variable under consideration. The precision of the measurement for each continuous variable will be used to determine the number of decimal places to present in tables, figures, and derived listings. Unless otherwise specified, min and max values will be reported with the same decimal as the units of measure; the mean, median will be reported to 1 greater decimal place, the SD will be reported to 2 greater decimal place, all of them will not be greater than 4 decimal place. Any values that require transformation to standard units (metric or International System [SI]) will be converted with the appropriate corresponding precision.

Categorical variables will be summarized using counts and percentages (95% confidence interval of percentage if necessary). Percentages will be presented to 1 decimal place unless otherwise specified.

Treatment group indicates the dose level of HH2710 (such as 25 mg BID) and total (if more than one dose level) for phase I and cohort in Phase II.

Baseline value, unless otherwise specified, will be defined as the last non-missing measurement (scheduled or unscheduled) collected prior to the initial administration of study drug. For example, if an assessment was performed at screening and Day 1 prior to initial dosing of study drug, then Baseline is the Day 1 measurement if the Day 1 value is not missing; if the Day 1 value is missing, then the screening value is Baseline, and so forth.

Change (absolute change) from baseline will be calculated as post-baseline value - baseline value.

Unscheduled visits: Subject data for safety or efficacy assessments (such as unscheduled labs) will be incorporated into the cycle windows appropriate to the scheduled visits. For summary by visit tables and figures, only scheduled visits will be included in the analysis.

Incomplete/missing data: Unless otherwise specified, for efficacy and safety analysis, no imputation will be used. If a partial dates need to be imputed for computational purposes, conservative conventions will be used as far as possible.

All statistical analyses will be performed using SAS 9.4 (SAS Institute, Cary, North Carolina, USA).

8.2 Major Protocol Deviations

Major Protocol Deviations (MPDs) categories are defined by the study team before the first subject's visit and updated during the MPD reviews throughout the study prior to database lock. These definitions of MPD categories, sub-category codes and descriptions will be used during the course of the study.

For phase I and phase II, a summary of the number and percentage of subjects with a major protocol deviation by type of deviation will be provided using the full analysis set. Individual subject listings of protocol deviations will be provided.

8.3 Demographic and Baseline Characteristics

For phase I and phase II, demographic (ie, age, age group [<65, ≥65], sex and race) and baseline disease characteristics will be summarized using descriptive statistics for the full analysis set. Though different names, these two sets have the same definition and subjects.

The baseline characteristics to be summarized include:

Weight (kg)

Height (cm)

Body mass Index (kg/m**2)

ECOG performance status

Tumor Histology and pathology type

Tumor Stage

Genetic mutation type

Number of metastases at baseline

Location of metastases at baseline

Subject received any prior systemic anti-tumor therapy: Number of prior lines or regimens of therapy, Best overall response

Received radiotherapy for Tumor

Received surgery for Tumor

8.4 Medical history

For phase I and phase II, medical history will be coded according to MedDRA (version 23.0 or higher).

The number and percentage of subjects experiencing a medical history will be summarized by the MedDRA System Organ Class and Preferred Term. Subjects reporting more than one condition/diagnosis within a System Organ Class will be counted only once for that System Organ Class.

For phase I, medical history will be based on the safety analysis set; and for phase II, medical history summaries will be based on the full analysis set.

8.5 Prior and Concomitant Medications/Procedures

For phase I, medication/procedure summaries will be based on the safety analysis set; and for phase II, medication/procedure summaries will be based on the full analysis set. All medications will be coded using WHOdrug global B3, 201903 or higher.

Medications used in the study will be classified in two parts:

1. Prior medication: medication that ended before the first dose of study drug, regardless of when dosing of the medication started.

2. Concomitant medication: medications ended after or on the first dose of study drug or medication with missing stop date, regardless of when dosing of the medication started. The following medication categories will also be summarized by ATC2 and preferred term.

1. Prior Anti-tumor Medication

2. Prior Non-Anti-tumor Medication

3. Post-Treatment Anti-tumor Medication

Missing or partial dates will be imputed for medication. Algorithm for missing or partial start date is:

Missing day: first day of the month is imputed;

Missing month: January is imputed;

Missing year: not imputed.

Algorithm for missing or partial end date is:

Missing day: last day of the month is imputed;

Missing month: December is imputed (31 December if day is also missing);

Missing year: not imputed.

