ClinicalTrials.gov ID: NCT04198818

Clinical Development

HH2710

Clinical Trial Protocol HH2710-G101

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

File type	Oncology Clinical Trial Protocol
IND Number	144684
Version No.	V2.0
Development phase	Phase I/II
File status	Final
Release date	21-Mar.-2022
Sponsor	Haihe Biopharma Co., Ltd. No. 865 ZuChongzhi Road, Pudong New Area, Shanghai, China (201203)

Signature Page of the Sponsor

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

Protocol Number: **HH2710-G101**

Version Date: **21-Mar-2022**

Version Number: **V2.0**

I have read the study protocol including all appendices and current Investigator's Brochure (IB) and agree with all the details of completing the study and relevant confidentiality provisions contained in the protocol. I have fully understood the study protocol, will comply with the Declaration of Helsinki, International Council for Harmonization (ICH) E6 GCP (including filing of essential documents), regulations of the National Medical Products Administration and relevant regulations, and conscientiously perform my duties.

Sponsor's name: Haihe Biopharma Co., Ltd.

Sponsor address: No. 865, ZuChongzhi Road, Pudong New Area, Shanghai, China. 201203

Approved by:

Signature:____ **Date:___**

Signature Page of the Investigator

Protocol Title: 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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I have read the study protocol including all appendices and current Investigator's Brochure (IB) and agree to carry out the study in compliance with it. I will provide data of the study protocol and corresponding guidance and assistance to all personnel taking part in the study under my management to ensure they are fully informed of matters associated with the drug and the study.

I will comply with the Declaration of Helsinki, International Council for Harmonization (ICH) E6 GCP (including filing of essential documents), and applicable requirements of the National Medical Products Administration, local health and regulatory authorities and Ethics Committee (EC) to carry out the trial. By accepting this document, I agree that I shall not publish or disclose any unpublished information contained in this document without the prior written permission of the sponsor.

Principal Investigator's Name:_____

Clinical Study Site:_____

Signature:_____ Date:_____

Version History

Version 1.2, [27-AUG-2019]
Initial creation

Version 1.3, [20-JAN-2021]
1) Company name has been updated. 2) In the protocol summary and the text, from the fourth dose group in the dose escalation phase, administration changed from "twice a day (BID)" to "once a day (QD)". 3) In the protocol summary and the Section 5.2, The content of QT interval has been updated in the Inclusion Criteria 10. 4) In the protocol summary and the Section 5.2, The content of hemoglobin has been updated in the Inclusion Criteria 11. 5) Two exclusionary criteria, exclusionary criteria 2 and exclusionary criteria 3, are added to the protocol summary and Section 5.3. 6) In the protocol summary and the Section 5.3, The content of Anticancer treatments has been updated in the Exclusion Criteria 9. 7) In the protocol summary and the Section 5.3, The content of Antibiotic treatment required has been updated to systemic medication required in the Exclusion Criteria 13. 8) In the protocol summary and the Section 5.3, The content of Contraception has been updated in the Exclusion Criteria 21. 9) “Grade 2 toxicity” has been clarified to “grade 2 adverse event” in Section 6.2.3. 10) The content description of neutropenia in Table 6-8 has been updated. 11) The prohibition of combination therapy in Section 6.4.3 has been updated. 12) In Table 7-1, the audit of the inclusion/exclusion criteria and safety follow-up have been updated.The footnote description in Table 7-1 has been updated. 13) The description of the replacement policy in Section 7.1.4.3 has been updated. 14) The content of survival follow-up in Section 7.1.5.3 has been updated.

15) The Laboratory assessment and 12-lead ECG in Section 7.2.1 have been updated.

16) The content of blood sample collection in Section 7.2.2.1 has been updated.

17) The content of PD in Section 7.2.3 has been updated.

18) The content of imaging assessment in Section 7.2.5 has been updated.

19) The content of Adverse events in Section 8.1 have been updated.

20) The description in the report in Section 8.2.2 has been updated.

21) "Drug safety department" in Section 8 has been updated to "Pharmacovigilance Department"

22) The description of biomarkers in the protocol summary, sections 1.2.1.3, section 4.1, section 5.1, section 7.1.1, section 7.2.4, and Tables 7-4 has been updated.

23) The content of the PK parameter description in Table 10-2 has been updated.

24) In the appendix 6, The QTc Fridericia formula has been updated.

Version 2.0, [21-Mar-2022]

1) To update the company address.

2) To update study design (dose level, frequency and patient number) based on emerging clinical data including safety, efficacy and PK data throughout the protocol.

3) To remove phase II exploratory objective and exploratory endpoint since it was not planned currently in protocol summary and section 3.

4) To update eye related exclusion criteria in protocol summary and section 5.3 exclusion criteria #17.

5) To update eye related management in table 6-6, table 6-8, section 7.1.table 7-1,section 7.2.1.1.

6) To update the risk-benefit assessment and safety part based on emerging data in section 1.3 and section 8.

7) To update LCH tumor assessment and management in table 6-6, table 6-8, section 7.2.5.

8) To change the sample collection plan since the central lab is not available in America in table 7-1, section 7.1.1, section 7.2.3,section 7.2.4.1.

9) In figure 4-1 update the flow chart.

10) In protocol summary and section 5.2 update the inclusion criteria #11.

11) In protocol summary and section 5.2 update the exclusion criteria #15.

12) In protocol summary, section 5 removed patients with other MAPK pathway gene mutation description.

13) In section 6.1.2 removed guideline for continuation of treatment.

14) Add the Permitted concomitant therapy requiring caution and/or action in section 6.4.2 and section 1.2.1.1.1.

15) In table 7-1 update the EOT visit within

16) In table 7-1 and section 7.2.1.8 removed chest X ray check

17) In table 7-1 and section 7.2.1.5 update the pregnancy test.

18) In table 7-1 add vital sign time window.

19) In table 7-1 and section 7.2.1.5 add HCV RNA and HBV DNA check description.

20) The EOT and EOS definition updated in section 7.1.4.1

21) In section 7.1.4.2 update the criteria for patient premature withdrawal

22) In section 7.2.1.5 removed urine protein check.

23) In section 7.2.1.7 add the time window for ECG.

24) Update the table 7-3 “PK blood sampling time for Phase I dose expansion stage and Phase II”.

25) In section 7.2.5 update efficacy assessment description.

26) In table 6-1 removed “level 7 1000mg”

27) update the table 6-4 provisional dose level.

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List of abbreviations

ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
APTT	Activated partial prothrombin time
AST	Aspartate aminotransferase
ATD	Accelerated titration designs
BED	Biological effective dose
BID	Twice daily
BOIN	Bayesian optimal interval
BOP2	Bayesian optimal phase 2
BP	Blood pressure
CLcr	Creatinine clearance rate
CNS	Central nervous system
CR	Complete remission/complete response
CRF	Case report/record form
CRM	Continual reassessment method
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CTEP	Cancer Therapy Evaluation program
CYPs	Cytochromes P450
CYP3A4	Cytochrome P450 isoform 3A4
DBP	Diastolic blood pressure
DCR	Disease control rate
DLT	Dose limiting toxicity
DoR	Duration of response
ECD	Erdheim-Chester disease
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern cooperative oncology group
eCRF	Electronic case report/record form
ECs	Ethics committees
EDC	Electronic data collection
EOT	End of treatment
ERK	Extracellular signal-regulated kinase
FFPE	Formalin-fixed, paraffin-embedded
FDA	Food and Drug Administration
GCP	Good clinical practice

HBV	Hepatitis B virus
HCV	Hepatitis C virus
HED	Human equivalent dose
hERG	Human ether-a-go-go-related gene
HIV	Human immunodeficiency virus
HNSTD	Highest non-severe toxic dose
IB	Investigator's brochure
IC_{50}	Half maximal inhibitory concentration
ICH	International Conference on Harmonization
ICF	Informed consent form
INR	International normalized ratio
IEC	Independent ethics committee
IRB	Institutional review board
LC/MS-MS	Liquid chromatography-tandem mass spectrometry
LCH	Langerhans cell histiocytosis syndrome
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MAPK	Mitogen-activated protein kinase
MBP	Mean blood pressure
MEDDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase/extracellular signal-related kinase
MUGA	Multi-gated acquisition
NCI	National cancer institute
NGS	Next generation sequencing
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamics
PD	Progressive disease
PFS	Progression-free survival
PHI	Protected health information
PI	Principal investigator
PI3K	Phosphatidylinositol 3-kinase
PK	Pharmacokinetics
PKS	Pharmacokinetic analysis set
PT	Prothrombin time
QD	Once daily
QT	A measure between Q and T waves in heart electrical system
QTc	Corrected QT interval

QTcF	Fridericia-corrected QT interval
RBC	Red blood cell
REB	Research ethics board
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended phase two dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Steering committee
SD	Standard deviation
SD	Sprague Dawley
SEC	Study evaluation completion
SFUV	Safety Follow-up Visit
SMC	Safety monitoring committee
SOC	System organ class
SS	Safety set
TEAEs	Treatment-emergent adverse events
TTP	Time to progression
TTR	Time to response
ULN	Upper limit of normal
WBC	White blood cell

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q21 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient Number /Subject Number (Patient No.)	A unique identifying number assigned to each patient/subject /healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival

Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Treatment group	A treatment group defines the dose and regimen or the combination and may consist of 1 or more cohorts. Cohorts are not expanded; new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

Protocol summary

Protocol number	HH2710-G101
Title	A First-in-Human, Open Label, Phase I/II Study to Evaluate the Safety, Tolerability and Pharmacokinetics of HH2710 in Patients with Advanced Tumors
Sponsor	Haihe Biopharma Co., Ltd.
Phase	Phase I/II
Location and sites	Multinational, Multicenter
Purpose and rationale	The purpose of this study is to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary efficacy of HH2710 administered orally in adult patients with advanced tumors.
Primary Objective(s) and Endpoints	**Phase I:** Primary objective: - To evaluate the safety, tolerability of HH2710 administered orally in patients with advanced tumors. - To identify the Maximum Tolerated Dose (MTD) and/or Recommended Phase II dose (RP2D). Primary endpoints: - 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:** Primary objective - To evaluate efficacy of HH2710 in patients with advanced tumors with alterations on the genes of the mitogen-activated protein kinase (MAPK) signaling pathway, at the recommended phase 2 dose (RP2D).

	Primary endpoints: - Tumor objective response rate (ORR) based on RECIST version 1.1.
Secondary Objective(s) and Endpoints	**Phase I:** Secondary objectives: - To characterize the pharmacokinetic profile of HH2710 and selected metabolites when administered orally in patients with advanced tumors. Secondary endpoints: - Peak plasma concentration (Cmax), peak time (tmax), area under the plasma concentration-time curve from time 0 to time (t) (AUC_{0-t}), plasma elimination half-life ($t_{1/2}$), plasma clearance rate constant (λz), apparent clearance (CL/F), apparent volume of distribution (Vz/F) **Phase II:** Secondary objectives: - To evaluate the efficacy of HH2710 in advanced tumor patients with MAPK signaling pathway genetic alterations. - To evaluate the safety of HH2710. Secondary endpoints: - Efficacy: 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. - Safety: 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 Objective(s) and Endpoints	**Phase I:** Exploratory objectives - To assess the preliminary efficacy of HH2710;. - To explore the changes of the pharmacodynamic (PD) markers of HH2710. Exploratory endpoints: - ORR, DoR, DCR, PFS and TTR;. - Changes in PD markers of HH2710 efficacy including

	phosphorylation of RSK (pRSK) and total RSK.
Study design	This is a First-in-Human, open-label, multicenter, 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. HH2710 will be administered orally on a continuous once daily (QD) or twice daily (BID) schedule, 21 days as a "Cycle". 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 to help to 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. <u>Accelerated titration part:</u> 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. <u>BOIN design part:</u> 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 will be assigned per treatment cohort. (ATD + BOIN design details please see Section 6.2.3) Part A (25/50/100 mg BID + QD dose escalation cohorts): To date 18 Jan 2022, 22 patients were enrolled in the dose escalation stage of 6 dose levels as 25mg BID (n=3), 50mg BID (n=3), 100mg BID (n=4), 400mg QD (n=4), 600mg QD(n=4), and 800mg QD (n=4), 4 patients were enrolled in the 600mg QD expansion cohort. PK data from 22 enrolled patients showed HH2710 was slowly eliminated after oral administration, the accumulation of the systemic exposure of HH2710 at steady state was about 3-4 fold. The half-life ($t_{1/2}$)of HH2710 ranged from 8.42 to 10.9 hr, suitable for once daily dosing. Based on the safety data at 6 dose levels, HH2710 was well tolerated from 25 mg BID to 400 mg QD. However, 1 of 4 patients at 800 mg dose cohort experienced DLT (Grade 3 Acneiform rash). 3 of 26 patients developed Grade 1-2 eye toxicity, 2 patients were from the 600mg dose group, and 1 from 800mg dose. Since the drug-related factor may have contributed, we

	have de-escalated to 300mg QD dose. 6.2.2And further dosing frequency and dose level may be adjusted based on available safety and PK data. Part B (Additional BID dose escalation cohorts): In order to determine the RP2D, additional BID dosing regimens will also be evaluated using BOIN design starting from 200mg BID dose and the total sample size in Part B is up to approximately 18 subjects. After the escalation is completed, select the MTD based on the isotonic regression as specified in [64]. 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: Additional up to 15 patients per cohort may be included in order to further evaluate the safety, PK and anti-tumor activities among biomarker-selected patients. The dose for provisional cohort of expansion phase will be based on available safety, PK/PD, preliminary efficacy data. Patients enrolled could have different tumor types but 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. 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 specified genetic alteration through molecular screening. (See details in section 4.1): – 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, *NRA*S 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.
Population	**Phase I**

	For the dose escalation stage, patients who have been diagnosed with histologically or cytologically documented, unresectable/metastatic tumors that are refractory or intolerant to standard therapy or for whom no curative standard therapy exists. – For LCH/ECD: Eligible patients must have multifocal disease and the diagnosis must be confirmed by pathological evaluation of the affected tissue. For the dose expansion stage, patients must have been diagnosed with histologically or cytologically documented, unresectable/metastatic tumors harboring MAPK pathway genetic alterations. Patients with a BRAF V600 mutation must have progressed on or after standard therapy, including BRAF and/or MEK inhibitors (≤3 lines). **Phase II** Patients must have been diagnosed with histologically or cytologically documented, unresectable/metastatic tumors harboring genetic alterations of the genes of MAPK pathway. Patients with a BRAF V600 mutation must have progressed on or after standard therapy, including BRAF and/or MEK inhibitors (≤3 lines). Patients will be enrolled in Cohorts 1-4 depending upon their tumor type.
Inclusion criteria	1. Provide signed and dated informed consent prior to initiation of any study-related procedures; 2. Male or female patients aged ≥ 18 years; 3. Phase I dose escalation stage: Patients who have been diagnosed with histologically or cytological documented, unresectable/metastatic tumors that are refractory or intolerant to standard therapy or for whom no curative standard therapy exists. – For LCH/ECD: Eligible patients must have multifocal disease and the diagnosis must be confirmed by pathological evaluation of the affected tissue. 4. Phase I expansion stage and Phase II stage: Histologically or cytologically documented unresectable/metastatic tumors with evidence of genetic mutations affecting MAPK pathway is required. Patients with a BRAF V600 mutation must have progressed on or after standard therapy, including BRAF and/or MEK inhibitors (≤3 lines). Patients entering the Phase 2 portion of the trial will be enrolled in Cohorts 1-4 depending upon their tumor type. – 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); – For LCH/ECD: Eligible patients must have multifocal disease and the diagnosis must be confirmed by pathological evaluation of the affected tissue. – Cohort 4: Patients with *RAS/RAF/MEK/ERK* mutated tumor types that are not included in other cohorts. 5. Patients in the Phase I dose escalation portion of the trial may have measurable (per RECIST v1.1) or evaluable disease. Patients in the Phase I expansion and Phase II portions of the trial must have measurable disease per RECIST v1.1. 6. Eastern Cooperative Oncology Group (ECOG) performance status≤ 1. 7. Predicted life expectancy of ≥ 3 months; 8. Adequate renal function defined as a creatinine clearance ≥ 60 mL/min (using Cockcroft-Gault formula, see **Appendix 14.3**); 9. Adequate hepatic function [total bilirubin ≤ 1.5 x UNL; AST (aspartate aminotransferase) and ALT (alanine aminotransferase) ≤ 3 x UNL or ≤ 5 x UNL if due to liver involvement by tumor]; 10. Adequate cardiac function, > institutional lower limit of normal e.g., left ventricular ejection fraction (LVEF) of ≥ 50% as assessed by ultrasound/echocardiography (ECHO) or multi-gated acquisition (MUGA) ; corrected QT interval (QTcF) < 460 ms (male patients), < 470 ms (female patients) (using QTc Fridericia's formula. See **Appendix 14.6**); 11. Adequate bone marrow function, patients must not have required blood transfusion or growth factor support ≤ 7 days before sample collection for the following： · Absolute neutrophil count ≥ 1.5 × 10^9/L; · Hemoglobin ≥ 9 g/dL; · Platelet count ≥100 × 10^9/L; · International normalized ratio (INR) ≤ 1.5; · Activated partial prothrombin time (APTT) ≤ 1.5 × ULN; 12. Willing and able to participate in the study and comply with all study requirements;
Exclusion criteria	Patients eligible to be included in this study are prohibited from having any of the following criteria:

	1. Gastrointestinal condition which could impair absorption of study medication; 2. Congenital long QT syndrome, or any known history of torsade de pointes (TdP), or family history of unexplained sudden death; 3. Clinically uncontrolled hypertension (after standard antihypertensive treatment, systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg); 4. Undergone a bone marrow or solid organ transplant; 5. Any toxicities from prior treatment that have not recovered to ≤ CTCAE Grade 1 before the start of study drug, with the exception of hair loss or fatigue; 6. Patients who have previously participated in clinical trials of ERK inhibitors drug; 7. Allergic to similar drugs or their excipients; 8. HIV (human immunodeficiency virus) infection, active hepatitis B or hepatitis C patients (HBsAg positive patients also detected HBV (hepatitis B virus) DNA ≥ 10^3 copies or ≥ 200 IU/ml; HCV antibody test results are positive, and HCV (hepatitis C virus) RNA PCR test results are positive); 9. Uncontrolled or severe intercurrent medical condition: − Unstable angina pectoris ≤3 months prior to starting study drug; − Acute myocardial infarction ≤3 months prior to starting study drug; 10. Symptomatic CNS metastases that are neurologically unstable or requiring increasing doses of steroids to control CNS disease. Note: Controlled CNS metastases are allowed. Radiotherapy or surgery for CNS metastases must have been completed >2 weeks prior to study entry. No new neurologic deficits on clinical examination and no new findings on CNS imaging are permitted. Steroid use for management of CNS metastases must be at a stable dose for two weeks preceding study entry; 11. Any cancer-directed therapy (chemotherapy, radiotherapy, hormonal therapy, biologic or immunotherapy, Chinese medicine/Chinese patent medicine with anti-tumor effect, etc.) within 28 days or 5 half-lives, whichever is shorter; 12. Major surgery within 4 weeks prior to first dose; 13. Any use of an investigational drug within 28 days or 5 half-lives (whichever is shorter) prior to the first dose of HH2710; 14. Pregnant or breast-feeding women; 15. Severe chronic or active infections requiring systemic antibacterial, antifungal or antiviral therapy, including tuberculosis infection, etc · Severe infections within 4 weeks prior to the first dose, including but

	not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia. · Received therapeutic oral or IV antibiotics within 2 weeks prior to the first dose of study drug. 16. Any important or severe medical illness or abnormal laboratory finding that would increase the risk of participating in this study; 17. A history or current evidence/risk of retinal vein occlusion, central serous retinopathy or choroidneovascularization (CNV) ; 18. Concurrent therapy with any other investigational agent; 19. Concomitant malignancies or previous malignancies with less than 2 years disease-free interval at the time of enrollment; (But basal cell carcinoma skin cancer, cervical CIS(carcinoma *in situ*), CIS of the breast, localized or low Gleason grade prostate cancer, and < T2 bladder cancer can be included) 20. Current treatment with agents including vitamins, supplements, and herbal supplements that are metabolized solely through CYP3A4 (see **Appendix 14.7**); 21. Severe chronic obstructive pulmonary disease, severe asthma, pneumoconiosis, asbestosis and other occupational lung diseases. 22. A history of acute or chronic pancreatitis, surgery of the pancreas, or any risk factors that may increase the risk of pancreatitis; 23. Contraception (See Appendix 4 Women of child-bearing age and contraceptive measures): Patients who do not meet the following conditions will be excluded, − For women: Negative pregnancy test for females of child-bearing potential; must be surgically sterile, postmenopausal (defined as no menstrual cycle for at least 12 consecutive months), or compliant with an acceptable contraceptive regimen (2 highly effective forms, such as oral contraceptives, condom with spermicide, etc.) during and for 6 months after the treatment period. Abstinence is not considered an adequate contraceptive regimen; − For men: Must be surgically sterile, or compliant with a contraceptive regimen (as above) during and for a minimum of 6 months after the treatment period.
Investigational and reference therapy	HH2710
Efficacy assessments	Tumor assessment per RECIST v1.1

Safety assessments	Incidence, type and severity of Adverse Events (AEs), physical examination findings, clinical laboratory values, vital signs and Electrocardiograms (ECGs).
Other assessments	− Plasma PK parameters; − Pharmacodynamics assessment on pre- and post-treatment newly obtained tumor samples and peripheral blood mononuclear cells (PBMCs); − The correlation between biomarkers and the response of HH2710.
Data analysis	The study data will be analyzed and reported based on all patients' in Phase I and Phase II up to the time when all patients have completed at least one cycle of treatment or discontinued the study. The study is descriptive in nature and is not designed to provide definitive results regarding antitumor activity. Descriptive statistics will be used to summarize all baseline patient characteristics, treatment administration, safety variables, and signs of antitumor activity. All patients who receive at least one dose of HH2710 will be included in the safety analysis. Incidence of serious and non-serious AEs, including those that are dose limiting, will be tabulated by dose, system organ class, and preferred term. All variables obtained at different observation time points will be statistically described according to the dose cohorts, unless a statistical description of certain time points is not specified in the study protocol. In general, descriptive variables are statistically described using number of observations, mean, median, standard deviation, minimum and maximum values, Q1 and Q3 values, while categorical variables use different frequency types and their relative percentages. A safety analysis of DLT and adverse events, as well as other safety indicators for HH2710, will be performed to guide dose escalation. The final analysis of the study will be based on data collected throughout the study. The sample size for Phase I of this study was determined by clinical considerations. A maximum sample size is 58 patients for the dose escalation (ATD + BOIN) to assess dose limiting toxicities (DLT), maximum tolerated dose (MTD), and the recommended Phase 2 dose (RP2D). For Phase I expansion, additional up to 15 patients per cohort may be included in order to further evaluate the safety, PK and anti-tumor activity among biomarker-selected patients. One or more dose levels and dosing frequencies (QD, or BID) may be expanded based on the available data. Patients enrolled could have different tumor types with specific MAPK pathway genetic alteration information. The total number of patients will depend upon the number of dose expansions necessary.

	In Phase II, a maximum of 108 patients with advanced tumors harboring MAPK genetic alterations tested through molecular screening, will be recruited into four cohorts to seek the evidence of response.
Key words	Phase I/II, HH2710, ERK inhibitor

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

A critical hallmark of carcinogenesis is the activation of cell-growth signaling cascades independent of appropriate growth stimulation [1]. One of cell growth control circuits is the mitogen-activated protein kinase (MAPK) pathway. In this pathway, growth ligands signal activate surface receptors, promote growth via downstream effectors in a kinase cascade system: RAS family GTPases activate RAF family protein kinases, which in turn trigger a phosphorylation cascade involving mitogen-activated protein kinase/extracellular signal-related kinase (MEK) and extracellular signal-regulated kinase (ERK) family kinases. ERK kinases activate a series of direct effectors, such as c-Myc/N-Myc/ER/c-Fos/Stat1/3 etc., which ultimately translate growth signaling into essential cellular functions including cell division, proliferation and cell survival(See **figure 1-1**).

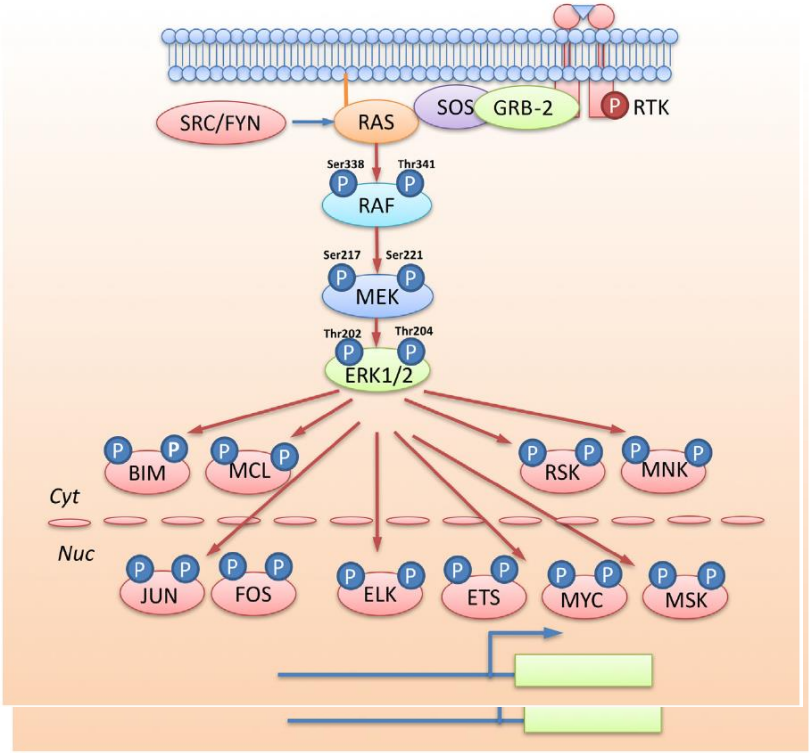


Figure 1-1. ERK regulates both cytosolic targets and nuclear transcription factors, thus promoting proliferation, survival and other malignant phenotypes.

Aberrant activation of the MAPK pathway and genetic alteration of its component is ubiquitous in cancer. Genetic alteration often causes constitutive activation of the signaling cascade in the absence of appropriate ligands. For example, members of the RAS GTPase family (KRAS, NRAS, and HRAS) were demonstrated to exhibit spontaneous, activating mutations in a variety of cancers,

including non-small cell lung, melanoma, pancreatic, and colorectal malignancies [2]. As an example, members of the RAF GTPase family BRAF mutation can be detected in melanoma, colorectal tumors, lung cancer, kidney cancers, ovarian cancers, hairy cell leukemia, pilocytic astrocytoma, breast, cholangiocarcinoma, chronic lymphocytic leukemia, Langerhans cell histiocytosis Syndrome (LCH), Erdheim-Chester disease (ECD), papillary thyroid cancer, prostate cancer, Glioblastoma, Ganglioglioma and many other related disease types [3].

Before 2010, the standard therapy for most patients with advanced melanoma was chemotherapy, which had low response rates and minimal impact on survival [4]. In 2002, activating missense mutations in the *BRAF* gene were identified in 40% to 60% of melanomas [5]. These *BRAF* mutations result in constitutive activation of the BRAF kinase protein and thus promote hyperactivation of the mitogen-activated protein kinase (MAPK) signaling pathway, an essential regulator of cell proliferation and survival [6]. Targeting aberrant MAPK signaling via the selective inhibition of mutant BRAF as well as the downstream protein mitogen-activated protein kinase (MEK) has shown significant antitumor activity in melanoma patients with *BRAF*-mutant melanoma [7][8][9].

In addition to BRAF, several other genes are commonly mutated in melanoma, and these may also provide novel therapeutic opportunities. The *NRAS* gene is mutated in 10% to 30% of cutaneous melanomas, and this leads to a constitutively active NRAS protein capable of stimulating the MAPK and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathways **[10]**.

Activating mutations in the *BRAF* gene, first described in lung cancers in 2002**[5][11]**, promote growth and survival of cancer cells that harbor *BRAF* gene mutation and are extremely sensitive to selective BRAF inhibitor therapy across multiple tumor types[12].

BRAF mutations are present in approximately 2–4% of lung adenocarcinomas, and approximately one-half are V600E mutations [5][13][14]. The clinical outcome in patients with *BRAF V600E* mutations is associated with shorter overall survival (OS) and lower response rates to platinum-based chemotherapy than in patients with wild-type BRAF [15][16][17].

A basket study exploring the response of vemurafenib in patients with a variety of solid tumors and hematologic malignancies, enrolled a cohort of 19 patients with *BRAF* V600E mutated non-small cell lung cancer (NSCLC) and demonstrated a promising overall response rate (ORR) of 42% [18], a cohort of 14 patients with *BRAF* V600E mutated Langerhans Cell histiocytosis Syndrome (LCH)/Erdheim-Chester disease (ECD) and demonstrated a promising overall response rate (ORR) of 43% [18].

Dabrafenib and trametinib used as single drug and combination therapy are approved in FDA and for treatment of melanoma, NSCLC, advanced undifferentiated thyroid carcinoma [19]. Vemurafenib and Cobimetinib are approved on the market too. But these inhibitors target to BRAF and MEK are limited by intrinsic and acquired resistance.

The RAS/RAF/MEK/ERK pathway is activated by many extracellular stimuli such as cytokines, neurotransmitters, hormones, cellular stress and cell adhesion which are important in driving the proliferation and promoting the survival of cancer cells, etc. After receptor ligation, Shc, Src homology (SH)-2, a SH2-domain containing protein, becomes associated with the c-terminus of the cytokine receptor [20][21][22]. Shc recruits the GTP-exchange complex Grb2/Sos resulting in the loading of membrane bound Ras with GTP[23][24]. Ras: GTP then recruits Raf to the membrane where it becomes activated, likely via a Src-family tyrosine kinase [25][26][27]. Raf is responsible for phosphorylation of the mitogen associated/extracellular regulated kinase-1 (MEK1)[28][29]. MEK1 phosphorylates extracellular regulated kinases 1 and 2 (ERKs 1 and 2) on specific threonine and tyrosine residues [28][29][30]. Activated ERK1 and ERK2 serine/threonine kinases phosphorylate and activate a variety of substrates including p90Rsk1[31][32][33][34][35]. p90Rsk1 can activate the cyclic-AMP response element binding protein (CREB) transcription factor [33]. Moreover, ERK can translocate to the nucleus and phosphorylate additional transcription factors such as Elk1, CREB and Fos which bind promoters of many genes, including IL-3, a cytokine important in stimulating the growth and survival of many cancer cells. The RAF/MEK/ERK pathway can also modulate the activity of many proteins involved in apoptosis including: Bcl-2, Bad, Bim, Mcl-1, caspase 9, and Survivin [36][37].

ERK inhibition has the potential to overcome or avoid resistance from upstream mutations[38]. The ERK family kinases are downstream components of MAPK signaling pathway that have been therapeutically targeted for years, there are no drugs is approved on the market so far. The ERK target drug BVD523 showed curative effect in melanoma, NSCLC, gallbladder adenocarcinoma, glioblastoma multiforme etc. Responses occurred in patients with *NRAS*-, *BRAF* V600-, and non-V600 *BRAF*-mutant solid tumors, with an acceptable safety profile. The most common treatment related adverse events were diarrhea (48%), fatigue (42%), nausea (41%), and dermatitis acneiform (31%)[39][40]. HH2710 is a small-molecule inhibitor of ERK1/2 kinases that we plan to explore in various tumors. Understanding the safety, tolerability and efficacy of HH2710 will be helpful to the drug of targeted therapies that can be used against the activated MAPK signaling pathway in many malignancies.

KRAS and *NRAS* mutations in *RAS* family genes occur in approximately 30% of all human cancers [41]. *KRAS* mutations prevalent in pancreatic (>90%)[42], colorectal (30%–50%)[43], biliary tract (3%–50%)[44], lung (25–30%)[45], ovarian (15%–39%)[46], and endometrial (18%) cancers[47], and *NRAS* mutations prevalent in melanoma (20%)[48].

The most notably *BRAF* at codon V600 mutations in *RAF* family genes are frequent, particularly in malignant melanomas (50%)[49], and in approximately 7% of a wide range of other cancers[5][50]. Atypical BRAF alterations (non-V600) are sporadically in numerous tumor types.

BRAF inhibitors (Approved drug vemurafenib and dabrafenib) are effective in BRAF V600–driven tumors,but have not been shown to be effective against *BRAF* non-V600 mutations. The current understanding of the mechanism by which this phenomenon occurs that BRAF V600

alterations can act as monomers to drive signaling, whereas specific atypical BRAF non-V600 alterations act in a dimer-dependent manner [51].

Mutations in *MEK* or *ERK* are rare. *MEK* mutations occurring in 5% to 8% of melanomas [49][52], and *ERK* mutations occurring in cervical cancer (8%)[53] and head and neck squamous cell carcinoma (1.5%)[54]. MEK inhibitors (Approved drug trametinib and cobimetinib) combined with BRAF inhibitor/or used as a single drug are effective in *BRAF* V600E/K driven tumors,but have very limited efficacy in *BRAF* non-V600 mutations. Collectively, activating mutations of MAPK/ERK pathway components are frequent events in a range of cancer types. Drugs targeting other components of the MAPK pathway exhibit promising therapeutic activity, while also being limited by unique toxicities and limited duration of efficacy.

1.2 Introduction to investigational treatment(s)

1.2.1 Overview of HH2710

The chemical name of HH2710 is 2-(2-Chloropyridin-3-yl)-1-(7-fluoro-5-(2-((1-methyl-1H-pyrazol-5-yl) amino) pyridin-4-yl) indolin-1-yl) ethan-1-one. The medication class is tumor target interventional treatment.

HH2710 is a small molecule that potently inhibits both ERK1 and ERK2 protein kinases in the nanomolar range. The kinase selectivity assessment towards a panel of over 400 protein kinases showed that HH2710 barely inhibited other kinases at a concentration up to 1 μM, except the substantial inhibition against ERK1 (MAPK1), ERK2 (MAPK2) and the MAPK pathway upstream kinases MEK and RAF proteins. Cellular assays largely excluded the impact of HH2710 on upstream kinases MEK and RAF. HH2710 potently inhibits growth and survival in cultured cancer cell lines; melanoma, colorectal and pancreatic lines harboring *BRAF* or *RAS* mutations are among those most susceptible to the drug. Orally administered HH2710 is effective as a single agent in animals bearing ectopic tumor xenografts, again preferentially in cancers where activating mutations in the MAPK pathway cause abundant ERK kinase activation.

HH2710 will be administered orally in humans. The free base of HH2710 was selected for manufacture of drug product in capsule form. Storage temperature: 10-30℃ , protected from light.

More information is available in the Investigator's Brochure (IB) for HH2710.

1.2.1.1 Preclinical experience

1.2.1.1.1 Preclinical drug metabolism and pharmacokinetics

Pharmacokinetic studies conducted in Sprague-Dawley rats and Beagle dogs suggest that HH2710 has an acceptable pharmacokinetic behavior. After intragastric administration, HH2710 is absorbed fast with a $t_{1/2}$ of 1.68~3.60 hrs (rat) and 1.40~2.54 hrs (dog), respectively. Within the dosage range of 10 to 40 mg/kg (rats, fasting) and 3 to 12 mg (dogs, fasting), the exposure of HH2710 is greater than dose proportional following intragastric gavage, and the bioavailability

was 46.9 – 86.5% (rat) and 47.8 – 72.6% (dog) in these two species. After intragastric administration of 10 to 40 mg/kg HH2710 to rats, the mean HH2710 C_{max} values were 2.95 to 10.6 μg/mL, and the mean HH2710 AUC $_{0-t}$ values were 13.1 to 96.4 μg·h/mL, respectively. After single intragastric administration of 3 to 12 mg/kg HH2710 to dogs, the mean HH2710 C_{max} values were 0.74 to 3.50 μg/mL, and the mean HH2710 AUC $_{0-t}$ values were 3.44 to 20.9 μg·h/mL, respectively. After the rats were given intragastric administration of HH2710, it was mainly distributed in the adrenal gland, liver, gastrointestinal tract, kidney and pancreas. The apparent volume of distribution at steady state (V_{ss}/F) of rats and dogs was 0.562 and 1.14 L/kg, respectively. HH2710 did not easily pass blood brain barrier and hardly entered blood cells. The value of apparent total plasma clearance was low with the value of 5.93 (rat) and 7.29 (dog) mL/min/kg. There is no sex difference in exposure and no obvious accumulation over consecutive daily administration for a week. Elimination is by metabolism (CYP3A) then excretion mainly in feces. Monooxidated metabolite HH3529 is the major metabolite of HH2710 produced through CYP3A.

The major metabolite HH3529: After a multiple intragastric administration of 10, 20 and 40 mg/kg HH2710 to rats, the exposures of HH3529 were approximately 57-121% of those of HH2710, increased proportionately with dose. Plasma concentrations of HH3529 peaked at 2-4 hours post-dose. After a multiple intragastric administration of 3, 6 and 12 mg/kg HH2710 to dogs, the exposures of HH3529 were only approximately 3% of those of HH2710.

HH2710 is a high permeability drug and can be rapidly distributed throughout the body with high plasma protein binding fraction. HH2710 has moderate inhibitory activity on CYP2C8, CYP2C9, CYP2C19 and CYP3A4/5 with IC_{50s} of 4.37 μM, 4.52 μM, 8.75 μM, 8.38 μM, and 7.03 μM , and has potential induction effect on CYP2B6 and CYP3A4 at 10 μM *in vitro*. HH2710 is a potential substrate of efflux transporter P-gp.

1.2.1.1.2 Preclinical pharmacology and pharmacodynamics studies

Preclinical studies have shown that HH2710 specifically inhibits the activity of ERK1/2 kinases, leading to significant anti-tumor activity *in vitro* and *in vivo*.

***In vitro* pharmacodynamics study**

HH2710 is a specific inhibitor of ERK1/2.

HH2710 exhibits potent inhibition on the serine/threonine kinase activity of recombinant ERK1/2 *in vitro*, with half maximal inhibitory concentration (IC_{50}) values of 4.5 ± 1. 7, 4.9 ± 0.8 nM, respectively. Biochemical test against a broad spectrum of 412 protein kinases did not observe the apparent activity towards most kinases at a concentration up to 1 μM except marginal activity against the upstream RAF and MEK. Further enzymatic kinetic assay using a competitive assay by introducing increasing concentrations of ATP show that HH2710 is an ATP-competitive inhibitor, which fits the most common mechanism of small-molecule kinase inhibitors.

The cellular activity of HH2710 against ERK1/2 kinase was measured by examine the direct substrate molecule RSK in MAPK pathway activated cancer cell lines, namely Colo-205 colorectal

cancer and A375 melanoma cancer cell lines both bearing *BRAF* V600E mutation. HH2710 significantly inhibited RSK phosphorylation in a dose-dependent manner.

HH2710 inhibits the growth of cancer cells with MAPK activation.

The cellular anticancer activity of HH2710 was assessed in a panel of cancer cells with MAPK activation in particular *BRAF* and *KRAS* activating mutation. Cancer cells without detectable genetic alterations in MAPK pathway molecules (designated as wild type) were chosen as control. HH2710 effectively inhibits the proliferation of cancer cells with *BRAF* or *KRAS* activating mutation, though the potency towards different cell lines are variable. Wild type cells in general showed much less sensitivity to HH2710, with IC_{50} > 10 μM.

***In vivo* pharmacodynamics study**

HH2710 inhibits the tumor growth in xenograft models via targeting ERK1/2.

The anti-tumor efficacy of HH2710 *in vivo* was examined in three human xenograft models Colo-205 (*BRAF*-V600E) colon carcinoma, A375 (*BRAF*-V600E) melanoma, and MiaPaCa-2 (*KRAS*-G12C) pancreatic cancer. In Colo-205 model, HH2710 showed significant antitumor activity at the dosage of 15, 30 and 60 mg/kg (twice per day, given orally) with the relative tumor volume at the endpoint (T/C value) of 45.47%, 29.31% and 21.32% respectively. In this model, HH2710 at 30 mg/kg was more effective than with the same dose of BVD-523 in controlling tumor growth. The similar tumor growth inhibitory effect of HH2710 was also observed on the other two xenograft models. HH2710 at dosage of 25-100 mg/kg (twice per day, given orally) caused a dose-dependent suppression of tumor growth with no obvious toxicity observed. Remarkable growth inhibition was observed at the dosage of 100 mg/kg, yielding the T/C values were 17.11-18.82% (A375) and 24.90-36.75% (MiaPaCa-2), respectively. Along with the tumor growth inhibition, the intra-tumoral level of RSK phosphorylation was dose-dependently decreased compared with the vehicle growth, indicating the diminished ERK signaling in tumor tissues.

We also evaluated the *in vivo* efficacy of HH2710 on single dose daily. The results indicated that HH2710, under the same total daily dosage, exhibited comparable efficacy on single dose to that of dose twice per day in two tested models, suggesting a potential advantage in reducing dosing frequency compared with the leading compound BVD-523.

In summary, HH2710 specifically inhibits the activity of ERK1/2 kinase, yielding significant anti-tumor activity in different types of tumors with MAPK pathway activation. The antitumor activity *in vivo* is improved compared with the clinical leading compound BVD523.

1.2.1.1.3 Safety and toxicity studies

In conclusion, under the conditions of this study, after a single dose of HH2710 30, 100 or 300 mg/kg via oral gavage in SD (Sprague Dawley) rats, the test article was well-tolerated both in female and male animals, and the Maximum Tolerated Dose (MTD) was greater than 300 mg/kg. After Beagle dogs were given a single dose of HH2710 100, 300 or 1000 mg/kg via oral gavage, the test article was tolerated in all dose groups, vomit and soft/fluid feces were mainly observed

post-dose, no abnormal change was found by gross observation during necropsy, and the maximum tolerated dose (MTD) was greater than 1000 mg/kg.

After SD rats were given 15, 50 and 150/100 mg/kg/day HH2710 via oral gavage, once daily, for 28 consecutive days, death occurred in the animals administered with the test article at 150 mg/kg/day since Day 5 and animals could tolerate when the dose was adjusted to 100 mg/kg/day from Day 9; the highest non-severe toxic dose (HNSTD) in females and males was 50 mg/kg/day (on Day 28, the mean AUC_{0-t} of HH2710 in females and males were 93500 ng·h/mL and 71500 ng·h/mL, respectively; and the mean AUC_{0-t} of its major metabolite HH3529 in females and males were 52100 ng·h/mL and 63400 ng·h/mL, respectively), and the main target organs of toxicity were considered to be immune tissue/organ, kidney, liver, heart, lung, kidney, femur, adrenal gland, pancreas and reproductive organs, in addition,, multiple organs/tissues (parenchyma/ vascular) mineralization was also noted. At the end of recovery phase, all the changes except tissue mineralization recovered or showed a recovery trend. After Beagle dogs were given 5, 15 and 60/30 mg/kg/day HH2710 via oral gavage, once daily, for 28 consecutive days, the dose of 60 mg/kg/day HH2710 was not tolerated by the animals and hence the dose was adjusted to 30 mg/kg/day, which was tolerated by most animals; the highest non-severe toxic dose (HNSTD) in male and female animals was 15 mg/kg/day (on Day 28, the mean AUC_{0-t} of HH2710 in female animals and male animals were 35200 ng·h/mL and 27100 ng·h/mL and the mean AUC_{0-t} of its major metabolite HH3529 in female animals and male animals were 649 ng·h/mL and 487 ng·h/mL, respectively), and the main target organs of toxicity were considered to be hemato-lymphoid tissues/organs, epithelial mucosal tissues, lungs, kidneys, heart, liver, male reproductive system, pancreas, gallbladder and adrenal glands, and the above changes in these tissues/organs were restored by the end of recovery phase.