Missing data algorithms will be reviewed to ensure the algorithm works. For example, end date will not be before the start date after the imputation.

8.6 Study Drug Exposure

Total number of cycles is defined as the maximum number of treatment cycles that a subject receives. Total cumulative dose (mg) is the sum of the actual doses that the subject receives across cycles. Total planned dose (mg) is the sum of the planned doses.

Actual exposed weeks = (Last dosing day – first dosing day +1)/7;

Total planned Dose (mg) = Planned dose* (Last dosing day – first dosing day +1);

Planned exposed weeks = 21*number of cycles/7;

Relative dose intensity is defined as follows:

Relative dose intensity = (total cumulative dose/actual exposed weeks)/ (Total planned /planned exposed weeks) *100%

The total number of cycles, total cumulative dose (mg), total planned dose (mg), relative dose intensity and categorized as < 80%, 80% - 120%, >120% will be summarized for each component of the dosing regimen for phase I and phase II.

A dose reduction, dose interruption, dose withdrawn and their reasons will be summarized by treatment group for phase I and phase II.

The study drug exposure will be summarized based on the safety analysis set.

8.7 Efficacy Analyses

The efficacy analysis will be based on full analysis set.

8.7.1.1 Best Overall Response

Best Overall Response (BOR) is defined as the best overall response recorded from the start of treatment until disease progression or initiation of alternative therapy or end of study. A summary of subjects achieving a best overall response in a given category (CR, PR, SD, PD, NE, and Missing) will be provided.

In phase II, BOR will be summarized by investigator.

8.7.1.2 Analysis of Primary Efficacy Endpoint

Objective response rate (ORR) will be calculated and summarized by treatment group, along with the 95% of confidence interval calculated by the Clopper-Pearson method.

8.7.1.3 Analysis of Secondary Efficacy Endpoint

If the sample size or the number of responders allow for meaningful interpretation, Kaplan-Meier method will be used to analyze the duration of response (DoR), the progression-free survival (PFS), time to response (TTR) and time to progression (TTP) for each tumor type, genetic mutation and other factors required by sponsor. If possible, a 95% of confidence interval band should be provided for each estimate.

For all the time-to-event endpoints (DoR, PFS, TTR and TTP), the survival curve will be estimated by the Kaplan-Meier estimate, and the first percentile, the median survival, the third percentile and their 95% CI will be provided.

For Time to Response (TTR) and Duration of Response (DoR), only subjects with BOR is CR/PR during the study treatment will be calculated.

DCR and 1-year overall survival (OS) rate will be estimated and analyzed by the same methods as those in ORR.

The listing of all the time-to-event endpoints will be provided.

See Appendix , B, C and E for detailed rule of Censor date for PFS and other time-to-event endpoints.

8.7.1.4 Analysis of Exploratory Efficacy Endpoint

If there exsits exploratory efficacy endpoints analysis, it will be included in separate analysis documents.

8.8 Safety Analyses

8.8.1.1 Adverse Events

AEs will be coded according to MedDRA (version 23 or higher). The severity of adverse events will be judged in accordance with NCI CTCAE 5.0. The number and percentage of subjects experiencing an AE will be summarized by System Organ Class and Preferred Term. AEs will be classified as pretreatment or treatment-emergent.

Treatment-emergent AEs (TEAEs) are defined as AEs that were reported or worsened on or after the start of study drug dosing and up to the safety follow-up.

For any SAE that occurs after the safety follow-up and was related to study drug, it will be considered to a TEAE.

Missing or partial dates will be imputed for AE. Algorithm for missing or partial start date is:

Missing day: if month/year equal to month and year of first dose date, then impute to date of the first dose; else impute to first day of the month.

Missing month: if year equal to year of first dose date, then impute to date of the first dose; else impute to Jan01 of the year.

Missing year: impute to first dose date if first dose date<AE end date, else impute to ICF date.

Algorithm for missing or partial end date is:

Missing day: last day of the month is imputed;

Missing month: impute to 31 December

Missing year: not imputed.

Missing data algorithms will be reviewed to ensure the algorithm works. For example, end date will not be before the start date after the imputation.

Only TEAEs will be summarized in tables.

The overall TEAE summary will include the following:

All TEAEs (regardless of relationship to study drug)

Grade ≥ 3 TEAEs

Treatment related TEAEs

Treatment related Grade ≥ 3 TEAEs

Serious TEAEs

Treatment related serious TEAEs

TEAEs leading to dose reduced

TEAEs leading to dose interrupted

TEAEs leading to study drug withdrawn

TEAEs leading to Death

Treatment related TEAEs leading to dose reduced

Treatment related TEAEs leading to dose interrupted

Treatment related TEAEs leading to study drug withdrawn

Treatment related TEAEs leading to Death

The TEAEs, TEAEs related to study drug, TEAEs leading to study drug withdrawn, Treatment related TEAEs leading to study drug withdrawn, Grade ≥ 3 TEAE, Treatment related Grade≥ 3 TEAEs, TEAE by worst CTCAE Grade, Treatment related TEAEs by worst CTCAE Grade, Serious TEAEs, Treatment related serious TEAEs, TEAE leading to dose reduced, Treatment related TEAEs leading to dose reduced, TEAE leading to dose interrupted, Treatment related TEAEs leading to dose interrupted, TEAEs leading to death, Treatment related TEAEs leading to death, TEAEs with an Incidence Rate ≥ 10% and Treatment related TEAEs with an Incidence Rate ≥ 10% summary will be presented by MedDRA system organ class and preferred term using frequency counts and percentages in descending order of frequency separately.

The number and percentage of subjects with death and the primary cause will summarized and listed for subjects in the Safety Analysis Set.

All AEs, Serious AEs and AEs leading to Death will be listed in an individual subject data listing.

8.8.1.2 Dose Limiting Toxicity (DLT)

The listing for dose limiting toxicity will be provided.

8.8.1.3 Laboratory Test Results

Hematology, blood biochemistry and urinalysis will be conducted in the screening period, treatment period and follow-up period according to study process, and examination frequency will be increased according to clinical indications.

Specific evaluation items include:

● Hematological test: red blood cell count, hemoglobin, hematocrit, reticulocyte count, platelet count and absolute leukocyte differential count (neutrophil, lymphocyte, eosinophils, monocyte, basophils);

● Blood biochemical test: Total protein, albumin, total bilirubin, direct bilirubin, ALT, AST, Gamma-glutamyl transferase, Creatine phosphokinase, Alkaline phosphatase, Lactate dehydrogenase, Blood urea nitrogen, Urea, Creatinine, Uric acid, Blood glucose, Chloride, Sodium, Potassium, Calcium, Phosphate, Amylase, Lipase and CKMB.

● Urinalysis: specific gravity, urine glucose, protein, white blood cell (qualitative) and red blood cell (qualitative).;

● Coagulation function test: prothrombin time, activated partial thromboplastin time and international normalized ratio;

● Pregnancy test (applicable to non-menopausal women);

An observed value and change from baseline in laboratory by visit descriptive table will be provided by treatment group.

For serum chemistry, hematology and urinalysis data, a shift table between the worst post-baseline clinical significance and baseline clinical significance will be provided by treatment group.

For liver safety, summaries of the liver chemistry elevations will be presented in the table according to Table .

Table 1 Liver Chemistry Elevations

Test	Categary
ALT or AST increased	>= 3 * ULN
	>= 5 * ULN
	>= 10 * ULN
	>= 20 * ULN
ALT increased	>= 3 * ULN
	>= 5 * ULN
	>= 10 * ULN
	>= 20 * ULN
AST increased	>= 3 * ULN
	>= 5 * ULN
	>= 10 * ULN
	>= 20 * ULN
TBIL increased	>= 1.5 * ULN
	>= 2 * ULN
ALP increased	>= 1.5 * ULN

In additional, ALT or AST >=3 * ULN and TBIL>= 2 * ULN and ALP < 2*ULN, ALT or AST >=3 * ULN and TBIL>= 2 * ULN, ALT and AST >=3 * ULN and TBIL>= 1.5 * ULN will also presented in this table.

The listing for abnormal findings in laboratory data will be provided.

8.8.1.4 Vital Signs

An observed value and change from baseline in vital sign by visit descriptive table will be provided by dose group.

The number and percentage of subjects with abnormal changes (defined in Appendix D) in systolic blood pressure, diastolic blood pressure, pulse/heart rate, respiratory rate and

temperature will summarized for subjects in the safety analysis set. A shift table between the worst post-baseline notable abnormalities and baseline notable abnormalities will be provided by treatment group.