After the SD rats were given a single dose of the vehicle or HH2710 (15, 50 and 100 mg/kg) via oral gavage, no significant drug-related changes were noted in the tidal volume (TV), respiratory minute volume (MV) or respiratory frequency (Rf) of animals in the HH2710 dose groups at each time point, and no significant impact on the central nervous system was observed.

After conscious Beagle dogs were given a single dose of HH2710 (5, 20 and 100 mg/kg) via oral gavage, increased heart rate (HR), decreased PR interval and decreased QT interval without changes in corrected QT (QTcR) in both genders, decreased of systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean blood pressure (MBP) in the males and decreased of SBP in the females were found at 100 mg/kg. All these changes were resolved within the observation period. And a slightly decreased of body temperature was temporarily noted at 3 hrs post-dose in the males of 100 and 20 mg/kg groups. No test article-related arrhythmia was observed in all animals.

In Ames test, HH2710 is not mutagenic to Salmonella typhimurium. In chromosomal aberration test, HH2710 did not induce chromosome aberrations in cultured CHL cells. In bone marrow

micronucleus test, HH2710 could not induce an increase in the micronucleated polychromatic erythrocyte of rat bone marrow.

In the human ether-a-go-go-related gene (hERG) study, in human embryonic kidney cell lines (hERG-HEK293) steadily expressing hERG channels, the hERG current inhibition rate by HH2710 at 0.3, 1, 3, 10 and 30 μmol/L was 1.1%, 6.9%, 17.8%, 41.1% and 73.2%, respectiv ely; and the IC_{50} value was 12.8 μmol/L.

1.2.1.2 Clinical experience

This is a first-in-human Phase I/II study. As of cutoff date 18 Jan 2022, 22 patients were enrolled in the dose escalation stage of 6 dose levels as 25mg BID (n=3), 50mg BID (n=3), 100mg BID (n=4), 400mg QD (n=4), 600mg QD(n=4), and 800mg QD (n=4), 4 patients were enrolled in the 600mg QD expansion cohort

Based on the safety data at 6 dose levels, HH2710 was well tolerated from 25 mg BID to 400 mg QD. However, 1 of 4 patients at 800 mg dose cohort experienced DLT (Grade 3 Acneiform rash). 3 of 26 patients developed Grade 1-2 eye toxicity, 2 patients were from the 600mg dose group, and 1 from 800mg dose, the AE outcome is following and drug-related factor may have contributed.

1.2.1.3 Biomarker strategy

1.2.1.3.1 Genetic Biomarkers for molecular screening

The alteration status of the MAPK signal pathway genes, such as RAS, RAF, MEK and ERK, will be used as genetic biomarkers for molecular screening to assess the eligibility of patient enrollment. For the Phase I dose escalation, the biomarker information will not be used as the criterial for enrollment, and the information will be collected and documented if available. For the Phase I dose expansion stages, the biomarker information will be collected and documented if available, where the test results of these biomarker from local laboratories will be used as one of the inclusion criteria for enrollment, and if the archival/fresh tumor tissue samples are available with signed consent, these samples will be collected for central testing in the future studies. For Phase II, the gene alteration status will be assessed through central testing, and in the case where the gene alteration status already known from local laboratories prior to central testing, the archival/fresh tumor tissue samples will be collected for central testing under signed consent.

1.2.1.3.2 Potential pharmacodynamics (PD) biomarker

In order to determine the on-target inhibition effect of ERK by HH2710, the phosphorylation of RSK (pRSK) and total RSK will be measured using blood samples from selected patients of Phase I stage.

1.2.2 Known potential risk

Based on mechanism of action, nonclinical study data, clinical safety data, and the same class drug safety profile of HH2710, hematological toxicity, hepatoxicity, nephrotoxicity, cardiotoxicity, interstitial lung disease and pancreatic toxicity are assessed as important potential risks.

Hematological toxicity

Hematological parameters changes were observed in 28-day repeat-dose toxicity study of HH2710 in dog. In HH2710 clinical data, the most common Hematological toxicity events were anemia, followed by leukopenia, neutropenia, and thrombocytopenia, and most of the adverse events were CTCAe1/2 grade.

Hepatoxicity

In 28-day repeat-dose toxicity study of HH2710 in rat, clinical pathology changes at 15 mg/kg/day, 50 mg/kg/day and 150/100 mg/kg/day dose level included increase in ALT, AST in both males and females. In HH2710 clinical data, the common hepatotoxic events were AST, ALT, ALP and GGT increased, and most of the hepatotoxic events were CTCAE grade 1/2.

Nephrotoxicity

In 28-day repeat-dose toxicity study of HH2710 in rat, clinical pathology changes at 50 mg/kg/day dose level on Day 29 included increase in CREA in males, and clinical pathology changes at 150/100 mg/kg/day dose level included increase in CREA in both gender on Day 29. No significant nephrotoxicity was observed in current clinical data.

Cardiotoxicity

The preclinical evidence suggests that following a single dose of HH2710 in conscious beagle dogs at 100 mg/kg, HH2710 could increase HR, decrease PR interval and QT interval without changing the corrected QT (QTcR) in both genders; and also decrease systolic arterial blood pressure (SBP), diastolic arterial blood pressure and mean atrial blood pressure in the males and decrease SBP in the females. The above changes can be recovered within the observation period of 25 hr. No significant cardiotoxicity was observed in current clinical data.

Interstitial lung disease

The preclinical evidence suggests chronic inflammation and alveolar macrophage aggregation in lungs were observed following HH2710 treatment at >=15 mg/kg/day dose level in 28-day repeat-dose toxicity study in rat. Interstitial lung disease cases were observed but causal relationship with study drug could not been figured out.

Pancreatic toxicity

In 28-day repeat-dose toxicity study in SD rats and Beagle dog, pancreas was one of the main target organs. No significant pancreatic toxicity was observed in current clinical data.

Besides ophthalmic toxicity and dermal toxicity also need to be monitored.

Inclusion and exclusion criteria and discontinuation criteria have been included in the protocol to minimize the risks described above.

HH2710 selectively inhibited ERK1 (MAPK1) and ERK2 (MAPK2). HH2710 potently inhibits growth of cultured cancer cell lines and xenograft models; melanoma, colorectal and pancreatic lines harboring BRAF, or RAS mutations are among those most susceptible to the drug. Overall, the observed safety of HH2710 is consistent with its mechanism of action and observations in non-clinical studies and is like that of other MAPK pathway mutation inhibitors. Safety data and risk characteristics will be continuously monitored, and safety risks will continue to be controlled reasonably and effectively.

2 Rationale

2.1 Study rationale and purpose

HH2710 is developed by Haihe Biopharma Co., Ltd. HH2710 is a highly potent, selective, reversible, ATP-competitive ERK1/2 inhibitor.

Most of the current oncology drug discovery and development work has shifted towards molecularly targeted therapies. A key focus has been on identifying inhibitors against components of pathways that drive tumor cell proliferation, survival, and metastasis such as MAPK pathway. MAPK signaling pathway plays a critical role in tumorigenesis through the RAS–RAF–MEK–ERK kinase cascade. ERK1/2, as the terminal master kinase of this MAPK pathway, influences cellular proliferation, differentiation, and survival through a variety of mechanisms [55]. Genetic alterations of MAPK pathway components are common in many cancer types.

The rationale for development of an ERK inhibitor in patients with MAPK pathway genetic alteration cancer would be that MAPK pathway genetic alteration activates the MAPK pathway, ERK is a key kinase of MAPK, ERK inhibition may be able to overcome some of resistance to upstream target drug therapy. Targeting the downstream MAPK kinase, ERK, could possibly evoke a unique and desirable balance of durable efficacy and suitable tolerability. Therefore, downstream inhibition of ERK is a promising therapeutic method to explore. The purpose of the study will therefore be to assess the anti-tumor activity of the ERK inhibitor in patients with MAPK pathway genetic alteration.

Based on the results from preclinical research HH2710 effectively inhibits proliferation and colony formation of a variety of tumor cell lines and the growth of tumors in a variety of mouse xenograft models (See **Section 1.2.1**). As such, HH2710 may represent a valuable addition to the current drugs useful for treating patients whose cancers exhibit the aberrant MAPK pathway activity. Therefore, development of HH2710 might address important unmet medical needs.

2.2 Rationale for the study design

This is a first-in-human study of HH2710 and is designed as an open-label, multicenter, Phase I/II study which is composed of a Phase I dose escalation and dose expansion stage and a Phase II dose extension stage.

Phase I: In Phase I dose escalation stage, the Bayesian optimal interval (BOIN) design incorporated with an accelerated titration designs (ATD) 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. The advantage of the ATD is to reduce the number of patients exposed to an ineffective dose, ensuring that patients can receive a higher and more effective dose. The rationale of employing the BOIN design [56][55][57] to find the MTD is that the BOIN design is implemented in a simple way similar to the traditional "3+3" design, but is more flexible and effective compared to those of the complex model-based designs, such as the continual reassessment method (CRM)[58].

In Phase I dose expansion stage, based on the FDA guidance "Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics Guidance for Industry", additional up to 15 patients per cohort may be included in order to further explore the safety, PK and anti-tumor activity among biomarker-selected patients. One or more dose levels may be expanded based on the available data.

Phase II: Dose extension stage: This stage is an open-label, dose extension study at RP2D to explore the anti-tumor response of patients with particular tumor types and/or cancers harboring MAPK genetic alteration. Because data on drugs targeting the upstream signaling molecules of the MAPK signaling pathway and clinical trial data for drugs targeting ERK (BVD523) suggest that melanoma, non-small cell lung cancer (NSCLC), Langerhans Cell Histiocytosis Syndrome (LCH)/ Erdheim-Chester disease (ECD), and thyroid cancer have certain effects [7][39][59]. Therefore, we prefer to focus on these cancers first and explore them separately. We monitor the efficacy endpoint using the Bayesian optimal phase 2 (BOP2) design [60] to avoid the treatment is inefficacious. Other tumor types with MAPK pathway alteration will be explored on efficacy once these tumor types find to be responsive to an efficacy signal.

The correlation of biomarker of this target and efficacy is not clear yet so we adopt adaptive design to screening for biomarker and population. See **Section 4.2**.

Clinical studies showed that the dose level identified using the "3+3" design often inaccurate, let patients receive either a sub-therapeutic or an overly toxic treatment. This results in a higher failure rate for the investigational drug in the later Phase I/II, II or III trial. To overcome this shortcoming, we used the novel Bayesian Optimal Interval design (BOIN) to search for the maximum tolerated dose of HH2710. The BOIN design is a model-assisted design where it minimizes the decision error during the dose escalation/de-escalation. Then, an isotonic regression is used to estimate the MTD that is closest to the pre-determined target toxicity rate. Several simulation studies showed

that BOIN design possesses a higher accuracy as the CRM design and at the same time, minimizes the chances of exposing patients to the sub-therapeutic and overly toxic environments. Moreover, BOIN design is more transparent and easier to implement in practice, similar to the "3+3" design.

In Phase II, the go/no-go decision is made by evaluating a set of posterior probabilities of the events of interest at each interim, which is optimized to maximize power or minimize the number of patients under the null hypothesis. The proposed design explicitly controls the type I error rate, thereby bridging the gap between Bayesian design and frequentist designs. In addition, the stopping boundary of the proposed design can be enumerated prior to the onset of the study. These features make the method design accessible to a wide range of users and regulatory agencies, and particularly easy to implement in practice. Simulation studies show that it has favorable operating characteristics with higher power and lower risk of incorrectly terminating the study than some existing designs.

2.3 Rationale for dose and regimen selection

Starting dose, dose escalation, the cohort size for dose expansion and extension are based upon accepted methodology for oncology Phase I/II study design. The 21-day dose limiting toxicities (DLT) assessment period was selected as the major toxicities leading to cessation of dose escalation in such studies (hematological, gastrointestinal, liver enzymes) are anticipated to present within this duration.

The selection of the starting dose is based on the following consideration: 1) the PK-PD relationship established in human tumor xenograft mouse models, 2) the estimated human exposure of HH2710 obtained by allometric scaling modeling of dog and rat PK parameters, 3) and the toxicology studies data in rat and dog.

The starting dose for the Phase I study of HH2710 in patients with advanced tumors were calculated in accordance with the International Conference on Harmonization (ICH S9) guidance "Nonclinical Evaluation for Anticancer Pharmaceuticals". The guidance recommends the starting dose should be based on either 1/10 of the severely toxic dose in 1/10 of animals (STD10) in rodent toxicity study or 1/6 of the HNSTD observed in non-rodent studies.

The starting dose for HH2710 in the first-in-human study was derived from 28-day GLP toxicology studies performed in rodent and non-rodent species and calculated as described by Senderowicz [61].

HH2710 safety profile was investigated in 4-week GLP toxicology studies in SD rats (15, 50 and 150/100 mg/kg/day) and Beagle dog (5, 15 and 60/30 mg/kg/day).

The rodent (SD rat) STD10 was considered to be between 50 and 100 mg/kg/day. Therefore 50 mg/kg/day has been used in this calculation. Converting this dose to a human equivalent dose (HED), and applying a 10-fold safety factor, translates to a safe starting dose of 48.6 mg/day.

The HNSTD in Beagle dog was 15 mg/kg/day. Converting this dose to a HED and applying the 6-fold safety margin, a safe starting dose of 81.15 mg/day was calculated.

In considerate of the dosing convenience, the proposed starting dose for the first Phase I/II clinical study with HH2710 in cancer patients (HH2710-G101) was 50 mg/day [62]. It is reasonable to administer twice daily (BID) that is 25mg twice daily.

The modeling was established based on 1) the results of human PK parameters predicted by HH2710 preclinical PK data, 2) the PK-PD relationship established in human tumor xenograft mouse models, 3) the estimated human exposure of HH2710 obtained by allometric scaling modeling of dog and rat PK parameters, 4) and the toxicology studies data in rat and dog.

According to the effect of HH2710 and BVD523 on the anti-tumor effect of *BRAF*-mutant COLO 205 cells in vitro and the modeling result, the concentration of HH2710 and BVD523 was inhibited by the corresponding concentration of COLO 205 cells, the relationship between PK/PD was established and the human onset effective dose was predicted to be 314mg BID. The preclinical in vivo pharmacodynamics test of HH2710 showed that the effective dose of tumor suppressive effect in nude mice was 60mg/kg BID, and the human equivalent dose (HED) was: HED = 60 mg/kg*(3/37) *60kg ≈ 292mgBID. By comprehensive consideration, the onset effective dose in human is 300mg BID.

The 28-day repeated toxicological experiments in HH2710 preclinical animals showed that species sensitivity of HH2710 is similar in Beagle dogs and rats. It is preliminarily assumed that HNSTD is a critical toxic dose with ≥2 adverse events (AE) occurred, and the metabolic characteristics in humans are similar to those in Beagle dogs and rats. The HNSTD of HH2710 in rats and Beagle dogs was determined to be 50 mg/kg/day and 15 mg/kg/day, respectively, and converted to human equivalent dose (HED), both of which were 487 mg/day. It is expected that the study drug-related ≥Grade 2 AE will begin to appear in the 487 mg/day.

According to toxicity study results and modeling analysis, HH2710 had lower toxic exposure in Beagle dogs, thus the dose of 903 mg/day in human was selected as the critical toxic dose.

The effective dose in human is 300mg twice daily (BID), the critical toxic dose is 450 mg/day or 350mg ~ 450 mg twice daily (BID). When the critical toxic dose is reaching, the safety of patients must be closely monitored. For a detailed description of all methodologies used, please refer to the Haihe HH2710 Dosing Documents.

According to the non-clinical data and the modeling results, the preliminary plan of dose escalation including different doses to determine the safety, tolerability, PK/PD of HH2710. Dosing frequency and dose level may be adjusted after Safety Monitoring Committee (SMC) discussion during the study base on available safety, PK/PD and preliminary efficacy data. To date 18-Jan, 2022, 22 patients were enrolled in the dose escalation stage of 6 dose levels as 25mg BID (n=3), 50mg BID (n=3), 100mg BID (n=4), 400mg QD (n=4), 600mg QD (n=4), and 800mg QD (n=4), 4 patients were enrolled in the 600mg QD expansion cohort. PK data from 22 enrolled patients showed HH2710 was slowly eliminated after oral administration, the accumulation of the systemic exposure of HH2710 at steady state was about 3-4 folds. The half-life ($t_{1/2}$) of HH2710 ranged from 8.42 to 10.9 hrs, suitable for once daily dosing. The HH2710 systemic exposure showed a

dose-related increase from 25mg BID to 800mg QD. No apparent dose- or time-dependence of PK was observed upon single and multiple dose administration. Based on the available PK and safety data, the sponsor decided to suspend 800mg QD escalation cohort and 600mg QD expansion cohort.

To determine the recommended phase II dose (RP2D), the sponsor plans to further evaluate the tolerability, biological activity, PK/PD, and preliminary efficacy of HH2710 at more dose levels with different dosing frequencies (QD or BID). In addition to the current QD dosing cohorts (designated as Part A), sponsor may add BID dosing cohorts in Part B based on available evidence. Part B will start from 200mg BID dose level. During the study, the Sponsor and Investigators may request that one or several dose level cohorts to be expanded to get more PK/PD and safety data, or that insert an intermediate dose between 2 adjacent planned escalation doses to be explored. Such requests will be discussed with the Investigator(s), Sponsor and Medical Monitor, and should be based on all data available at that time, including safety and clinical activity, determinations of pharmacokinetics, pharmacodynamics, and cumulative toxicity.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.5
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 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: – To evaluate efficacy of HH2710 in patients with advanced tumors with MAPK signaling pathway genetic alterations, at the recommended phase 2 dose (RP2D).	**Phase II:** – Tumor objective response rate (ORR) based on RECIST v1.1.	
Secondary		Refer to Section 10.5
Phase I: – To characterize the pharmacokinetic profiles of HH2710 and selected metabolites when administered orally in patients with advanced tumors.	**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).	

Objective	Endpoint	Analysis
Phase II – To evaluate the efficacy of HH2710 in advanced tumor patients with MAPK signaling pathway genetic alterations; – To evaluate the safety of HH2710.	**Phase II** – Efficacy: 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; – Safety: 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		Refer to Section 10.6
Phase I: – To assess the preliminary efficacy of HH2710; – To explore the changes of the pharmacodynamics (PD) markers of HH2710.	**Phase I:** – ORR, DoR, DCR, PFS and TTR; – Changes in PD markers of HH2710 efficacy including phosphorylation of RSK (pRSK) and total RSK.	

4 Study design

4.1 Description of 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. HH2710 will be administered orally on a continuous twice daily (BID) schedule, 21 days as a "Cycle"

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 100 mg twice daily (BID). It may be adjusted according to the available data. Because one subject at 25mg had adverse event grade≥2, the dose escalation process was shift to a BOIN design at 25mg dose level.

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 **Section 6.2.3**)

Part A (25/50/100 mg BID + QD dose escalation cohorts):

To date 18 Jan 2022, 22 patients were enrolled in the dose escalation stage of 6 dose levels as 25mg BID (n=3), 50mg BID (n=3), 100mg BID (n=4), 400mg QD (n=4), 600mg QD(n=4), and 800mg QD (n=4), 4 patients were enrolled in the 600mg QD expansion cohort PK data from 22 enrolled patients showed HH2710 was slowly eliminated after oral administration, the accumulation of the systemic exposure of HH2710 at steady state was about 3-4 fold. The half-life ($t_{1/2}$) of HH2710 ranged from 8.42 to 10.9 hr, suitable for once daily dosing.

Based on the safety data at 6 dose levels, HH2710 was well tolerated from 25 mg BID to 400 mg QD. However, 1 of 4 patients at 800 mg dose cohort experienced DLT (Grade 3 Acneiform rash). 3 of 26 patients developed Grade 1-2 eye toxicity, 2 patients were from the 600mg dose group,

and 1 from 800mg dose. Since the drug-related factor may have contributed, we have de-escalated to 300mg QD dose. And further dosing frequency and dose level may be adjusted based on available safety and PK data.

Part B (Additional BID dose escalation cohorts):

In order to determine the RP2D, additional BID dosing cohorts may also be evaluated based on available clinical data using BOIN design starting from 200mg BID dose and the total sample size in Part B is up to approximately 18 subjects. After the escalation is completed, select the MTD based on the isotonic regression as specified in [64]. 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:

Additional up to 15 patients per cohort may be included in order to further explore the safety, PK and anti-tumor activities among biomarker-selected patients. The dose for provisional cohort of expansion phase will be based on available safety, PK/PD and preliminary efficacy data. Patients enrolled could have different cancer 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.

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 sample size in Cohort 1 and Cohort 2 is justified according to the Bayesian optimal phase 2 (BOP2) design [60]. Specifically, let n denote the interim sample size and N denote the maximum

sample size. Let p_{eff} denote the probability of efficacy (response rate) and define the null hypothesis$H_0: p_{eff} \leq 0.05$, representing that the treatment is inefficacious. We will stop enrolling patients and claim that the treatment is not promising if

$$- \quad Pr(p_{eff} > 0.05|data) < \lambda(\frac{n}{N})^{\alpha},$$

where λ=0.75 and α=0.2 are design parameters optimized to minimize the chance of incorrectly claiming that an efficacious treatment is not promising (i.e., type II error) under the alternative hypothesis $H_1: p_{eff} = 0.16$, while controlling the type I error rate at 0.1 (i.e., the chance of incorrectly claiming that an inefficacious treatment is promising is no more than 10%). Assuming a Beta (0.05,0.95) prior distribution for p_{eff}, the above decision rule corresponds to the following stopping boundaries and yields a statistical power of 0.8201 under H_1:

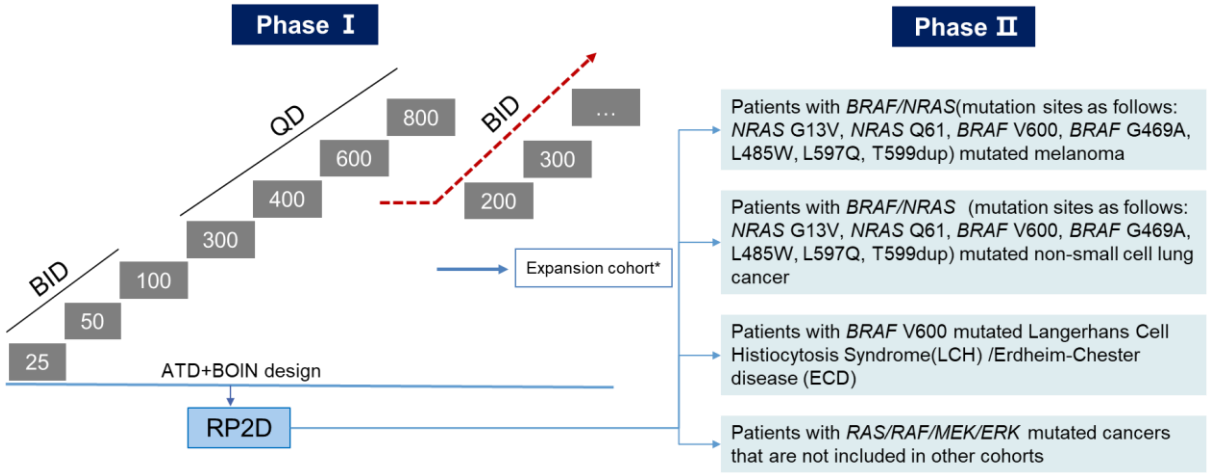
Table 4-1 Optimized stopping boundaries for cohort 1 and cohort 2 in Phase II

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

Based on Table 10-1, we will perform an interim analysis for the first 23 patients. When at least 2 patients experience CR or PR or SD(SD≥6m) 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 is greater than 3; otherwise we conclude that the treatment is not promising. An internal data review committee will use information collected from patients in the first stage to determine whether additional recruitment should be continued and if continued, whether biomarkers and/or indications need to be adjusted and whether amendment(s) to the protocol should be implemented for a better assessment of anti-tumor response.

The planned sample size for cohort 3 and cohort 4 are 9 patients and 27 patients, respectively. For detailed information on the sample size of the study, please refer to Section 10.4. of this protocol.

Figure 4-1 Study Flow Chart



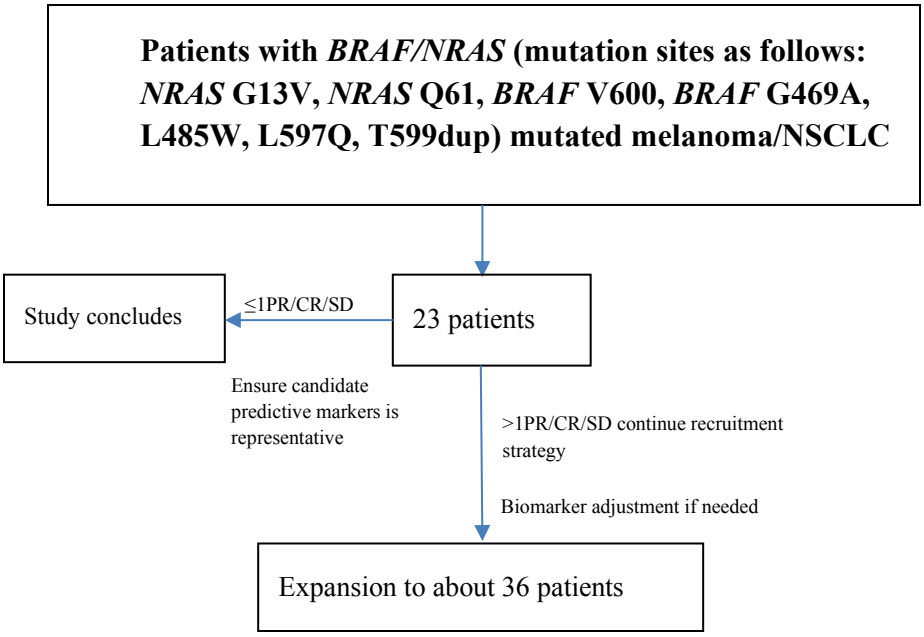
4.2 Timing of interim analyses and design adaptations

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 these patients have completed the assessment. Any additional interim analyses can be conducted as requested by the sponsor for safety and/or efficacy monitoring while the study is ongoing.

A sponsor-led data review committee will be used 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 each cohort by the committee when cohort 1 and cohort 2 have recruited and completed the assessment for the first 23 patients. For safety, the committee will review data when every 6 or 12 patients who 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. The proposed interim analysis sketch map for cohort 1 and 2 is shown below in 错误!未找到引用源。**2**.

Figure 4-2 the proposed interim analysis sketch map for cohort 1 and 2



Notes: SD≥6 months

4.3 Definition of end of the study

The study will end when the treatment period, safety follow-up, disease follow-up and survival follow-up have completed for all patients as described in **Section 7.1**.

Completion of the survival follow-up period will occur once 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, see **Section 7.1**.

The disease and survival follow-up evaluations might not be completed in case Haihe decides to stop enrollment prematurely. In such cases, end of study will be upon the Study Evaluation Completion (SEC) or the last patient treated, including the completion of the safety follow-up period.

See **Section 10.5** Statistical Methods and Data Analysis for details of timing of the primary analysis and final reporting of data.

4.4 Early study termination

The study can be terminated at any time for any reason (such as safety or efficacy) by Haihe.

Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in **Section 7.1.4.1** for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing Institutional Review Boards (IRBs) and/or ethics committees (ECs) of the early termination of the study.

5 Population

5.1 Patient population

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

Phase I

For the dose escalation stage, patients who have been diagnosed with histologically or cytologically documented, unresectable/metastatic tumors that are refractory or intolerant to standard therapy or for whom no curative standard therapy exists.

- For LCH/ECD: Eligible patients must have multifocal disease and the diagnosis must be confirmed by pathological evaluation of the affected tissue.

For the dose expansion stage, patients must have been diagnosed with histologically or cytologically documented, unresectable/metastatic tumors harboring MAPK pathway genetic alterations. Patients with a BRAF V600 mutation must have progressed on or after standard therapy, including BRAF and/or MEK inhibitors (≤3 lines). .

Phase II

Patients must have been diagnosed with histologically or cytologically documented, unresectable/metastatic tumors harboring MAPK pathway genetic alterations. Patients with a BRAF V600 mutation must have progressed on or after standard therapy, including BRAF and/or MEK inhibitors (≤3 lines). Patients will be enrolled in Cohorts 1-4 depending upon their tumor type.

In some cases, re-screening is allowed, details refer to **Section 7.1.2**.

5.2 Inclusion criteria

Patients eligible for inclusion in this study must meet all of the following criteria:

1. Provide signed and dated informed consent prior to initiation of any study-related procedures;
2. Male or female patients aged ≥ 18 years;
3. Phase I dose escalation stage: Patients who have been diagnosed with histologically or cytological documented, unresectable/metastatic tumors that are refractory or intolerant to standard therapy or for whom no curative standard therapy exists.
   - For LCH/ECD: Eligible patients must have multifocal disease and the diagnosis must be confirmed by pathological evaluation of the affected tissue.
4. For Phase I expansion stage and Phase II stage: Histologically or cytologically documented unresectable/metastatic tumors with evidence of genetic mutations affecting MAPK

pathway is required. Patients with a BRAF V600 mutation must have progressed on or after standard therapy, including BRAF and/or MEK inhibitors (≤3 lines). Patients entering the Phase 2 portion of the trial will be enrolled in Cohorts 1-4 depending upon their tumor types.

- Cohort 1: Patients with *BRAF/NRAS* (mutation sites including: *NRAS G13V, NRAS Q61, BRAF V600, BRAF* G469A, L485W, L597Q, T599dup) mutated melanoma;
- Cohort 2: Patients with *BRAF/NRAS* (mutation sites including: *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);
    - For LCH/ECD: Eligible patients must have multifocal disease and the diagnosis must be confirmed by pathological evaluation of the affected tissue.
- Cohort 4: Patients with *RAS/RAF/MEK/ERK* mutated tumor types that are not included in other cohorts.

5. Patients in the Phase I dose escalation portion of the trial may have measurable (per RECIST v1.1) or evaluable disease. Patients in the Phase I dose expansion and Phase II portions of the trial must have measurable disease per RECIST v1.1.
6. Eastern Cooperative Oncology Group (ECOG) performance status≤1.
7. Predicted life expectancy ≥ 3 months;
8. Adequate renal function defined as a creatinine clearance ≥ 60mL/min (using Cockcroft-Gault formula, see **Appendix 14.3**)];
9. Adequate hepatic function [total bilirubin ≤ 1.5 x UNL; AST (aspartate aminotransferase) and ALT (alanine aminotransferase) ≤ 3 x UNL or ≤ 5 x UNL if due to liver involvement by tumor];
10. Adequate cardiac function, > institutional lower limit of normal e.g., left ventricular ejection fraction (LVEF) of ≥ 50% as assessed by ultrasound/echocardiography (ECHO) or multi-gated acquisition (MUGA); corrected QT interval (QTcF) < 460 ms (male patients), <470ms (female patients) (using QTc Fridericia's formula. See **Appendix 14.6**);
11. Adequate bone marrow function ： patients must not have required blood transfusion or growth factor support ≤ 7 days before sample collection for the following ： ,
    - absolute neutrophil count ≥ 1.5×10^9/L;
    - hemoglobin ≥ 9g/dL;

- platelet count ≥100 × 10^9/L;
- International normalized ratio (INR) ≤ 1.5;
- activated partial prothrombin time (APTT) ≤ 1.5 × ULN;

12. Willing and able to participate in the trial and comply with all trial requirements;

5.3 Exclusion criteria

Patients eligible for this study must not meet any of the following criteria:

1. Gastrointestinal condition which could impair absorption of study medication;
2. Congenital long QT syndrome, or any known history of torsade de pointes (TdP), or family history of unexplained sudden death;
3. Clinically uncontrolled hypertension (after standard antihypertensive treatment, systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg);
4. Undergone a bone marrow or solid organ transplant;
5. Any toxicities from prior treatment that have not recovered to ≤ CTCAE Grade 1 before the start of study drug, with the exception of hair loss or fatigue;
6. Patients who have previously participated in clinical trials of ERK inhibitors drug;
7. Allergic to similar drugs or their excipients;
8. HIV(human immunodeficiency virus) infection, active hepatitis B or hepatitis C patients (HBsAg positive patients also detected HBV(hepatitis B virus) DNA ≥ 10^3 copies or ≥ 200 IU/ml; HCV (hepatitis C virus) antibody test results are positive, and HCV RNA PCR test results are positive);
9. Uncontrolled or severe intercurrent medical condition:
   - Unstable angina pectoris ≤3 months prior to starting study drug;
   - Acute myocardial infarction ≤3 months prior to starting study drug;
10. Symptomatic CNS metastases that are neurologically unstable or requiring increasing doses of steroids to control CNS disease. Note: Controlled CNS metastases are allowed. Radiotherapy or surgery for CNS metastases must have been completed >2 weeks prior to study entry. No new neurologic deficits on clinical examination and no new findings on CNS imaging are permitted. Steroid use for management of CNS metastases must be at a stable dose for two weeks preceding study entry;
11. Any cancer-directed therapy (chemotherapy, radiotherapy, hormonal therapy, biologic or immunotherapy, Chinese medicine/Chinese patent medicine with anti-tumor effect,etc.) within 28 days or 5 half-lives, whichever is shorter;

12. Major surgery within 4 weeks prior to first dose;
13. Any use of an investigational drug within 28 days or 5 half-lives (whichever is shorter) prior to the first dose of HH2710;
14. Pregnant or breast-feeding women;
15. Severe chronic or active infections requiring systemic antibacterial, antifungal or antiviral therapy, including tuberculosis infection, etc
    - Severe infections within 4 weeks prior to the first dose, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.
    - Received therapeutic oral or IV antibiotics within 2 weeks prior to the first dose of study drug
16. Any important medical illness or abnormal laboratory finding that would increase the risk of participating in this study;
17. A history or current evidence/risk of retinal vein occlusion, central serous retinopathy or choroidneovascularization (CNV).
18. Concurrent therapy with any other investigational agent;
19. Concomitant malignancies or previous malignancies with less than 2 years disease-free interval at the time of enrollment; (But basal cell carcinoma skin cancer, cervical CIS(carcinoma in situ), CIS of the breast, localized or low Gleason grade prostate cancer, and < T2 bladder cancer can be included;
20. Current treatment with agents including vitamins, supplements, and herbal supplements that are metabolized solely through CYP3A4(See **Appendix 14.7**);
21. Severe chronic obstructive pulmonary disease, severe asthma, pneumoconiosis, asbestosis and other occupational lung diseases.
22. A history of acute or chronic pancreatitis, surgery of the pancreas, or any risk factors that may increase the risk of pancreatitis;
23. Contraception (See Appendix 4 Women of child-bearing age and contraceptive measures):

    Patients who do not meet the following conditions will be excluded,

    - For women: Negative pregnancy test for females of child-bearing potential; must be surgically sterile, postmenopausal (defined as no menstrual cycle for at least 12 consecutive months), or compliant with an acceptable contraceptive regimen (2 highly effective forms, such as oral contraceptives, condom with spermicide, etc.) during and for 6 months after the treatment period. Abstinence is not considered an adequate contraceptive regimen;

- For men: Must be surgically sterile, or compliant with a contraceptive regimen (as above) during and for a minimum of 6 months after the treatment period.

6 Treatment

6.1 Study treatment

A treatment cycle is defined as 21 days for the purposes of scheduling procedures and evaluations.

The investigational product in the study is shown as below:

- Active ingredient: HH2710;
- Strength: 25 mg capsule,100 mg capsule;
- Excipients: include but not limit to Lactose, Silicified Microcrystalline Cellulose, Talc, Colloidal silicon Dioxide, Crospovidone, and Magnesium Stearate;
- Storage temperature: 10-30℃ , protected from light.

6.1.1 Dosing regimen

The dosing and treatment schedule, as shown in the below.

Table 6-1 Proposed Dose and treatment schedule of Phase I

Bayesian optimal interval (BOIN) design incorporated with an accelerated titration Schedule of HH2710				
Dose Level	Dose of HH2710	Patient	Pharmaceutical form and route of administration	Frequency and/or Regimen
Level 1	25mg	3	Capsules for oral use	QD at C1D1, then BID from C1D2 (21 days/cycle)
Level 2	50mg	3	Capsules for oral use	BID (21 days/cycle)
Level 3	100mg	3+N[#]	Capsules for oral use	BID (21 days/cycle)
Level 4	300mg	3+N[#]	Capsules for oral use	QD (21 days/cycle)
Level 5	400mg (Total daily dose*)	3+N	Capsules for oral use	QD/BID (21 days/cycle)
Level 6	600mg (Total daily dose*)	3+N	Capsules for oral use	QD/BID (21 days/cycle)

Level 7	800mg (Total daily dose*)	3+N	Capsules for oral use	QD/BID (21 days/cycle)
#: The number of pts enrolled in each dose is specified by the BOIN rules; *：Proposed daily dose is the total dose each day with QD or BID dose frequency. Dosing frequency and dose level may be adjusted on the basis of available pharmacokinetic data and safety.				

Table 6-2 Dose and treatment schedule of Phase II

Dose extension Schedule of HH2710			
Dose Level	Dose of HH2710	Pharmaceutical form and route of administration	Frequency and/or Regimen
1	RP2D	Capsules for oral use	QD or BID (21 days/cycle)

In Phase I, the first 3 patients will be administered orally (in the fasted state) HH2710 capsule once daily (QD) at the first day, then sampling for PK, from the second day, HH2710 capsule will be administered orally on a continuous twice daily (BID) schedule, on a flat scale of mg/day and not individually adjusted by weight or body surface area. The fourth and later patients will be administered with HH2710 capsule twice daily (BID) from the first day of cycle 1, patients will be instructed to take their study medication 12±2 hour interval . Based on human PK data, from the fourth dose level, the patients will be administered with HH2710 capsule once daily (QD). The Investigator must instruct the patient to take the study drug exactly as prescribed.

- Except on days of single dose PK sampling, patients should take HH2710 capsule follow the doctor's advice at approximately the same time each day starting at Cycle 1 Day 1, Patient should not eat until 2 hours after HH2710 administration.
- Each dose of HH2710 is to be taken with a glass of water (at least 8 ounces–approximately 250 mL) and consumed over as short a time as possible (i.e., Not slower than 1 capsule every 2 minutes).
- Patients should be instructed to swallow the capsules whole and not to chew them.
- Patients will be instructed to take their study medication follow the doctor's advice. The study medication should be taken with at least 8 ounces water at the same time each day in the fasted state (2 hours before food or 2 hours after food). If a dose is not taken within 2 hours of the planned dosing time, the missed dose should not be replaced.
- On days when PK blood samples are to be collected, patients will be instructed to hold their dose until arrival at the study site. HH2710 will be administered at the site in the morning. The exact time of drug administration should be recorded in the appropriate eCRF (Electronic Case Report/Record Form). The PK blood draws will be supervised by a member of the

research team. If a patient vomits within 4 hours of HH2710 dosing, the time and severity of vomiting should be recorded on the eCRF.

- Patient who is observed to vomit an intact capsule after dosing in the clinic during the PK measurements may receive a substitute dose of drug. However, patients should be instructed NOT to take a substitute capsule if vomiting occurs after self-dosing at home. Missed doses should be skipped and not taken as a double dose at the next dosing time point.
- All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the source document and/or drug account record eCRF page.

6.1.2 Treatment duration

All patients will be treated with HH2710 orally, beginning on Cycle 1 Day 1. Each cycle will have 21 days, until he/she meets the criteria for withdrawal (**Section 7.1.4.1** and **6.3**)

6.2 Dose escalation guidelines

Phase I Dose escalation stage: the Bayesian optimal interval (BOIN) design incorporated with an accelerated titration will be used to assess the safety and tolerability, and furthermore, to help find the MTD, and/or to establish the RP2D combined with data from other sources.

6.2.1 Starting dose

The selection of the starting dose is based on the following consideration: 1) the PK-PD relationship established in human tumor xenograft mouse models, 2) the estimated human exposure of HH2710 obtained by allometric scaling modeling of dog and rat PK parameters, 3) and the toxicology studies data in rat and dog.

The starting dose for the Phase I study of HH2710 in patients with advanced tumors were calculated in accordance with the International Conference on Harmonization (ICH S9) guidance "Nonclinical Evaluation for Anticancer Pharmaceuticals". The guidance recommends the starting dose should be based on either 1/10 of the severely toxic dose in 10% of animals (STD10) in rodent toxicity study or 1/6 of the HNSTD observed in non-rodent studies.

The starting dose for HH2710, for patients enrolled in this study, is set at 25 mg twice daily (BID), orally administered continuously. The selection of the starting dose follows the ICH S9 guidelines for choosing a starting dose for a first-in-human conducted in patients with cancer, and is shown in Table 6-1.

HH2710 safety profile was investigated in 4-week GLP toxicology studies in SD rats (15, 50 and 150/100 mg/kg/day) and Beagle dog (5, 15 and 60/30 mg/kg/day).

The rodent (SD rat) STD10 was considered to be between 50 and 100 mg/kg/day. Therefore 50 mg/kg/day has been used in this calculation. Converting this dose to a human equivalent dose (HED) and applying a 10-fold safety factor, translates to a safe starting dose of 48.6 mg/day.

The HNSTD in Beagle dog was 15 mg/kg/day. Converting this dose to a HED and applying the 6-fold safety margin, a safe starting dose of 81.15mg/day was calculated.

Consider the convenience of medication, the recommended safe starting daily dose has been adjusted to 50 mg/day in this protocol.

Table 6-3 Calculation of the MRSD for HH2710

Species	STD10 or HNSTD (mg/kg/day)	1/10 STD (rat) 1/6 HNSTD (dog)	Conversion Factor[a]	HED (mg/kg/day)	MRSD[b] (mg/day)
rat	50	5	0.162	0.81	48.6
dog	15	2.5	0.541	1.35	81.15

HED = (1/10 STD or 1/6 HNSTD) * Conversion Factor

[a] Conversion factor from 2005 FDA guidance [63]

[b] Assumes a 60 kg human

6.2.2 Provisional dose levels

Table 6-4 describes the starting dose and the dose levels that may be evaluated during this study.

Table 6-4 Provisional dose levels

Dose level	Proposed daily dose* (BID/QD)	Increment from previous dose
-1**	25 mg QD	-50%
1	25 mg (BID)	(starting dose)
2	50 mg (BID)	100%
3	100 mg (BID)	100%
4	300 mg (QD)	50%
5	400 mg (BID/QD)	33%
7	600 mg (BID/QD)	50%
8	800 mg (BID/QD)	33%

Dose level	Proposed daily dose* (BID/QD)	Increment from previous dose

*It is possible for additional and/or intermediate dose levels to be added during the course of the study. Cohorts may be added at any dose level below the MTD in order to better understand safety, PK or PD. Proposed daily dose is the total dose each day with QD or BID dose frequency.

**Dose level -1 represent treatment doses for patients requiring a dose reduction from the starting dose level.

The starting dose level rationale see **Section** 错误!未找到引用源。.

According to the non-clinical data and the modeling results, the preliminary plan of dose escalation including different doses (25mg, 50mg, and 100mg, BID;300mg QD, 400mg (BID/QD), 600mg (BID/QD), and 800mg (BID/QD))**.**

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 re-initiated to better understand the safety, tolerability and PK of HH2710 in dose escalation stage.