A vital sign data listing will be provided.

8.8.1.5 Physical Examination

General physical examination: including General appearance, Skin, Neck, Eyes, Ears, Nose, Throat, Lungs, Heart, Abdomen, Back, Lymph nodes, Extremities, Vascular, Neurological and other.
For each general physical examination, a shift table between the worst post-baseline clinical significance and baseline clinical significance will be provided by dose group.

The listing for abnormal PE findings will be provided. The listing for abnormal ophthalmological examinations will be provided in another listing.

8.8.1.6 Analysis of 12-lead ECG

12-lead ECG: Including heart rate, PR interval, QRS interval, QT interval, QTcF interval and diagnosis.
An observed value and change from baseline in ECG by visit descriptive table will be provided by dose group.
A shift in Clinical Evaluation table from baseline to worst post-baseline value will be presented.

A 12-lead ECG listing will be provided for all subjects in the Safety analysis Set.

8.8.1.7 Analysis of ECOG

A shift table between the worst post-baseline ECOG Performance Status and baseline ECOG Performance Status will be provided by dose group.

8.9 Pharmacokinetic Analysis

Pharmacokinetic parameters will be determined with non-compartmental analysis method with PK Analysis Set.

Samples for PK analysis of HH2710 and selected metabolites will be obtained from all Phase I/II patients during their first cycle of treatment (Cycle 1). PK samples will also be obtained from additional patients in Phase II depending on the outcome of initial PK analysis.

Below is the list of various PK parameters that will be calculated after Dose 1 (Day 1) and at Steady State (Day 22).

Table 2 PK parameters Description

PK Parameter (plasma)	Description
C_{max}	Peak plasma concentration determined manually by visual inspection of plasma concentration vs. time figures on the untransformed (linear) scale of measurement

t_{max}	Time to reach the peak plasma concentration determined manually by visual inspection of plasma concentration vs. time figures on the untransformed (linear) scale of measurement
AUC_{0-12}	Area under the plasma concentration-time curve from 0 to 12 hours postdose, calculated by linear/log trapezoidal method
AUC_{0-last}	Area under the plasma concentration-time curve from time 0 to time of last observation after dosing calculated by linear/log trapezoidal method
Lambda_z (λ_z)	Terminal phase rate constant, determined by linear regression of at least 3 points on the terminal phase of the log-linear plasma concentration-time curve. The correlation coefficient (r2) for the goodness of the fit of the regression line through the data points has to be 0.85 or higher for the value to be considered reliable. If the WinNonlin data points are not on the linear portion of the terminal slope, the data points will be selected manually prior to calculation of Lambda_z
$t_{1/2}$	Terminal half-life, defined as 0.693 (ln2) divided by Lambda z
CL/F	The total body clearance of drug from the plasma (volume x time-1)
V_z/F	The apparent volume of distribution during terminal phase (associated with λ_z)(volume)

Descriptive statistics [n, arithmetic mean, standard deviation, coefficient of variation (CV), median, minimum, maximum, geometric mean, geometric standard deviation geometric CV] will be used to summarize PK parameters by treatment. For $t_{1/2}$ and t_{max}, regular descriptive statistics and 95% confidence intervals about the arithmetic mean will be calculated, for each dose.

A listing of blood PK concentrations and parameters will be provided.

8.10 Pharmacodynamics Analysis

Pending for medical confirmation.

8.11 Exploratory Biomarker Endpoints Analysis

If there exists exploratory biomarker endpoints analysis, it will be included in separate analysis documents.

8.12 Changes From Protocol-specified Analyses

1 year survival rate instead of 1 year overall survival time will be summarized in SAP.

Percentages will be presented to 1 decimal place unless otherwise specified in SAP.

For baseline characteristics, SAP will present Previous Anti-tumor Therapy Type: medication, surgery and radiotherapy instead of previous chemotherapy and previous immunotherapy.

Updated Safety Set to Safety Analysis Set and All-Treated Set to Full analysis set and keep the algorithm the same as protocol.

Members of the review committee will be internal and external to the sponsor.

Remove “Final Analysis section”. By default, primary analyses are final analysis.

Remove “Percentages will be rounded to the nearest whole number (zeroes are not displayed) with values of “< 1%” and “> 99%” shown as necessary for values falling near the boundaries” from general principles section.

9. Literature Citations / References

Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol. 2007*;25:579-586.