6.2.3 Guidelines for dose escalation and determination of (MTD/RP2D)

Phase I dose escalation stage:

The ATD + BOIN design is described as follows. Suppose the target toxicity rate for the MTD is ϕ= 0.3 and the maximum sample size is 58 including up to 40 subjects for 25/50/100 mg BID + QD dose escalation cohorts (Part A) and up to 18 subjects for the additional BID dose escalation cohorts (Part B). Part B dose escalation will be conducted separately using BOIN design. We will enroll and treat patients in cohorts of size 3. To guide dose-escalation decisions, if the observed DLT rate at the current dose is ≤ 0.236, the next cohort of patients will be treated at the next higher dose level; if it is ≥ 0.359, the next cohort of patients will be treated at the next lower dose level. For the purpose of overdose control, doses j and higher levels will be eliminated from further examination if $Pr(p_j > 0.3 \mid data) > 0.95$, where p_j is the true DLT rate of dose level j, j= 1,…,7. When the lowest dose is eliminated, stop the trial for safety. The trial design is illustrated in Figure 6-1 and described through the following three steps:

1. Perform accelerated titration as follows: treat the first patient at dose level 1. If no ≥ Grade 2 adverse event is observed, escalate the dose to the next higher level. Continue this one-patient-per-dose dose escalation process until any Grade ≥ 2 adverse event is observed or a dose level of 200 mg is reached, and then treat an additional 2 patients (at least 3 patients at that and all subsequent dose levels) at the first occurrence of a Grade 2 toxicity (i.e., the accelerated titration design should cease) or a dose level of 200 mg is reached. Hereafter, patients are treated in cohorts of size 3 as described in steps 2 and 3.
2. To assign a dose to the next cohort of patients, conduct dose escalation/de-escalation according to the rule displayed in Table 6-5. When using Table 6-5, please note the following:

a. “Eliminate” means that we eliminate the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic.

b. When we eliminate a dose, automatically de-escalate the dose to the next lower level. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.

c. If none of the actions (i.e., escalation, de-escalation or elimination) is triggered, we treat the new patients at the current dose.

d. If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new patients at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point terminate the trial for safety.

e. If the current dose is the highest dose and the rule indicates dose escalation, treat the new patients at the highest dose.

3. Repeat step 2 until the maximum sample size (i.e., 40 for Part A or 18 for Part B) is reached or stop the trial if the maximum number of patients treated at the current dose reaches (i.e., 15 for Part A or 12 for Part B).

Figure 6-1 Flowchart for study conduct using the BOIN design

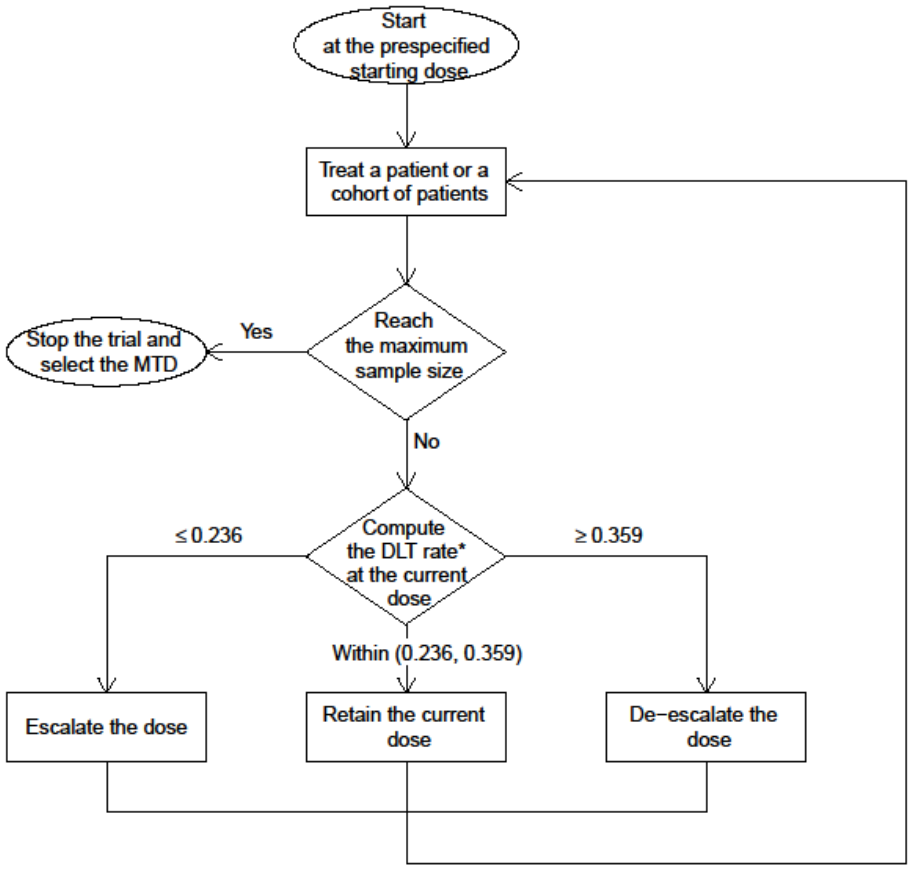


Table 6-5 Dose escalation/de-escalation rule for the BOIN Design

Number of patients treated at the current dose	3	4	5	6	7	8	9	10	11	12	13	14	15
Escalate if # of DLT <=	0	0	1	1	1	1	2	2	2	2	3	3	3
Stay if # of DLT =	1	1	NA	2	2	2	3	3	3	3/4	4	4/5	4/5
Deescalate if # of DLT >=	2	2	2	3	3	3	4	4	4	5	5	6	6
Eliminate if # of DLT >=	3	3	4	4	5	5	5	6	6	7	7	8	8

Dose expansion stage:

In order to further explore the safety, pharmacokinetics and efficacy during dose-escalation, dose expansion cohorts will be added in Phase I stage of the study. We plan to recruit up to 15 patients per cohort.

Patients with different cancer types enrolled in the dose expansion stage must have confirmation of specific MAPK pathway genetic alteration. During the study, the sponsor and investigators may request one or several dose levels and different dose regimens (QD, or BID) cohorts to further explore more PK and PD data. Such requests will be discussed with the investigator(s), sponsor and medical monitor(s), and should be based on all data available at that time, including safety and clinical activity, determinations of pharmacokinetics, pharmacodynamics, and cumulative toxicity. There are no specific stopping criteria for this part of the study, however, emerging data from the expansion phase will be monitored regularly by the data review committee.

MTD estimation:

After the escalation is completed, select the MTD based on the isotonic regression as specified in [64]. 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.

Biologically Effective Dose (BED)

The Biologically Effective Dose (BED) is the dose chosen by the sponsor and is based on all available preclinical data and clinical safety, efficacy, PK, and PD data.

Definition of RP2D

The RP2D is defined as the dose level chosen by the sponsor (in consultation with the investigators) for the dose extension in Phase II, based on safety, tolerability, efficacy, PK, and PD data collected during the dose escalation stage and/or phase I dose expansion of the study. RP2D maybe adjust if not suitable.

Determination of RP2D

Prior to beginning the phase II stage, there will be a comprehensive review of all safety, PK, and/or PD data from cycle 1 and subsequent cycles of phase I dose escalation and expansion to determine the risk/benefit profile of the MTD. Based on this review, the phase II stage will begin at the MTD/RP2D if the MTD is tolerated. The dose studied in phase II stage, MTD/RP2D, is defined as final recommended dose.

If the MTD is not found when the dose is increased to the maximum dose, or if the risk and benefit ratio of the MTD is not suitable for RP2D, then the Biologically Effective Dose (BED) is determined based on all available preclinical data and clinical safety, efficacy, PK and PD data. This BED was chosen as the recommended dose of Phase II recommended dose (RP2D).

6.2.3.1 Implementation of Dose Escalation Decisions

To implement dose escalation decisions, the available toxicity information (including adverse events and laboratory abnormalities that are not DLTs), and/or the available PK and PD information will all be evaluated by the investigators and Haihe clinical study personnel (including

the study physician and statistician) during a dose decision meeting by teleconference. Drug administration at the next higher dose level may not proceed until the investigator receives written confirmation from Haihe indicating that the results of the previous dose level were evaluated and that it is permissible to proceed to a higher dose level.

6.2.3.2 Dose cohort modification

Provisional dose level cohorts are listed in Table 6-4. Possible changes in dose administration according to the BOIN include but are not limited to:

- Enrollment of a new cohort to the current dose level;
- Enrollment of a new cohort to a dose below the starting dose for the study;
- Enrollment of a new cohort to an intermediate dose between the current and preceding dose;
- Enrollment of a new cohort to an intermediate dose between the current and the next planned dose;
- Termination of any further escalation of study drug.

6.2.3.3 Intra-Patient dose escalation

Intra-patient dose escalation is not permitted at any time with the first four cycles of treatment.

After the first four cycle is completed, individual patients may be considered for treatment at a dose of HH2710 higher than the dose to which they were initially assigned. In order for a patient to be treated at a higher dose of HH2710, he or she must have tolerated the lower dose for at least two cycles of therapy (i.e. he or she must not have experienced any HH2710-related toxicity CTCAE grade ≥ 2 at the lower dose originally assigned). Moreover, the new, higher dose with which the patient is to be treated must be a dose that has completed DLT evaluation and has not exceeded the maximum tolerated dose (MTD). There is no limit to the number of times a patient may have his or her dose of HH2710 increased. For any further increase after the initial intra-patient dose escalation, the following rules apply: the patient must have experienced no CTCAE grade ≥ 2, HH2710-related toxicity over at least two cycles of therapy at the lower dose, and the higher dose being considered must have been fully DLT evaluated and shown not to exceed the MTD. Consultation and agreement with Haihe must occur prior to any intra-patient dose escalation occurring. These changes must be recorded on the Dosage Administration Record eCRF. Data from the first cycle of treatment at the new dose level will not be formally included into the statistical model describing the relationship between dose and occurrence of DLT. However, this data will be incorporated into the clinical assessment of safety within a dose escalation teleconference.

6.2.4 Definitions of dose limiting toxicities (DLTs)

DLT is defined as: any toxicity meeting the specified criteria and considered at least possibly related to HH2710 (i.e., any toxicity for which a clear alternative etiology such as disease

progression has not been identified) should be considered a DLT per National Cancer Institute Common Terminology Criteria for Adverse events (NCI-CTCAE V5.0) standard, which met any of the following, NCI-CTCAE V5.0 will be used for all grading, and compliance of 80% (i.e. 17 of 21 days) in Cycle 1 is required for a patient to be included in the DLT evaluation. For the purpose of dose-escalation decisions, DLTs will be considered and included in the BOIN. The criteria for defining dose-limiting toxicities see Table 6-6.

Table 6-6 Criteria for defining dose-limiting toxicities

TOXICITY	DLT CRITERIA
Blood and lymphatic system disorders	≥ Grade 4 hematologic toxicity
	Grade 3 thrombocytopenia with bleeding or with requirement of transfusion of platelets
	Any grade febrile neutropenia
	Note: Given the high frequency of events related to underlying disease in subjects of LCH, the investigator should confirm the causality of these events before judgement of DLTs, based on severity or duration is longer than that expected with standard-of-care treatment or other clinical evidence
Cardiac disorders	Asymptomatic decrease of LVEF > 10% compared to baseline and the LVEF is below the institution's LLN b. Left ventricular systolic dysfunction CTCAE Grade ≥ 3 Other cardiac disorders CTCAE Grade ≥ 3
Vascular disorders Hypertension	Persistent hypertension CTCAE Grade ≥ 3 requiring more than one drug or more intensive therapy than previously administered.
General disorders and administration site conditions	Fatigue CTCAE Grade 3 for > 72 hours
Skin and subcutaneous tissue disorders: Rash and/or photosensitivity	Rash/photosensitivity CTCAE Grade 3 for > 72 hours despite skin toxicity treatment, photosensitivity Grade 4
Eye disorders	Any grade of retinal vein occlusion (RVO)
Gastrointestinal disorders	Diarrhea CTCAE Grade 3 > 72 hrs., despite the use of anti-diarrhea therapy; Diarrhea Grade 4
	Nausea/ vomiting CTCAE Grade 3 > 72 hrs., despite the use of anti-emetic therapy; Vomiting Grade 4

TOXICITY	DLT CRITERIA
	Pancreatitis CTCAE Grade ≥ 3
Investigations[a]	
	Blood bilirubin CTCAE Grade ≥ 3
	ALT/AST > 3 ULN and concomitant TBL > 2 ULN in the absence of evidence of biliary obstruction (i.e., significant elevation of ALP) or some other explanation of the injury (e.g., viral hepatitis, alcohol hepatitis) of any duration (i.e. Hy's law)
	AST or ALT CTCAE Grade 3 for > 72 hours AST or ALT CTCAE Grade 4
	Serum alkaline phosphatase CTCAE Grade 3
	Serum lipase and/or serum amylase (asymptomatic) CTCAE Grade 3 > 72 hours
	Serum lipase and/or serum amylase CTCAE Grade 4
	Serum creatinine CTCAE Grade ≥ 3
	Serum CK/CPK CTCAE Grade 3 for > 72 hours Serum CK/CPK CTCAE Grade 4
	Neutrophil count CTCAE Grade 3 for > 72 hours
	Neutrophil count CTCAE Grade 4
	Platelet count CTCAE Grade 3 with signs of bleeding
	Platelet count CTCAE Grade 4
	ECG QTc interval prolonged CTCAE ≥ Grade 3
	Electrolyte imbalance Grade 4; Asymptomatic electrolyte imbalance Grade 3 > 72 hours
Other hematologic & non-hematologic toxicities	Any other CTCAE Grade ≥ 3 toxicity except: Lymphocyte count decreased (lymphopenia) CTCAE Grade ≥ 3 unless clinically significant
Other clinically significant/unacceptable toxic events not listed, judged by the SMC as DLT;	

TOXICITY	DLT CRITERIA
All AEs of the specified grade and toxicity must be considered a DLT if they cannot definitively be attributed to disease progression or other extraneous cause.	
[a] For any CTCAE Grade 3 or 4 hepatic toxicity that does not resolve within 7 days to CTCAE Grade ≤ 1 (or CTCAE Grade ≤ 2 if liver infiltration with tumor present), an abdominal CT scan must be performed to assess if it is related to disease progression. CTCAE V5.0 will be used for all grading. Patients may receive supportive care (e.g. Packed red blood cells) as per local institutional guidelines. *G-CSF may be used to treat patients who have developed dose-limiting neutropenia, as per institutional guidelines, following discontinuation of HH2710 treatment. Optimal therapy for vomiting or diarrhea will be based in institutional guidelines, with consideration of the prohibited medications listed in this protocol. Grade 3 laboratory investigations other than serum creatinine, bilirubin, AST or ALT will not be considered a DLT unless they are associated with clinical manifestations and judged by the SMC.* *For the exceptions provided, the Grade 3 AEs should resolve to ≤ Grade 1 within 72 hours*	

In order to define DLT, patients should not be prophylactically prescribed antiallergic drugs support, antiemetics, antidiarrheals, or antipyretics. If a patient experiences grade 2 or greater nausea, diarrhea, vomiting, and/or skin lesion, medical intervention should occur.

The investigator must notify the Sponsor immediately of any unexpected CTCAE grade ≥ 3 adverse events or laboratory abnormalities. Prior to enrolling patients into a higher dose level, CTCAE grade ≥ 2 adverse events will be reviewed for all patients at the current dose level.

The study will set up a Safety Monitoring Committee (SMC) to oversee safety, dose escalation decisions, MTD or BED, recommended doses for Phase II, determination of RP2D, and other key research decisions. At each dose level (DL), the SMC will determine the number of patients enrolled in the next DL, the dose increase, and the frequency of the most appropriate use based on all available PK and safety data (once daily [QD] or twice daily [BID]). However, if the sponsor's opinion differs from SMC, the decision process will be described in the SMC charter. SMC members include at least the main investigator, a PK expert, a drug safety physician, and a medical monitor. The investigator will continue to monitor the safety of all patients until the end of the safety follow-up visit (SFUV).

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. The following guidelines need to be applied:

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

All dose modifications should be based on the worst preceding toxicity.

Each patient is only allowed 2 dose reductions as showed in Table 6-7.

If a patient requires a dose interruption of > 14 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study. Patients who discontinue the study for a study related adverse event or an abnormal laboratory value must be followed as described in Table 6-.

Table 6-7 Dose adjustment of HH2710

	HH2710(mg)
Dose	Starting Dose
First dose reduction	75% of the starting dose*
Second dose reduction	50% of the starting dose*

* The actual reduced dose should take into account the drug specification

Adjust reference values in the table below according to the CTCAE V5.0 used in the study.

The criteria for interruption and re-initiation of HH2710 treatment is showed in Table 6-

Table 6-8 Criteria for interruption, re-initiation of HH2710 treatment and permanently discontinuation

Recommended dose modifications for HH2710	
Worst toxicity **CTCAE Grade[a] (value)**	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing[b]**
No toxicity	Maintain dose level
Investigations (Hematologic)	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1500/mm^3)	Maintain dose level
Grade 2 (ANC < 1500 - 1000/mm^3)	Maintain dose level
Grade 3 (ANC < 1000 - 500/mm^3)	Discontinue HH2710: – If elevation lasts for ≤ 7 days: Resume treatment 1 same dose level – If elevation lasts for >7 days: Resume treatment at â 1 dose level
Grade 4 (ANC < 500/mm^3)	Discontinue dose until resolved to ≤ Grade 2, then â 1 dose level If there is no recovery to ≤ Grade 2 or there is recurrent grade 3 or 4 neutropenia, G-CSF/Neulasta may be given at physician discretion. If no recovery to ≤ Grade 2, permanently discontinue HH2710
Thrombocytopenia	
Grade 1 (PLT < LLN - 75,000/mm^3)	Maintain dose level
Grade 2 (PLT < 75,000 - 50,000/mm^3)	Maintain dose level

Recommended dose modifications for HH2710	
Worst toxicity **CTCAE Grade[a] (value)**	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing[b]**
Grade 3 (PLT < 50,000 - 25,000/mm^3)	Discontinue dose until resolved to ≤ Grade 2, then: – If resolved in ≤ 7 days, then maintain dose level – If resolved in > 7 days, then â 1 dose level If no recovery to ≤ Grade 2, permanently discontinue HH2710 Second occurrence: discontinue until toxicity resolves to ≤ Grade 2, reduce to by another dose level. 3rd occurrence permanently discontinue HH2710.
Grade 4 (PLT < 25,000/mm^3)	Discontinue dose until resolved to ≤ Grade 2, then â 1 dose level If no recovery to ≤ Grade 2, permanently discontinue HH2710 Second occurrence: discontinue until toxicity resolves to ≤ Grade 2, reduce to by another dose level. 3rd occurrence permanently discontinue HH2710.
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5℃)	Discontinue dose until resolved, then â 1 dose level
First episode	Discontinue HH2710 until afebrile and ANC > 1000. Add Filgrastim/Neulasta per physician discretion.
Second episode	Discontinue HH2710 until afebrile and ANC >1000. Add Filgrastim/ Neulasta per treating physician discretion. Restart HH2710 at dose reduced by one dose level and monitor as clinically.

Recommended dose modifications for HH2710	
Worst toxicity **CTCAE Grade[a] (value)**	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing[b]**
Third episode	Discontinue HH2710 until afebrile and ANC >1000. Add Filgrastim/ Neulasta per treating physician discretion. Restart HH2710 reduced by another dose level and monitor as clinically indicated.
Fourth episode	Permanently discontinue HH2710 and continue follow-up protocol.
Investigations (Hematologic) for LCH	Manage as per institutional standard or global guidance.
Investigations (Renal)	
Serum creatinine	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (>1.5 - 3.0 x baseline; > 1.5 - 3.0 x ULN)	Discontinue dose until resolved to ≤ Grade 1 or baseline, then maintain dose level
Grade 3 (>3.0 x baseline; > 3.0 - 6.0 x ULN)	Permanently discontinue HH2710
Grade 4 (> 6.0 x ULN)	Permanently discontinue HH2710
Investigations (Hepatic)*	
Bilirubin	
Grade 1 (>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal)	Maintain dose level

Recommended dose modifications for HH2710	
Worst toxicity **CTCAE Grade[a] (value)**	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing[b]**
Grade 2 (>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal)	Discontinue dose until resolved to ≤ Grade 1, then: – If resolved in ≤ 7 days, then maintain dose level – If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal)	Discontinue dose until resolved to ≤ Grade 1, then: – If resolved in ≤ 7 days, then ↓ 1 dose level – If resolved in > 7 days, then discontinue patient from study drug treatment
Grade 4 (>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal)	Permanently discontinue HH2710
AST or ALT	
Grade 1 (>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	Maintain dose level
Grade 2 (>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal)	Maintain dose level
Grade 3 (>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal)	Discontinue dose until resolved to ≤ Grade 1 (or ≤ Grade 2 if liver metastases present), then: – If resolved in ≤ 7 days, then maintain dose level – If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal)	Permanently discontinue HH2710

Recommended dose modifications for HH2710	
Worst toxicity **CTCAE Grade[a] (value)**	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing[b]**
ALT/AST > 3 ULN and concomitant TBL > 2 ULN in the absence of evidence of biliary obstruction (i.e., significant elevation of ALP) or some other explanation of the injury (e.g., viral hepatitis, alcohol hepatitis) of any duration (i.e. Hy's law)	Permanently discontinue HH2710
Investigation (metabolic)**	
amylase and/or lipase elevation	
Grade 1 (> ULN - 1.5 x ULN) Grade 2 (>1.5-2.0xULN; >2.0-5.0xULN and asymptomatic) Grade 3 (>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic) Grade 4 (>5.0 x ULN and with signs or symptoms)	Maintain dose level Maintain dose level Discontinue dose of until resolved to Grade ≤ 2, then: – If resolved in ≤ 7 days, then maintain dose level – If resolved in > 7 days, then ↓ 1 dose level Permanently discontinue HH2710.
Cardiac general	
Grade 1 or 2 Grade 3 Grade 4	Maintain dose level Discontinue dose until resolved to ≤ Grade 1, then â 1 dose level Discontinue dose and discontinue patient from study drug treatment

Recommended dose modifications for HH2710	
Worst toxicity **CTCAE Grade[a] (value)**	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing[b]**
Electrocardiogram QT corrected (QTc) interval prolonged	
Grade 1 or 2 Heart Failure	Maintain dose level
Grade 3 Heart Failure	Permanently discontinue HH2710 and discontinue patient from study drug treatment
Grade 4 Heart Failure	Permanently discontinue HH2710 and discontinue patient from study drug treatment
Grade 2 Ejection Fraction (EF) Decreased (resting EF: 50-40%; or 10-19% drop from baseline)	Discontinue HH2710 until ejection fraction returns to a value greater than the institutional lower limit of normal and the absolute decrease from baseline is $\leq$ 15%, then maintain dose level.
Grade 3-4 EF Decreased (resting EF 39-20%; or ≥20% drop from baseline)	Permanently discontinue HH2710
Grade 1 and 2 (QTcF 450-500ms)	Maintain dose level
Grade 3 (QTcF ≥501 ms on at least two separate ECGs)	Discontinue dose until resolved to Grade ≤ 2, then: – If resolved in ≤ 7 days, then maintain dose level – If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (QTcF ≥501 ms or >60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious)	Permanently discontinue HH2710
Eye disorders	
Retinal vein occlusion (RVO)	Permanently discontinue HH2710.

Recommended dose modifications for HH2710	
Worst toxicity **CTCAE Grade[a] (value)**	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing[b]**
Other Grade 1 or 2 eye AEs	Discontinue dose until resolved to baseline, HH2710 could be restarted after assessed by ophthalmologist and investigator, maintain dose level or one dose level reduced as clinically indicated.
≥ Grade 3 ocular/vision symptoms interfering with ADL (Activities of daily living) or requiring medical intervention	Permanently discontinue HH2710.
Vascular disorders	
Hypertension	
Grade 1 and 2 Grade 3 Grade 4	Maintain dose level Discontinue dose until resolved ≤ Grade 1, then ↓ 1 dose level Permanently discontinue HH2710
Gastrointestinal	
Pancreatitis	
Grade 2 Grade ≥ 3	Maintain dose level Permanently discontinue HH2710
Diarrhea***	
Grade 1 and 2	Maintain dose level, but initiate anti-diarrhea therapy

Recommended dose modifications for HH2710	
Worst toxicity **CTCAE Grade[a] (value)**	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing[b]**
Grade 3 Grade 4	Discontinue dose until resolved to ≤ grade 1, then ↓ 1 dose level Permanently discontinue HH2710
Skin and subcutaneous tissue disorders	
Rash/photosensitivity	
Grade 1 and 2 Grade 3, despite skin toxicity therapy Grade 4, despite skin toxicity therapy	Maintain dose level. Consider to initiate institute appropriate skin toxicity therapy (such as antihistamines, topical corticosteroids and low-dose systemic corticosteroids) Discontinue dose until resolved to Grade ≤ 1, then: – If resolved in ≤ 7 days, then↓ 1 dose level – If resolved in > 7 days, then discontinue HH2710 Permanently discontinue HH2710
General disorders and administration site conditions	
Fatigue/ Asthenia	
Grade 1 or 2 Grade 3	Maintain dose level Discontinue dose until resolved to ≤ grade 1, then: – If resolved in ≤ 7 days, then maintain dose level – If resolved in > 7 days, then ↓f resolved in
Other adverse events****	

Recommended dose modifications for HH2710	
Worst toxicity **CTCAE Grade[a] (value)**	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing[b]**
Grade 1 or 2	Maintain dose level
Grade 3	Discontinue dose until resolved to ≤ grade 1, then↓1 dose level
Grade 4	Permanently discontinue HH2710Discontinue dose for ≥ grade 3 vomiting or grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic (as per local practice)

All dose modifications should be based on the worst preceding toxicity.

[a] Common Toxicity Criteria for Adverse Events (CTCAE V5.0)

[b] If the investigator considers it to be at patient's best interest to resume therapy before the toxicity has resolved to Grade 1 or 2 mentioned above, this may be permitted on a case by case basis, following discussion with Haihe.

* Note: If Grade 3 or 4 hyper-bilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level* and continue treatment at the discretion of the investigator.

**Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥ Grade 3 of amylase and/or lipase. If asymptomatic Grade 2 elevations of lipase and/or amylase occur again at the reduced dose, patients will be discontinued permanently from study treatment.

***Note: antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea

****Note: This is a general guidance for the other AEs except the above mentioned, and it is recommended that the specialists were involved for special case, and AE must be under adequate treatment before discontinuing.

6.3.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first.

Appropriate clinical experts such as ophthalmologist, endocrinologist, dermatologist, psychiatrists etc. should be consulted as deemed necessary.

Table 6-9 outlines the follow-up evaluation recommended for toxicities of specific types and CTCAE grades.

Table 6-9 Follow-up evaluations for selected toxicities

TOXICITY	FOLLOW-UP EVALUATION
Blood and lymphatic system disorders	Test twice weekly until ≤ CTCAE grade 1, then restart treatment. Continue to test weekly until resolution to baseline or stabilization.
Investigations (hematologic) Neutropenia ≥ CTCAE grade 3 Thrombocytopenia ≥ CTCAE grade 3	Test twice weekly until ≤ CTCAE grade 1, then restart treatment. Continue to test weekly until resolution to baseline or stabilization. Perform physical exam for check on bruising in case of major thrombocytopenia.
Investigations (hepatic) Total bilirubin ≥ 2 x ULN OR AST/ALT ≥ CTCAE grade 3 (> 5 x ULN)	Test twice weekly until ≤ CTCAE grade 1, (or ≤ CTCAE grade 2 for ALT/AST if liver metastases are present) then restart treatment. Continue to test weekly until resolution to baseline or stabilization. Patients with total bilirubin > ULN (any duration) should have fractionation of bilirubin into total/direct or indirect/direct components and any additional work-up as clinically indicated by these results. Follow-up of hyperbilirubinemia should proceed as per the guidelines above, irrespective of the results of fractionation.
Investigations (metabolic) Amylase or lipase ≥ CTCAE grade 3	Test twice weekly until ≤ CTCAE grade 2, then restart treatment. Continue to test weekly until resolution to ≤ CTCAE grade 1 or stabilization. A CT scan or equivalent imaging procedure to assess the pancreas, liver, and gallbladder is recommended within 7 days of the first occurrence of any ≥

	CTCAE grade 3 result, to exclude disease progression or potential other liver disease. In patients with serum triglycerides ≥ 500 mg/dL, urine amylase also needs to be tested.
Cardiac disorders ECG abnormalities indicative of ischemic event	Monitor toxicity until resolution to grade 1 or baseline. If applicable, monitor ECGs twice weekly until normalization or stabilization.
Investigations (creatinine) creatinine≥ CTCAE grade 3	If serum creatinine ≥ CTCAE grade 3 has been demonstrated, this parameter must be repeated at least twice a week until resolution to ≤ CTCAE grade 1 or baseline, and then at least weekly until either initiation of re-treatment or until stabilization. Patients will be instructed to increase hydration until resolution to ≤ CTCAE grade 1 or baseline.
Ophthalmological disorders	Follow the advice of an ophthalmologist

6.3.3 Anticipated risks and safety concerns of the study drug

Overall, appropriate eligibility criteria and specific DLT definitions, as well as specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events, i.e., skin toxicity and diarrhea are provided in IB. Refer to preclinical toxicity and or clinical data of other MAPK drugs found in the IB.

6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications or the Procedures and Significant Non-Drug Therapies CRF.

6.4.2 Permitted concomitant therapy requiring caution and/or action

HH2710 inhibits CYP2C8, CYP2C9, CYP2C19, CYP3A4/5 (midazolam, as substrate) and CYP3A4/5 (testosterone, as substrate) *in vitro* with IC_{50s} of 4.37 μM, 4.52 μM, 8.75 μM, 8.38 μM, and 7.03 μM. The drug-drug interaction potential of HH2710 due to inhibition of CYP2C8, CYP2C9, CYP2C19 and CYP3A4/5 is low based on its clinical exposure. Caution should be taken

when substrates of CYP2C8, CYP2C9, CYP2C19 and CYP3A4/5 are combined with HH2710, in particular those with a narrow therapeutic margin.

HH2710 induces CYP2B6 and CYP3A4 at 10 μM *in vitro*. The drug-drug interaction potential of HH2710 due to induction of CYP2B6 and CYP3A4 is low based on its clinical exposure. Caution should be taken when sensitive substrates of CYP2B6 and CYP3A4 are combined with HH2710.

6.4.3 Prohibited concomitant therapy

Anticancer therapy (chemotherapy, biologic or radiation therapy, surgery or Chinese medicine/Chinese patent medicine with anti-tumor effect) other than the study treatments must not be given to patients while the patient is on the study. If such agents are required for a patient, then the patient must be discontinued from the study.

In vitro data indicate Drug HH2710 is metabolized primarily by CYP3A, therefore strong inhibitors of CYP3A4 (e.g., clarithromycin, itraconazole, ketoconazole, telithromycin, etc.) and strong CYP3A4 inducers (e.g., carbamazepine, rifampicin, St. John's wort, etc.) should be avoided. Gastric acid reducing agents and sensitive substrates of CYP2C8, CYP2C9, and CYP2C19 also should be avoided. Refer to **Appendix 14.7** for a list of prohibited medications. This list may not be comprehensive.

Current treatment with agents including vitamins, supplements, and herbal supplements that are metabolized solely through CYP3A4 should be prohibited.

In vitro data indicate HH2710 is a potential P-gp substrate. Strong P-gp inhibitor will likely increase the exposure level of HH2710. Strong P-gp inhibitor should be avoided (Refer to **Appendix 14.8**).

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the study. The Patient No. consists of the Site Number (Site No.) (As assigned by Haihe to the investigative site) with a sequential patient number suffixed to it, so that each patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Patient No. available to the investigator through the iMedidata electronic data collection (EDC) interface.

6.5.2 Treatment assignment or randomization

No randomization is needed in this study. The treatment assignment is decided by the investigator.

6.5.3 Treatment blinding

Not applicable. This is an open-label study.

6.6 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) HH2710 will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

Table 6-8 Preparation and dispensing

Study treatments	Dispensing	Preparation
HH2710	Capsules including instructions for administration are dispensed by study personnel on an outpatient basis. Patients will be provided with adequate supply of study treatment for self-administration at home until at least their next scheduled study visit.	Not applicable

6.6.1 Study drug packaging and labeling

The study medication packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the treatment arms and a [specific visit or dose/dose level]. Responsible site personnel will identify the study treatment package(s) to dispense to the patient according to the designed dosage. Site personnel will add the patient number on the label. Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug and the medication number but no information about the patient.

The packaging of study drug HH2710 is capsule in bottle.

The HH2710 capsules will be provided in an open-labeled packaging with space to enter the patient's identification number. The label will also include name/drug code and quantity of HH2710, clinical protocol number, batch number, administration instructions, storage instructions, and expiry date.

The contents of the label will be in accordance with all applicable regulatory requirements.

6.6.2 Drug supply and storage

Study drug HH2710 will be centrally supplied by Haihe. Study drug must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study drug should be stored according to the instructions specified on the drug labels and in the IB.

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study drug and packaging on a regular basis, at the end of the study or at the time of study drug discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Haihe monitor or to the Haihe address provided in the investigator folder at each site.

6.6.4 Disposal and destruction

The unused, waste or returned study drug supply can be destroyed by the third party authorized by the sponsor

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 list all the assessments and indicates with an “X”, the visits when they are performed. All data obtained from these assessments must be supported in the patient’s source documentation.

Screening evaluation must be performed ≤28 days of cycle 1 Day 1 except for the pregnancy test which is to be performed within 3 days prior to the first dose of study treatment. Laboratory and radiological assessments performed as part of standard of care prior to signing informed consent

may be used if performed within the screening time window. The time window for tumor biopsies in the Phase I/II may be longer than 28 days.

During the course of the study visits, test and/or procedures should occur on schedule whenever possible. From C2D8, a visit window of +/- 3 days is allowed (with the exception of 30 days safety follow-up visit, for which a visit window of +7 days is allowed).

There is a +/- 7 days window on, tumor response assessment and chest radiological examination after starting study drug.

In particular, full PK sampling with multiple post-dose time points on Day 1 and Day 15 of cycle 1 and other days should be performed on the specified days. (Please refer to PK sampling schedule Table 7-7-2 and 错误!未找到引用源。7-3). The first three patients should perform single dose full PK sample collecting in the first day.

The assessment type please see **Section 7.2**.

Unscheduled visit: Additional visits can be performed as appropriate and at the discretion of the investigator

Table 7-1 Visit evaluation Schedule of Assessments and Procedures

		Screening period		Study treatment period								follow up period		
Visit name	Protocol Section	0 molecular screening		Cycle 1 Day 1 through 21			Cycle 2 Day 22 through 42			Cycle 3-X 21d/cycle, visit on 1st day of every 2 cycles	End of treatment visit (EOT)/early discontinuation (Section 7.1.4)	Safety follow up	Progress Disease follow up	Survival follow-up (Section 7.1.5.2)
			1 Screening	2 Baseline	3 Tx	4 Tx	5 Tx	6 Tx	7 Tx	8 Tx	Within 7 days of the last dose	30 days after the last dose.	Once every 6 weeks after the final dose	Every 3 months, to 1 year
Visit Day			-28 to -1	1 ± 0	8 ± 1	15 ± 1	22 ± 1	29 ±3	36 ± 3	43 ±3	N/A	+ 7	±7	±7
Obtain molecular screening consent (Phase I expansion and Phase II extension)	7.1.1	X												
Informed consent	7.1.2		X											
Inclusion/exclusion criteria	5.2, 5.3		X											
Biomarker detection	7.1.1	X[1]	X											
Medical history/tumor history/tumor treatment history	7.1.2.2		X[2]	X	X	X	X	X	X	X	X			
Tumor diagnosis and severity	7.1.2.2		X											
Concomitant medication/treatment	7.1.2.2		X	X	X	X	X	X	X	X	X	X		

		Screening period		**Study treatment period**								**follow up period**		
Visit name	Protocol Section	0 molecular screening		Cycle 1 Day 1 through 21			Cycle 2 Day 22 through 42			Cycle 3-X 21d/cycle, visit on 1st day of every 2 cycles	End of treatment visit (EOT)/early discontinuation (Section 7.1.4)	Safety follow up	Progress Disease follow up	Survival follow-up (Section 7.1.5.2)
			1 Screening	2 Baseline	3 Tx	4 Tx	5 Tx	6 Tx	7 Tx	8 Tx	Within 7 days of the last dose	30 days after the last dose.	Once every 6 weeks after the final dose	Every 3 months, to 1 year
Visit Day			-28 to -1	1 ± 0	8 ± 1	15 ± 1	22 ± 1	29 ±3	36 ± 3	43 ±3	N/A	＋ 7	±7	±7
Demography	7.1.2.2		X											
Physical examination	7.2.1.1		X	X	X	X	X	X	X	X	X			
Measure height (cm)	7.2.1.3		X											
Measure weight (kg)	7.2.1.3		X	X			X			X	X			
ECOG	7.2.1.4		X	X	X	X	X	X	X	X	X			
Vital signs	7.2.1.2		X	X[6]	X	X[6]	X	X	X	X	X			
Ophthalmology exam	7.2.1.1		X	X	X	X	X			X	X			
Pregnancy test	7.2.1.5		X	X[3]			X[4]			X[4]	X[4]			
Study drug dispensed	6.6.3			X	X	X	X	X	X	X				
Study drug administration	6.1.1			X[5]	X	X	X	X	X	X				
Blood Pharmacokinetic samples (Phase I dose escalation)[9]	7.2.2.1			X		X	X			X				

		Screening period		Study treatment period								follow up period		
Visit name	Protocol Section	0 molecular screening		Cycle 1 Day 1 through 21			Cycle 2 Day 22 through 42			Cycle 3-X 21d/cycle, visit on 1st day of every 2 cycles	End of treatment visit (EOT)/early discontinuation (Section 7.1.4)	Safety follow up	Progress Disease follow up	Survival follow-up (Section 7.1.5.2)
			1 Screening	2 Baseline	3 Tx	4 Tx	5 Tx	6 Tx	7 Tx	8 Tx	Within 7 days of the last dose	30 days after the last dose.	Once every 6 weeks after the final dose	Every 3 months, to 1 year
Visit Day			-28 to -1	1 ± 0	8 ± 1	15 ± 1	22 ± 1	29 ±3	36 ± 3	43 ±3	N/A	＋ 7	±7	±7
Blood Pharmacokinetic samples (Phase I dose expansion and Phase II)[10]	7.2.2.1			X		X								
Pharmacodynamic samples (Phase I only)	7.2.3			X		X								
Tumor assessment by RECIST v1.1(CT MRI,etc)	7.2.5		X							X	X		X	
Hematology	7.2.1.5		X	X[7]	X	X	X	X	X	X	X	X		
Blood chemistry			X	X7	X	X	X	X	X	X	X	X		
Urinalysis			X	X[7]	If clinically indicated							X		
Coagulation			X	X[7]								X		
Thyroid function			X	X[8]								X		
HBV, HCV, HIV test[11]	7.2.1.5		X											

		Screening period		**Study treatment period**								**follow up period**		
Visit name	Protocol Section	0 molecular screening		Cycle 1 Day 1 through 21			Cycle 2 Day 22 through 42			Cycle 3-X 21d/cycle, visit on 1st day of every 2 cycles	End of treatment visit (EOT)/early discontinuation (Section 7.1.4)	Safety follow up	Progress Disease follow up	Survival follow-up (Section 7.1.5.2)
			1 Screening	2 Baseline	3 Tx	4 Tx	5 Tx	6 Tx	7 Tx	8 Tx	Within 7 days of the last dose	30 days after the last dose.	Once every 6 weeks after the final dose	Every 3 months, to 1 year
Visit Day			-28 to -1	1 ± 0	8 ± 1	15 ± 1	22 ± 1	29 ±3	36 ± 3	43 ±3	N/A	＋ 7	±7	±7
Electrocardiogram (ECG)	7.2.1.7		X	X	X	X	X	X	X	X	X	X		
ECHO cardiogram or MUGA	7.2.1.6		X	At the investigator's discretion if there are signs or symptoms of cardiotoxicity.								X		
Troponin	7.2.1.5		X											
Adverse events (AEs)	8		X	X	X	X	X	X	X	X	X	X		
Compliance by pill count	6.6.3				X	X	X	X	X	X	X			
Obtain unused drug	6.6.3				X	X	X	X	X	X	X			
Anti-tumor treatment information and survival	7.1.5											X	X	X
Survival	7.1.5.2													X

Table footnotes:

1. The local report of MAPK pathway gene status must be documented in the source files at the site, if enrollment eligible patient's MAPK pathway gene status has been determined by local laboratory testing. For phase Ib/II, Each enrollment eligible patient must provide adequate archival and/or freshly FFPE tumor samples, which will be used for a MAPK pathway gene status determination at a Sponsor Designated Central Laboratory.

2. Full medical history at screening, review/update of history only at subsequent visits.
3. Serum pregnancy test is mandatory at screening visit. After screening and baseline, urine pregnancy test which if positive, confirm with serum test. Whereas serum pregnancy test is required at EOT visit. Note that procedures performed during screening within 3 days prior to dosing do not need to be repeated on C1D1.
4. After screening and baseline, urine pregnancy test which if positive, confirm with serum test.
5. Study drug to be taken QD at cycle1 day 1, and study drug to be taken twice daily (BID) from second day of cycle 1 only in the first 3 patients. The fourth and later patients will be administered with HH2710 capsule twice daily (BID) from the first day of cycle 1. From the fourth dose level. The patients will be administered with HH2710 capsule once daily (QD) orBID. The investigator should instruct the patient when dispensing the drug. Vital sign exam is detected at pre-dose, and 2h, 4h, after dose in C1D1, and C1D15, and be detected pre-dose in other setting time points.
6. On C1D1 and C1D15, vital sign exam should be detected at pre-dose, 2h after dose, and 4h after dose. At other time points, the vital signs exam can be detected at pre-dose.
7. If the Screening results within 7 days before C1D1 are judged to be normal by the investigator, C1D1 may be waived.
8. If the Screening results within 28 days before C1D1 are judged to be normal by the investigator, C1D1 may be waived.
9. Dense pharmacokinetic sampling will be done in the dose escalation portion of the trial. Sparse pharmacokinetic sampling will be done every two cycles prior to Day 1 dosing in all patients in the dose escalation between Cycle 1 (not included) to Cycle 9 (including Cycle 9)(Cycle 3 Day 1, Cycle 5 Day 1, Cycle 7 Day 1 , Cycle 9 Day 1).A pre-dose sample is included in Table 7-3 for patients in the dose escalation portion of the trial.
10. Sample at pre-dose, 2h, 4h, 6h and 8h post dose will also be obtained at Cycle 1 Day 1 and Cycle 1 Day 15 for patients in the phase I dose expansion stage and Phase II portions of the trial.
11. If HCV antibody test result is positive, HCV RNA test should be conducted, and HBsAg antigen positive patients should be tested for HBV DNA level.

7.1.1 Molecular screening

For the Phase I does escalation, patients with regardless of MAPK pathway gene alteration status can participate clinical screening. If enrollment eligible patient's MAPK pathway gene status has been determined by local laboratory testing, the pre-existing test result should be submitted for documentation (applicable in all sites).

For the Phase I expansion stage, local laboratory test results of MAPK pathway gene alteration status will be used to determine the eligibility of patient participating in clinical screening procedure. Each enrollment eligible patient must provide adequate archival and/or fresh FFPE tumor samples, which will be used for a MAPK pathway gene status determination at a Sponsor Designated Central Laboratory (only applicable in China sites). The MAPK pathway gene status from local labs should be confirmed by investigator, and must be documented in the source files at the sites (applicable in all sites).