Clopper CJ and Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial, *Biometrika*. 1934; 26(4):404-413.

O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics. 1979;35:549-556.

Liu S, et al., Bayesian Optimal Interval Designs for Phase I/II Clinical Trials. Journal of the Royal Statistical Society. 2015, 64(3): 507-523

10. Appendices

10.1 Appendix A Censor rule for PFS, DoR

No.	Situation	Events or Censor	Analysis date*
1	No baseline assessment	Censor	First dose date
2	No post-baseline assessment, no Death	Censor	First dose date
3	PD during the study (except #5, #7)	Events (PD)	PD date
4	Any kind of Death (except #5, #7)	Events (Death)	Death date
5	PD or Death after missed two consecutive assessment	Censor	Last assessment date before the missed two consecutive assessment
6	Have at leatest one post-baseline assessment, no PD, no Death	Censor	Last assessment date
7	Initiating alternative anti-cancer therapy	Censor	Last assessment date before initiating alternative anti-cancer therapy

* If there are multiple assessment date on one tumor assessment, choose the earliest assessment date when overall response is PD, and choose the latest assessment date when overall response is CR/PR/SD.

10.2 Appendix B Censor rule for TTR

No.	Situation	Events or Censor	Analysis date*
1	CR, PR before PD, Death, alternative anti-cancer therapy or missed two consecutive assessment.	Events	First CR, PR date
2	No CR/PR/ alternative anti-cancer therapy/ missed two consecutive assessment/PD/Death	Censor	Last assessment date
3	No CR/PR, have PD or Death	Censor	First date of PD or Death
4	No CR/PR before alternative anti-cancer therapy	Censor	Last assessment date before initiating alternative anti-cancer therapy
5	No CR/PR before missed two consecutive assessment	Censor	Last assessment date before the missed two consecutive assessment

* If there are multiple assessment date on one tumor assessment, choose the earliest assessment date when overall response is PD, and choose the latest assessment date when overall response is CR/PR/SD.

10.3 Appendix C Censor rule for TTP

No.	Situation	Events or Censor	Analysis date*
1	No baseline assessment	Censor	First dose date
2	No post-baseline assessment, no Death	Censor	First dose date
3	PD during the study (except #5, #7)	Events (PD)	PD date
4	Any kind of Death (except #5, #7)	Censor	Death date
5	PD or Death after missed two consecutive assessment	Censor	Last assessment date before the missed two consecutive assessment
6	Have at leatest one post-baseline assessment, no PD, no Death	Censor	Last assessment date
7	Initiating alternative anti-cancer therapy	Censor	Last assessment date before initiating alternative anti-cancer therapy

* If there are multiple assessment date on one tumor assessment, choose the earliest assessment date when overall response is PD, and choose the latest assessment date when overall response is CR/PR/SD.

10.4 Appendix D. Laboratory Grading and Notable Vital Sign Values

Laboratory Values

Safety laboratory values below a distinct limit (eg. detection limit, documented as "< [limit]") will be substituted by half of the limit and values above a distinct limit (documented as "> [limit]") will be substituted by the limit itself for all analyses.

A Grade (based on CTC AE version 5.0 [v5.00: November 27, 2017]) will be assigned to each laboratory result as detailed in Table 2. Depending on the toxicity definition, the same result may be assigned to two grading for deviations towards higher or lower values. In case no lower limit of normal is provided for the absolute lymphocyte, neutrophils or leukocyte counts it will not be differentiated between grade 1 and grade 0 results for these parameters. Values not meeting any of the criteria will be assigned a grade 0.