For the Phase II stage, patients with known MAPK pathway gene mutations from previous local laboratory testing can participate in clinical screening procedures. For enrolled patients with a pre-existing known MAPK pathway gene status, archival and/or fresh FFPE tumor samples must be provided for a confirmatory detection of MAPK pathway gene status by a Sponsor Designated Central Laboratory. The MAPK pathway gene status from local labs should be confirmed and recorded by investigator, and must be documented in the source files at the sites (applicable in all sites).

Alternatively, for patients without known MAPK pathway gene mutation, archival and/or fresh FFPE tumor biopsy samples must be provided for the MAPK pathway gene mutation pre-screening test by the Sponsor Designated Central Laboratory. In order to avoid false negatives in the use of tissue blocks that were archived prior to treatment failure, freshly collected or archived after a treatment failure, tissue samples can be collected from patients with previous standard treatments, chemotherapy intolerance, or patients who are clinically unsuitable for chemotherapy.

The detailed instructions for the sample collection, handling and shipping are outlined in the (HH2710-G101 Laboratory Manual).

Tumor samples (or its derivatives) may be stored for up to 10 years (or comply with local laws and regulations, whichever comes with longer time window), and may be used to develop and validate future HH2710 companion diagnostic tests and for additional exploratory work to further elucidate the mechanism of disease recurrence.

7.1.2 Screening examination

Written informed consent needs to be obtained from the patient prior to any screening procedures for main study. The patient will undergo screening procedures as part of screening visit, as indicated in the assessment schedule (

		Screening period		Study treatment period								follow up period	
ame	Protocol Section	0 molecular screening		Cycle 1 Day 1 through 21			Cycle 2 Day 22 through 42			Cycle 3-X 21d/cycle, visit on 1st day of every 2 cycles	End of treatment visit (EOT)/early discontinuation (Section 7.1.4)	Safety follow up	Progress Diseas follow up
			1 Screening	2 Baseline	3 Tx	4 Tx	5 Tx	6 Tx	7 Tx	8 Tx	Within 7 days of the last dose	30 days after the last dose.	Once every 6 weeks after the final dose
)ay			-28 to -1	1 ± 0	8 ± 1	15 ± 1	22 ± 1	29 ±3	36 ± 3	43 ±3	N/A	＋ 7	±7
olecular ent (Phase I d Phase II ion)	7.1.1	X											
consent	7.1.2		X										
xclusion ia	5.2, 5.3		X										
detection	7.1.1	X1	X										
ory/tumor treatment ry	7.1.2.2		X2	X	X	X	X	X	X	X	X		
nosis and ity	7.1.2.2		X										
nitant treatment	7.1.2.2		X	X	X	X	X	X	X	X	X	X	
raphy	7.1.2.2		X										
amination	7.2.1.1		X	X	X	X	X	X	X	X	X		
ight (cm)	7.2.1.3		X										
eight (kg)	7.2.1.3		X	X			X			X	X		
G	7.2.1.4		X	X	X	X	X	X	X	X	X		
igns	7.2.1.2		X	X6	X	X6	X	X	X	X	X		

		Screening period		Study treatment period								follow up period	
ame	Protocol Section	0 molecular screening		Cycle 1 Day 1 through 21			Cycle 2 Day 22 through 42			Cycle 3-X 21d/cycle, visit on 1st day of every 2 cycles	End of treatment visit (EOT)/early discontinuation (Section 7.1.4)	Safety follow up	Progress Disease follow up
			1 Screening	2 Baseline	3 Tx	4 Tx	5 Tx	6 Tx	7 Tx	8 Tx	Within 7 days of the last dose	30 days after the last dose.	Once every 6 weeks after the final dose
Day			-28 to -1	1 ± 0	8 ± 1	15 ± 1	22 ± 1	29 ±3	36 ± 3	43 ±3	N/A	＋ 7	±7
ogy exam	7.2.1.1		X	X	X	X	X			X	X		
cy test	7.2.1.5		X	X3			X4			X4	X4		
lispensed	6.6.3			X	X	X	X	X	X	X			
ministration	6.1.1			X5	X	X	X	X	X	X			
acokinetic ase I dose ion)[9]	7.2.2.1			X		X	X			X			
acokinetic ase I dose Phase II)[10]	7.2.2.1			X		X							
lynamic ase I only)	7.2.3			X		X							
ssment by v1.1(CT etc)	7.2.5		X							X	X		X
ology	7.2.1.5		X	X7	X	X	X	X	X	X	X	X	
emistry			X	X7	X	X	X	X	X	X	X	X	
ysis			X	X7	If clinically indicated							X	
ation			X	X7								X	
unction			X	X8								X	
HIV test11	7.2.1.5		X										
gram (ECG)	7.2.1.7		X	X	X	X	X	X	X	X	X	X	
iogram or GA	7.2.1.6		X	At the investigator's discretion if there are signs or symptoms of cardiotoxicity.								X	

		Screening period		Study treatment period								follow up period	
ame	Protocol Section	0 molecular screening		Cycle 1 Day 1 through 21			Cycle 2 Day 22 through 42			Cycle 3-X 21d/cycle, visit on 1st day of every 2 cycles	End of treatment visit (EOT)/early discontinuation (Section 7.1.4)	Safety follow up	Progress Diseas follow up
			1 Screening	2 Baseline	3 Tx	4 Tx	5 Tx	6 Tx	7 Tx	8 Tx	Within 7 days of the last dose	30 days after the last dose.	Once every 6 weeks after the final dose
)ay			-28 to -1	1 ± 0	8 ± 1	15 ± 1	22 ± 1	29 ±3	36 ± 3	43 ±3	N/A	+ 7	±7
nin	7.2.1.5		X										
nts (AEs)	8		X	X	X	X	X	X	X	X	X	X	
y pill count	6.6.3				X	X	X	X	X	X	X		
sed drug	6.6.3				X	X	X	X	X	X	X		
treatment nd survival	7.1.5											X	X
val	7.1.5.2												

), to determine if the patient is eligible for study participation. However, the results of routine tests may be useful even if they are performed prior to obtaining informed consent. The procedures must be performed with 28 days of treatment start (unless otherwise specified). If some indicators are abnormal and do not meet the inclusion/exclusion criteria, but it is possible to recover in a short time, these indicators can be redetected.

Medical History

A full medical history will include evaluation (past or present) of the following systems and/or conditions: general, head and neck, eyes, ears, nose, throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, urogenital, musculoskeletal/extremities, skin, neurological/psychiatric, endocrine/metabolic, hematological/lymphatic, allergies/drug sensitivities, past surgical procedures, substance abuse or any other diseases or disorders.

Full medical history is needed at screening, review/update of history only is performed at subsequent visits.

7.1.2.1 Information to be collected on screening failure

A patient who signed an ICF but failed to be started on treatment for any reason will be considered a screen failure. Both, patients who signed a molecular pre-screening ICF but are considered ineligible after molecular pre-screening or fail to have a result report (i.e. no tumor in sample, poor

sample quality, assay failure), as well as patients, who are found not eligible after signing the main study ICF will be considered as screening failures and data will be handled in the same manner. The screening failure reason will be entered on the Screening Phase Disposition eCRF Page.

The demographic information, informed consent, and inclusion/exclusion pages must also be completed for Screening Failure patients. No other data will be entered into the clinical database for patients who are screening failures, unless the patient experienced a Serious Adverse Event during the molecular screening and/or screening period (**Section 8.2.2** for SAE reporting details).

Physical examinations should be symptom driven after the Screening Visit. Ophthalmological examinations will be performed by an ophthalmologist at screening, at each visit of C1, day 1 of C2, then day 1 of every 2 cycles.

7.1.2.2 Patient demographics and other screening/baseline characteristics

Data to be collected will include general patient demographics, relevant medical history and current medical conditions, diagnosis and extent of tumor, details of prior anti-neoplastic treatments, prior medication, procedures, and significant non-drug therapies, Hepatitis B and C status and any other assessments that are done for the purpose of determine eligibility for inclusion in the study.

Full medical history at screening, review/update of history only at subsequent visits.

7.1.3 Treatment period

Patient may continue treatment of HH2710 until the patient experienced unacceptable toxicity, disease progression, and/or treatment is discontinued at the discretion of the investigator or by patient refusal (For details, see **Section 7.1.4**)

7.1.4 End of treatment visit including study completion and premature withdrawal

7.1.4.1 Early discontinuation of the study

Termination of treatment includes early termination of treatment (discontinuation of dose due to the reason other than disease progression) and end of treatment (due to disease progression). If the blood routine, blood biochemistry, urine test, coagulation function, 12-lead ECG, serum/urine pregnancy test (if applicable) results within 7 days before termination of treatment evaluated by the investigator are normal, these checks can be waived.

When the patient terminates the study treatment, a visit should be scheduled as soon as possible, and the time should be scheduled within 7 days of the last study of drug administration or the decision to prematurely terminate the study drug treatment, at which time all the examination listed in the end of treatment (EOT) visit are required to be evaluated. If the patient decides to withdraw from the study during a routine visit, the visit is treated as an EOT visit and the patient does not need to return to the research site to receive the visit.

The completion of the treatment end page should be completed and the date and reason for the patient to stop the study treatment should be filled out. If the patient withdraws from the study early or the patient does not return to the interview, the investigator must determine the primary reason for the patient to withdraw from the study early and record this information on the EOT eCRF page.

The end of treatment visit is not considered the end of the study.

Patients may discontinue from the study treatment for reasons that include, but are not limited to, the following:

- Radiographic disease progression per RECIST v1.1
- Pregnancy
- Any medical condition that the investigator determines may jeopardize the patient's safety, if he or she were to continue the study treatment
- Use of any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents for the treatment of cancer).
- Patient noncompliance

It is agreed that for reasonable cause, either the Investigator or the Sponsor may terminate this study, provided a written notice is submitted at a reasonable time in advance of intended termination. If discontinuation is by the investigator, notice is to be submitted to Haihe Biopharma Co., Ltd. If discontinuation is by the Sponsor, notice will be provided to each investigator.

Patients may discontinue study for reasons which include, but are not limited to, the following:

- Patient withdrawal of consent
- Death
- Lost to follow up
- Patients have completed all study assessments

7.1.4.2 Criteria for patient premature withdrawal

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. If a patient who does not meet enrollment criteria is inadvertently enrolled, that patient should be withdrawn from the study and the Sponsor or contracted CRO (Contract Research Organization) must be contacted. An exception may be granted in rare circumstances when a subject is enrolled who does not meet the inclusion/exclusion criteria of the protocol, but where there is a compelling safety reason to allow the patient to continue treatment (such as, compassion use). the Investigator must obtain documented approval from the Sponsor or Sponsor designee to allow the patient to continue in the study.

In addition, patients will be withdrawn from study drug in the following circumstances:

- The Investigator decides that the patient should be withdrawn. If this decision is made because of an intolerable AE or a clinically significant laboratory value, the study drug is to be discontinued and appropriate measures are to be taken. The contracted CRO or its designee is to be notified immediately;
- The patient is unwilling to continue in the study. Withdrawal of informed consent;
- Lack of compliance with protocol;
- The Investigator or the Sponsor, for any reason, stops the study;
- Disease progression (at the discretion of the PI);
- Patient becomes pregnant (withdrawal is required);
- Patient is lost to follow-up.

Patients who discontinue the study early will have early termination procedures performed as shown in the Schedule of Events.

Patients will also to be withdrawn at any time if the Investigator concludes that it would be in the patient's best interest for any reason. Protocol violations do not lead to patient withdrawal unless they constitute a significant risk to the patient's safety. Patients can voluntarily withdraw from the study for any reason at any time. They are to be considered withdrawn if they state an intention to withdraw, fail to return for visits, became lost to follow up for any reason.

7.1.4.3 Replacement policy

Phase I Dose escalation stage:

Patents who are withdrawn from the study will be replaced except those who withdrew because of an intolerable drug-related AE during the DLT observation period in phase I dose escalation.

Patients will not be replaced on study. However, if a subject is considered as non-evaluable enrollment of a new patient to the current cohort will be considered if there is less than the required number of evaluable patients. During the DLT observation period, patients who are withdrawn from the study will be replaced except those who withdrew because of an intolerable drug-related AE. Enrollment of new patients may be considered until at least the minimum number or at most the maximum number of evaluable patients is achieved within the cohort. Minimum and maximum numbers of evaluable patients per cohort are defined in **Section** 错误!未找到引用源。.

Phase I Expansion and Phase II stage:

During the Phase I dose expansion and Phase II stage, no replacements will be needed.

7.1.5 Follow up period

7.1.5.1 Safety follow up

All patients must have safety follow up evaluations for 30 days, after the last dose of study treatment.

- Collection of AEs/SAEs, except for AEs/SAEs that occur after starting new antitumor treatment;
- ECG, Clinical lab test (blood routine, blood biochemistry, urine tests, thyroid function, and coagulation);
- New antitumor treatment and survival condition;
- Concomitant medication/treatment;
- Tumor evaluation will be continued in patients who discontinue treatment not for progressive disease until progressive disease, withdrawal of informed consent form, loss to follow-up, death or termination of study, whichever occurs first.

Follow-up of progressive disease

Patients who discontinue study treatment without disease progression will continue to receive a 6-week tumor assessment (CT or MRI) until malignant tumor progression and/or subsequent initiation of systemic anticancer therapy (whichever is earlier).

7.1.5.2 Follow-up of survival

Telephone follow-up will be conducted every 3 months since the occurrence of progressive disease or the starting of new antitumor treatment to collect patients' information on subsequent antitumor treatment and survival condition. It was completed 1 year after disease progression or initiation of new anti-tumor therapy. If patients have started new antitumor treatment after the final dose prior to end-of-treatment visit, they will directly enter the survival visit without receiving the end-of-treatment visit.

If patients terminate treatment prior to the occurrence of progressive disease, they should take part in survival follow-up to collect patients' information on subsequent antitumor treatment and survival condition.

Patients lost to follow up should be recorded as such on the CRF. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

7.2 Assessment types

7.2.1 Safety assessments

Safety will be monitored by assessing *(Vital sign laboratory test result*, *ECG etc)* as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to **Section 8**.

7.2.1.1 Physical examination

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

Physical examinations should be symptom driven after the Screening Visit.

Ophthalmological examinations will be performed by an ophthalmologist at screening, at each visit of C1, day 1 of C2, then day 1 of every 2 cycles.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF.

7.2.1.2 Vital signs

Vital sign exam is detected at pre-dose, and 2h, 4h, after dose in C1D1, and C1D15, and be detected pre-dose in other setting time points.

Vital signs include pulse/heart rate, respiratory rate, temperature, blood pressure measurements. After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured with an appropriately sized cuff. If the result is abnormal, repeat the measurement or change the instrument measurement to confirm. The repeat sitting measurements will be made at 1-2 minute intervals. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

7.2.1.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. (Note: CRFs are designed to collect the data in the units they are measured in; e.g., height in cm or in and weight in kg).See

		Screening period		Study treatment period								follow up period	
ame	Protocol Section	0 molecular screening		Cycle 1 Day 1 through 21			Cycle 2 Day 22 through 42			Cycle 3-X 21d/cycle, visit on 1st day of every 2 cycles	End of treatment visit (EOT)/early discontinuation (Section 7.1.4)	Safety follow up	Progress Diseas follow up
			1 Screening	2 Baseline	3 Tx	4 Tx	5 Tx	6 Tx	7 Tx	8 Tx	Within 7 days of the last dose	30 days after the last dose.	Once every 6 weeks after the final dose
Day			-28 to -1	1 ± 0	8 ± 1	15 ± 1	22 ± 1	29 ±3	36 ± 3	43 ±3	N/A	＋ 7	±7
olecular ent (Phase I d Phase II ion)	7.1.1	X											
consent	7.1.2		X										
xclusion ia	5.2, 5.3		X										
detection	7.1.1	X1	X										
ory/tumor treatment ry	7.1.2.2		X2	X	X	X	X	X	X	X	X		
nosis and ity	7.1.2.2		X										
nitant treatment	7.1.2.2		X	X	X	X	X	X	X	X	X	X	
raphy	7.1.2.2		X										
amination	7.2.1.1		X	X	X	X	X	X	X	X	X		
ight (cm)	7.2.1.3		X										
eight (kg)	7.2.1.3		X	X			X			X	X		
G	7.2.1.4		X	X	X	X	X	X	X	X	X		
igns	7.2.1.2		X	X6	X	X6	X	X	X	X	X		
ogy exam	7.2.1.1		X	X	X	X	X			X	X		
cy test	7.2.1.5		X	X3			X4			X4	X4		
dispensed	6.6.3			X	X	X	X	X	X	X			
ministration	6.1.1			X5	X	X	X	X	X	X			

		Screening period		Study treatment period								follow up period	
ame	Protocol Section	0 molecular screening		Cycle 1 Day 1 through 21			Cycle 2 Day 22 through 42			Cycle 3-X 21d/cycle, visit on 1st day of every 2 cycles	End of treatment visit (EOT)/early discontinuation (Section 7.1.4)	Safety follow up	Progress Diseas follow up
			1 Screening	2 Baseline	3 Tx	4 Tx	5 Tx	6 Tx	7 Tx	8 Tx	Within 7 days of the last dose	30 days after the last dose.	Once every 6 weeks after the final dose
)ay			-28 to -1	1 ± 0	8 ± 1	15 ± 1	22 ± 1	29 ±3	36 ± 3	43 ±3	N/A	+ 7	±7
acokinetic ase I dose ion)[9]	7.2.2.1			X		X	X			X			
acokinetic ase I dose Phase II)[10]	7.2.2.1			X		X							
lynamic ase I only)	7.2.3			X		X							
ssment by v1.1(CT etc)	7.2.5		X							X	X		X
ology	7.2.1.5		X	X7	X	X	X	X	X	X	X	X	
emistry			X	X7	X	X	X	X	X	X	X	X	
ysis			X	X7	If clinically indicated							X	
ation			X	X7								X	
unction			X	X8								X	
HIV test11	7.2.1.5		X										
gram (ECG)	7.2.1.7		X	X	X	X	X	X	X	X	X	X	
iogram or GA	7.2.1.6		X	At the investigator's discretion if there are signs or symptoms of cardiotoxicity.								X	
nin	7.2.1.5		X										
nts (AEs)	8		X	X	X	X	X	X	X	X	X	X	
y pill count	6.6.3				X	X	X	X	X	X	X		
sed drug	6.6.3				X	X	X	X	X	X	X		

		Screening period		Study treatment period								follow up period	
ame	Protocol Section	0 molecular screening		Cycle 1 Day 1 through 21			Cycle 2 Day 22 through 42			Cycle 3-X 21d/cycle, visit on 1st day of every 2 cycles	End of treatment visit (EOT)/early discontinuation (Section 7.1.4)	Safety follow up	Progress Disease follow up
			1 Screening	2 Baseline	3 Tx	4 Tx	5 Tx	6 Tx	7 Tx	8 Tx	Within 7 days of the last dose	30 days after the last dose.	Once every 6 weeks after the final dose
Day			-28 to -1	1 ± 0	8 ± 1	15 ± 1	22 ± 1	29 ±3	36 ± 3	43 ±3	N/A	＋ 7	±7
treatment nd survival	7.1.5											X	X
val	7.1.5.2												

, 错误!未找到引用源。.

7.2.1.4 Eastern Cooperative Oncology Group Performance

ECOG performance scores (**Appendix 14.2**) will be assessed within 14 days prior to the first dose and subsequent visits including the SFUV.

7.2.1.5 Laboratory evaluations

Laboratory tests include blood routine, blood biochemistry, urine tests, thyroid function, and coagulation. If the results of within 7 days before C1D1 are judged to be normal by the investigator, the blood routine, blood biochemistry, urine test, and coagulation function of C1D1 may be waived; if the thyroid function test C1D1 can be provided within 28 days by the regular medical institution issued, and there is no abnormal report on the thyroid function test with normal range, the C1D1 examination can be exempted. After Cycle 2, clinical chemistry (to include calcium and inorganic phosphorus), hematology may be performed once per cycle or more frequently at the investigator's discretion.

Hematology: red blood cell count, hemoglobin, hematocrit, reticulocyte count, neutrophil, lymphocyte, eosinophil, mononuclear cell, basophil, platelet count.

Blood chemistry including LFTs and KFTs: LFTs include total protein, albumin, total and direct bilirubin, ALT, AST, gamma-glutamyl transferase, creatine phosphokinase (CK/CPK), alkaline phosphatase and lactate dehydrogenase; KFTs include blood urea nitrogen, creatinine and uric acid; other blood chemistry includes blood glucose, chloride, sodium, potassium, calcium, phosphate, amylase, and lipase, lactate dehydrogenase (LDH), CKMB (Creatine Kinase MB Isoenzyme).

Coagulation function tests: prothrombin time (PT), activated partial prothrombin time (APTT) and international normalized ratio (INR);

Serum virology: HBV, HCV, and HIV. If HCV antibody test result is positive, HCV RNA test should be conducted, and HBsAg antigen positive patients should be tested for HBV DNA level.

Thyroid: T3 [free], T4 [free], TSH

Urinalysis: gravity, protein, glucose and blood will be performed. Any significant findings on dipstick will be followed up with a microscopic evaluation where WBC and RBC sediments will also be measured.

Blood samples for hematology, blood chemistry and coagulation tests, and urine samples for urinalysis will be collected according to the schedule shown in **Table 7-1** ,**Table 7-2 and Table 7-3**.

Blood sampling for viral serology will be performed at screening for detection of HBV, HCV, and HIV according to local practice.

Pregnancy assessment: For child-bearing potential patients: Pregnancy test for pregnancy is performed on C1D1, C2D1, and every 2 cycles from Cycle 3when applicable. Serum pregnancy test is mandatory at screening visit. After screening and baseline, urine pregnancy test which if positive, confirm with serum test. Whereas serum pregnancy test is required at EOT visit. If needed, Serum HCG (β-HCG) will be examined.