Table 1. Grading of Select Laboratory Parameters

Laboratory Parameter [Unit]	Grade 1	Grade 2	Grade 3	Grade 4
Lymphocytes [G/L]	0.8 - < LLN	0.5 - < 0.8	0.2 - < 0.5	< 0.2
Neutrophils [G/L]	1.5 - < LLN	1.0 - < 1.5	0.5 - < 1.0	< 0.5
Leukocytes [G/L]	3.0 - < LLN	2.0 - < 3.0	1.0 - < 2.0	< 1.0
Platelets [G/L]	75 - < LLN	50 - < 75	25 - < 50	< 25
Hemoglobin [g/L]*	100 - < LLN	80 - < 100	< 80	not defined
Albumin [g/L]	30 - < LLN	20 - < 30	< 20	not defined
AST*	> ULN – 3*ULN	> 3*ULN – 5*ULN	> 5*ULN – 20*ULN	> 20*ULN
ALT *	> ULN – 3*ULN	> 3*ULN – 5*ULN	> 5*ULN – 20*ULN	> 20*ULN
GGT	> ULN – 2.5*ULN	>2.5*ULN – 5*ULN	> 5*ULN – 20*ULN	> 20*ULN
Bilirubin	> ULN – 1.5*ULN	>1.5*ULN – 3*ULN	> 3*ULN – 10*ULN	> 10*ULN
Fibrinogen^	%change of BL <25% decrease or 0.75*LLN - < LLN	25%- <50% decrease of BL or < 75*LLN – 0.5*LLN	50% - <75% decrease of BL or < 0.5* LLN – 0.25*LLN	>= 75% decrease of BL or < 50mg/dL or < 0.25*LLN
Calcium [mmol/L]*	2.0 - < LLN	1.75 - < 2.0	1.5 - < 1.75	< 1.5
Potassium [mmol/L]*	not defined	3.0 - < LLN	2.5 - < 3.0	< 2.5
Lipase	> ULN – 1.5*ULN	> 1.5*ULN – 2.0*ULN	> 2.0*ULN – 5.0*ULN	> 5.0*ULN
Amylase	> ULN – 1.5*ULN	> 1.5*ULN – 2.0*ULN	> 2.0*ULN – 5.0*ULN	> 5.0*ULN

BL: baseline value, LLN: Lower limit of normal, ULN: Upper limit of normal

***: Clinical criteria from CTC AE 5.0 grading were not considered in order to assign grades**

^: In case of conflicting criteria the higher grade will be assigned, % change only used when baseline is <LLN

Vital Signs

Notable values for vital signs are defined according to the following table:

Table 2. Notable Abnormalities of Vital Signs

Vital Sign	Notable Abnormalities
Pulse rate/Heart rate (bpm)	>100 <60
Respiratory Rate (bpm)	>24

Vital Sign		Notable Abnormalities
		<12
Blood pressure (mmHg)	Systolic	160
		90
	Diastolic	105
		50
Weight (kg)		change from baseline >10% (in both directions)
Body temperature (°C)		> 39

10.5 Appendix E Definitions

ORR

Objective response rate is defined as the percentage of patients who have at least one confirmed response of CR or PR defined by RECIST 1.1 prior to any evidence of progression.

DoR

Duration of response will be defined as the time from the date of first documented response, (that is subsequently confirmed) until date of documented progression or death in the absence of disease progression, the end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR.

DCR

Disease control rate is defined as the proportion of subjects with advanced tumors among whom achieve a best overall response CR/PR/SD after treatment with HH2710.

PFS

PFS is defined as the time from date of first dosing until the date of objective disease progression as defined by RECIST 1.1 or death (by any cause in the absence of progression) regardless of whether the subject withdraws from HH2710 treatment or receives another anticancer therapy prior to progression.

Overall Survival

Overall survival is defined as the interval between the date of first dose and the date of patient death due to any cause. Patients who have not died at the time of the statistical analysis will be censored at the time they were last known to be alive.

TTR

TTR is defined as the duration from the first day of study treatment until the first documented response (CR or PR).

TTP

TTP is defined as the duration from the first day of study treatment until the first documented progression (PD).

Baseline
For data analyses, baseline will be defined as the value measured on day 1 of the start of HH2710. The protocol specifies that all study procedures on day 1 should be completed before the initiation of HH2710 which will be the assumption in the analysis unless the time of the assessment is recorded. If a day 1 value is not available, the latest value before the day of the start of HH2710 may be used.

End of Treatment Date
The end of HH2710 therapy date is the date the decision was made to end investigational product reported on the end of investigational product administration CRF.

End of Study
For a subject: a subject ends the study when they die, consent is withdrawn, or they are lost to follow-up. The end of study date will be captured on the end of study CRF.

For the study as a whole: the end of study as a whole is defined as a minimum of 80% of patients in the Phase II stage have died, have been lost to follow-up, or have been followed for survival for minimum 12 months after the first dose of study treatment.

Treatment-emergent Adverse Event
TEAE are defined as AEs that were reported or worsened on or after the start of study drug dosing and up to the safety follow-up.