Clinical laboratory tests will be reviewed for results of potential clinical significance at all time points throughout the study. The Investigator will evaluate any change in laboratory values. If the Investigator determines a laboratory abnormality to be clinically significant, it is considered a laboratory AE; however, if the abnormal laboratory value is consistent with a current diagnosis, it may be documented accordingly.

Cardiac function test: Troponin will be measured at screening. And any indication of abnormalities may result in further investigations.

7.2.1.6 Echocardiogram or MUGA (multiple gated acquisition) scan

Left ventricular ejection fraction (LVEF) should be measured at screening, at the investigator's discretion if there are signs or symptoms of cardiotoxicity during the study, and at the SFUV.

LVEF can be measured via echocardiogram or MUGA scan. A delegated qualified staff should be responsible for LVEF measurement. LVEF must be within normal range.

7.2.1.7 12-lead Electrocardiogram

A standard 12-lead ECG will take place on screening and subsequent visits. Patients should be supine for 5 minutes prior to the ECG. ECGs will be obtained prior to dosing(-60min), one hour post-dose(±20min) , three hours post-dose(±30min) , four hours post-dose(±30min) , and eight hours post-dose(±60min) on Cycle 1 Day 1 and Cycle 2 Day 1. ECG measurement timepoints will

match PK sampling timepoints, ECG measurement must be taken within 15 min before PK sampling at each time points. The timepoints may be modified when the PK data (HH2710 and selected metabolites) in humans is available.

Standard ECG parameters, including heart rate, QRS, PR, RR, QT, and the QT interval corrected for heart rate using Frederica‘s formula will be measured.

ECG trace report will be collected and archived at patient chart and study file respectively.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History CRF page. Clinically significant findings must be discussed with Haihe prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page.

7.2.2 Pharmacokinetics

7.2.2.1 Blood sample schedule

Study drug will be taken QD at cycle1 day 1 and twice daily from the second day of cycle 1 in the first 3 patients. First dose in clinic on days when PK sampling occurs i.e., Cycle 1 Day 1 and Cycle 1 Day15, remaining doses on all other days to be self-administered by patient.

In order to detect PK of a single administration, for the first 3 patients, a single administration will be given on the first day, administration twice daily from the second day. Patients will undergo serial blood sampling 2ml for PK analysis during cycle 1 on day 1 at pre-dose and 15min, 30min, 1, 2, 3, 4, 6, 8 hours post-dose, and 12 hours post-dose (if available); on day 2 at pre-dose; on cycle1 day 7 (pre-dose), cycle1 day 10 (pre-dose), day 15 at pre-dose and 15min, 30min, 1, 2, 3, 4, 6, and 8 hours post-dose, and 12 hours post dose (if available); and day 16 at pre-dose. On day 22, prior to dose administration, a final blood sample was collected for pharmacokinetic analyses. See Table 7-2, 错误!未找到引用源。3.

Serial blood samples will be collected from all patients to assess single dose and multiple dose plasma PK of HH2710 and its metabolite. PK parameters will be derived from each individual plasma concentration-time profiles. Refer to **Section 10.6.4** for list of PK parameters that will be estimated.

PK blood sample collection and handling

Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. At specified time points described in Table 7-2 and 错误!未找到引用源。3, 2 mL blood draws will be collected into tubes containing K2 EDTA and gently inverted several times to thoroughly mix the anticoagulant. Tubes will be centrifuged to separate plasma and plasma will

immediately be transferred into labeled 2 mL polypropylene screw-cap tubes. Plasma samples will be placed in a freezer in an upright position until shipment to the bioanalytical laboratory for analysis.

All sampling is relative to the ingestion of HH2710. On days and time points where blood PD samples are to be drawn, the PK sample must be drawn first. The exact collection date and time of all samples must be documented on the PK blood collection CRF pages. The date and exact time of dosing, as well as the date and actual time of blood sampling must be recorded on the CRF.

Refer to the [HH2710-G101 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK samples.

Intensive PK sampling will be done in the dose escalation portion of the trial. Additional PK sampling will be drawn every two cycles prior to Day 1 dosing in all patients in the dose escalation between Cycle 1 to Cycle 9 (e.g. Cycle 3 Day 1, Cycle 5 Day 1, Cycle 7 Day 1, Cycle 9 Day 1) (**Table 7-2**).

PK samples at pre-dose, 2h,, 4h, a 6h, 8h, and 24h post dose will also be obtained at Cycle 1 Day 1 and Cycle 1 Day 15 for patients in the Phase I dose expansion stage and Phase II portions of the trial (**Table 7-3**).

Table 7-2: PK blood sampling time for Phase I dose escalation stage

CxDx	C1D1	C1D1	C1D1	C1D1	C1D1	C1D1	C1D1	C1D1	C1D1	C1D1	C1D2	C1D7	C1D10	C1D15	C1D15
No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Time	pre-dose	15min	30min	1h	2h	3h	4h	6h	8h	12h (If available)	24h (pre-dose)	pre-dose	pre-dose	pre-dose	15min
Window (min)	-30	±5	±5	±5	±10	±10	±10	±30	±30	±60	-30	-30	-30	-30	±5
Blood Sampling	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL
CxDx	C1D15	C1D15	C1D15	C1D15	C1D15	C1D15	C1D15	C1D15	C1D16	C2D1	C3D1	C5D1	C7D1	C9D1	NA
No.	16	17	18	19	20	21	22	23	24	25	26	27	28	29	NA
Time	30min	1h	2h	3h	4h	6h	8h	12h (If available)	pre-dose	pre-dose	pre-dose	pre-dose	pre-dose	pre-dose	NA
Window(min)	±5	±5	±10	±10	±10	± 30	±30	±60	-30	-30	-30	-30	-30	-30	NA

Blood Sampling	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	NA

Table 7-3: PK blood sampling time for Phase I dose expansion stage and Phase II

CxDx	C1D1	C1D1	C1D1	C1D1	C1D1	C1D2	C1D15	C1D15	C1D15	C1D15	C1D15	C1D16
No.	1	2	3	4	5	6	7	8	9	10	11	12
Time	pre-dose	2h	4h	6h	8h	24h	pre-dose	2h	4h	6h	8h	24h
Window(min)	-30	±10	±10	±30	±30	±60	-30	±10	±10	±30	±30	±60
Blood Sampling	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2mL	2ml	2ml

7.2.2.2 Analytical method

Plasma samples were analyzed for HH2710 and metabolites using validated liquid chromatography-tandem mass spectrometry (LC/MS-MS) methods. Standard pharmacokinetic parameters were obtained using Phoenix WinNonlin 6.4 with a noncompartmental method. Relationship between dose and exposure was calculated using standard least-squares regression analysis.

7.2.3 Pharmacodynamics Biomarker Assessment

To confirm on-target and pathway inhibition by HH2710, RSK phosphorylation (pRSK/ total RSK) will be examined as a target biomarker in patient whole-blood sample pre-and post- HH2710 oral dosing in Phase I, Patients will undergo serial blood sampling for PD of HH2710 during cycle 1, and if applicable, during subsequent dosing cycles. This test will be done in sites that are capable of sample collection and processing for Pharmacodynamics.

Whole-blood sample will be collected on C1D1 and C1D15 (pre-dose, 4, and 24 hours post-dose) (time window is the same as related PK sampling time). Then peripheral blood mononuclear cells (PBMC) will be isolated and stimulated by PMA, followed by cell lysis and analyzed by ELISA for pRSK/RSK.

Biomarker sample collection information should be captured on sample collection CRF(s) and/or Central Laboratory paper requisition form(s).

Detailed instructions for the collection, handling, and shipping of samples for biomarker development are outlined in the HH2710-G101 Laboratory Manual.

7.2.4 Genetic Biomarkers Assessment

7.2.4.1 Genetic biomarker assessments in tumor samples during molecular screening

For the Phase I dose escalation, patients with regardless of MAPK pathway gene alteration status can participate clinical screening. If enrollment eligible patients' MAPK pathway gene status has been determined by local laboratory testing, the gene alteration status information from local test reports must be documented in the source files at the sites.

For Phase I dose expansion, local laboratory test results of MAPK pathway gene alteration status will be used to determine the eligibility of patient participating in clinical screening procedure. Each enrollment eligible patient must provide adequate archived and/or fresh FFPE tumor samples, which will be used for a MAPK pathway gene status determination at a Sponsor Designated Central Laboratory (only applicable in China sites). The MAPK pathway gene status from local labs should be confirmed and recorded by investigator, and must be documented in the source files at the sites (applicable in all sites).

For Phase II, patients with known MAPK pathway gene mutations from previous local laboratory testing can participate in clinical screening procedures. For enrolled patients with a pre-existing known MAPK pathway gene status, archived and/or fresh FFPE tumor samples must be provided for a confirmatory detection of MAPK pathway gene status by a Sponsor Designated Central Laboratory.

Alternatively, for patients without known MAPK pathway gene mutation, archived and/or freshly FFPE tumor biopsy samples must be provided for the MAPK pathway gene mutation pre-screening test by the Sponsor Designated Central Laboratory.

Patients must sign an informed consent form , to allow the collection of available test results of local laboratory and/or archived or fresh FFPE tumor tissue samples for the determination of the MAPK pathway gene alteration status at a Sponsor-Designated Central Laboratory .

In order to avoid false negatives in the use of tissue blocks that were archived prior to treatment failure, freshly collected or archived after a treatment failure, tissue samples can be collected from patients with previous standard treatments, chemotherapy intolerance, or patients who are clinically unsuitable for chemotherapy. The detailed instructions for the sample collection, handling and shipping are outlined in the (HH2710-G101 Laboratory Manual).

Table 7-4 Biomarker sample collection plan

Sample Type	Volume	Visit	Time point
Tumor samples			

Sample Type	Volume	Visit	Time point
Mandatory Either tumor block or a minimum of 10 slides from archival paraffin tumor tissue, or a freshformalin-fixed tumor biopsy	N/A	Phase Ib/II: before Day-28 and Day -28 –0 Requires patient's written consent on the Additional Biomarker ICF.	Anytime
Optional Fresh FFPE tumor biopsy tissue	N/A	Phase Ib/II: anytime when drug resistance occurred before Day-28 and Day -28 –0 Requires patient's written consent on the Additional Biomarker ICF.	Anytime
		Unscheduled if needed	Anytime
Blood samples			
Mandatory whole-blood samples (collection of whole-blood sample and PBMCs to measure marker "pRSK/RSK" to assess PD)	10 mL	C1D1	Pre-dose
	10 mL	C1D1	4 hours post-dose
	10 mL	C1D1	24 hours post-dose
	10 mL	C1D15	Pre-dose
	10 mL	C1D15	4 hours post-dose
	10 mL	C1D15	24 hours post-dose

7.2.5 Efficacy assessments

Screening assessments and each subsequent assessment must include computed tomography (CT) scan (with oral/IV contrast, unless contraindicated) or magnetic resonance imaging(MRI) of the chest, abdomen, and pelvis. Other known or suspected sites of disease must be included in the imaging assessment(neck, brain, ect). Each lesion that is measured at baseline must be measured by the same method (either same radiologic/nuclear method or by physical exam) throughout the study so that the comparison is consistent. Ultrasound should not be used to measure tumor lesions.

Assessments of current disease status will be obtained at Screening, Cycle 3–Day 1, and every 2 cycles thereafter, and will be obtained at EOT visit and Progression Disease follow up visit(patients without Progression Disease, approximately every 6 weeks±7 days after the last dosing times). All assessments that meet the criteria for partial response (PR) or complete response (CR) require a confirmation after approximately 6 weeks (±7 days) to determine PR or CR.

CT scans were performed per routine site protocols and assessed by site radiologists; no central read assessments were included in this analysis.

For efficacy endpoint overall survival, collect the information every 3 months by phone calls, or registered letters. Lost-to-follow up is defined as no response despite of three documented phone calls and three times registered letter being sent.

Disease relevant assessment criteria should be used according to RECIST v1.1 criteria. Refer to the appendices of the protocol for such guidance documents. See **Appendix 14.1**. Patients with LCH/ECD, FDG-PET-CT could be optionally performed at baseline and every 3 to 6 months following the initiation of treatment, and the interval between scans can be increased once disease has stabilized at investigator's discretion. Additional examination (brain MR, cardiac MRI or other examinations based on organ involvement) which are deemed as appropriate to support tumor assessment could be performed at investigator's discretion.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definition of Adverse Event（AE）

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events if they induce clinical signs or symptoms, require therapy, require changes in study medication(s) and other abnormalities are assessed by the investigator as clinical significance.

Progression of malignancy should be documented or recorded as a part of efficacy evaluation, but not be reported as an adverse event. Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression) will be reported as per usual guidelines with proper attribution regarding relatedness to the drug.

8.1.2 Adverse Events Follow up and Reporting

Monitoring of adverse event begins when the patient's signed informed consent has been obtained and continued until the subject completes the safety follow-up.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms (e.g. anemia instead of low hemoglobin). When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event. When an abnormal laboratory or test result

corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional adverse event.

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

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

8.1.3 Assessment of Adverse Events

As far as possible, each adverse event should be evaluated to determine the following:

1. The severity grade (CTCAE Grade 1-5)

   Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. If CTCAE grading does not exist for an adverse event, mild, moderate, severe, life-threatening and fatal (corresponding to Grades 1 - 5, respectively) will be used.

   - Grade 1 -Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
   - Grade 2 -Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
   - Grade 3 -Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare ADL.
   - Grade 4 -Life-threatening consequences; urgent intervention indicated.
   - Grade 5 -Death related to AE.

   Note：A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined in Section 8.2.1.

2. Its duration (Start and end dates)

3. Its relationship to the study treatment.

   Not related: There is alternative cause for the event which is better plausible to explain the event.

   Related: there is a “reasonable possibility” that the drug caused the event.

   To assess the relationship, carefully consider the following points:

   - Time interval between AE and study drug administration, including time sequence and

reasonability
- Effects of other drugs or therapeutic interventions
- Effect of study indication or co-existent medical conditions
- If AE improved after study drug discontinuation or dose reduction
- If AE re-appeared upon study drug re-administration
- Mechanism of the study drug

4. Action taken with respect to study or investigational treatment due to adverse event (no change, dose decreased, dose interrupted, withdrawn, dose increased, not applicable)
5. All adverse events should be treated appropriately, whether medication or therapy was given should be recorded on the CRF. (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1 .

8.2 Serious Adverse Event (SAE)

8.2.1 Definition of SAE

An adverse event is considered “serious” if it results in at least one of the following outcomes:

- Is fatal;
- Is life-threatening: refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe;
- Requires inpatient hospitalization or prolongation of existing hospitalization;

  Note that hospitalizations for the following reasons should not be reported as serious adverse events:

  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition;
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent;
  - Social reasons and respite care in the absence of any deterioration in the patient’s general condition;
- Results in persistent or significant disability/incapacity;
- Constitutes a congenital anomaly/birth defect;
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above;

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

8.2.2 Serious Adverse Event Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided main informed consent and until completion of the safety follow-up must be reported to Haihe Pharmacovigilance team within 24 hours upon the awareness of its occurrence.

Any SAEs experienced after the safety follow-up period should be reported to Haihe Pharmacovigilance team only if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on HaiHe Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to the study treatment, complete the SAE Report Form in English, and send the completed, signed form by e-mail within 24 hours to the Haihe Pharmacovigilance Team. For SAE causing the death, the investigator should provide the Autopsy report or related medical reports if available.

The e-mail address and contact information of HaiHe Pharmacovigilance Team, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and acknowledgement of receipt must be kept with the case report form documentation at the study site.

8.2.3 SAE Follow-up

Any follow up information to the SAEs should also be sent to Haihe Pharmacovigilance Team by using SAE Report Form stating that this is a follow-up to the previously reported SAE and reported to Haihe PV team within 24 hours in the same way as initial report. The follow-up information should include but not limit to whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation, et al.

The reported SAEs would be processed and assessed according to Haihe standard procedures by Haihe PV team. In order to assess SAE causality accurately, Haihe may require further information from the investigator in sending an urgent or a routine follow-up query. The investigator can

provide more follow-up information by replying to the query form or updating the SAE report form.

8.2.4 Serious and Unexpected Suspected Adverse Reaction

If an SAE is assessed by Haihe as unexpected according to the current version of Investigator's Brochure and there is a reasonable possibility that the Haihe study treatment cause the event, the case would fulfil the definition of 'Serious and Unexpected Suspected Adverse Reactions (SUSARs)'. All investigators involved in any study with HH2710 as investigational product, would be informed about the SUSARs cases, newly identified important safety issues or other safety documents, and relevant ethics committees/IRB would also be informed according to relevant requirements.

Haihe will submit Serious and Unexpected Suspected Adverse Reactions (SUSARs) and other safety information to the healthy authorities in accordance with national regulatory requirements in participating countries.

8.3 Reporting of Pregnancy

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Haihe within 24 hours upon investigator awareness. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Haihe Clinical Trial Pregnancy Form and reported by the investigator to the Haihe Pharmacovigilance Team. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

The consent from the female partner of male patients should be obtained before any information about the pregnancy is collected.

8.4 Emergency unblinding of treatment assignment

This study is an open label study, therefore this section is not applicable.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator's Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Steering Committee

The steering committee (SC) will be established comprising investigators participating in the study.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical study team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the Steering Committee will be defined in a Steering Committee charter.

9 Data collection and management

9.1 Data confidentiality

Information about study patients will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed patient authorization informing the patient of the following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research patient to revoke their authorization for use of their PHI.

In the event that a patient revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the patient experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

9.2 Data collection

The electronic case report form (eCRF) will be adopted for study data collection and management. Investigators shall timely, truthfully, completely record relevant data of each patient in the study. Information of all patients who has signed an informed consent shall be collected in the Case Report Form.

The sponsor or the data management party entrusted by the sponsor will provide the electronic data collection (EDC) system to study site. Relevant personnel will apply for corresponding account to login the EDC system after training. The investigator will enter the data generated in the study and follow the eCRF completion guideline. Finally, the principal investigator or personnel authorized shall sign an electronic signature for the confirmed data.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

During the study, the PK/PD and biomarker specimens were collected by each site and then sent to the central laboratory designated by Haihe. Staff of the site will input the information required by the protocol in eCRF pages, and in the specimen information form of designated CRO. And the CRA (Clinical Research Associate) will review the eCRF to confirm the information is accurate and complete. Samples and/or data will be processed centrally and the results will be sent electronically to Haihe (or a designated CRO).

9.3 Data review

The CRA will periodically monitor the source data to guarantee the consistency with that recorded in the eCRF. The medical monitors will review eCRF data from the medical perspective, and data manage personnel will check the integrity and logicality of eCRF data.

In terms of problems found during the data review, relevant personnel will create data queries to sites in the EDC system, and personnel at site will answer the queries and make necessary changes to the data. All records of data revision and relevant operations are trailed in the EDC system.

9.4 Database locking and archiving

After all study data are collected cleaned and locking conditions are reached through data review, database will be locked. Locked data will be sent to statistical analysts for analysis.

After the completion of the study, patient eCRF in PDF form shall be generated from EDC and saved on CD-ROM which will be submitted to the sponsor and each site. Study documents shall be archived and managed in accordance with the requirements addressed in GCP.

9.5 Database management and quality control

For studies using eCRFs, Haihe personnel (or designated CRO) will review the data entered by investigational staff for consistency, completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification

system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Samples and/or data will be processed centrally and the results will be sent electronically to Haihe (or a designated CRO).

10 Statistical methods and data analysis

This section describes the statistical methods and data presentations to be used in the summary and analysis of safety, tolerability, pharmacodynamics (PD), pharmacokinetics (PK), and preliminary efficacy data for the study drug. Background information is provided for the overall study design and objectives. The reader is referred to the previous sections on this protocol for details of study conduct and data collection.

Unless otherwise specified, 'Phase I' in this section is referred to as the dose-finding phase of the study, in which the BOIN design is used to assess the MTD and/or RP2D of the study drug. 'Phase II' is referred to as the extension phase where the preliminary efficacy is evaluated for each selected patient cohorts.

10.1 Study Endpoints

Study endpoints see **Section 3**.

10.2 Analysis sets

10.2.1 **All-Treated** Set

The All-treated set includes all patients who have received at least one dose of study medication. This set will be used for efficacy analysis.

10.2.2 Safety Set

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

10.2.3 Pharmacokinetic analysis set

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.

10.2.4 **Pharmacodynamics** analysis set

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.

10.3 Covariates and Subgroups

No covariates will be accounted for in Phase I (dose-finding). In Phase II (cohort extension), analyses will be stratified by tumor types and/or genetic mutations in order to evaluate the preliminary efficacy. Patient to the request of the sponsor, any further analyses could be conducted based on any additional covariates/subgroups. The details of these analyses will be described in the statistical analysis plan (SAP).

10.4 Sample Size Considerations

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 up to 15 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.

The sample size in Cohort 1 and Cohort 2 is justified according to the Bayesian optimal phase 2 (BOP2) design [60]. Specifically, let n denote the interim sample size and N denote the maximum sample size. Let p_{eff} denote the probability of efficacy (response rate) and define the null hypothesis$H_0: p_{eff} \leq 0.05$, representing that the treatment is inefficacious. We will stop enrolling patients and claim that the treatment is not promising if

$$Pr(p_{eff} > 0.05|data) < \lambda(\frac{n}{N})^{\alpha},$$

where λ=0.75 and α=0.2 are design parameters optimized to minimize the chance of incorrectly claiming that an efficacious treatment is not promising (i.e., type II error) under the alternative hypothesis $H_1: p_{eff} = 0.16$, while controlling the type I error rate at 0.1 (i.e., the chance of incorrectly claiming that an inefficacious treatment is promising is no more than 10%). Assuming a Beta (0.05,0.95) prior distribution for p_{eff}, the above decision rule corresponds to the following stopping boundaries and yields a statistical power of 0.8201 under H_1:

Table 10-1 Optimized stopping boundaries for cohort 1 and cohort 2 in Phase II

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

Based on Table 10-1, we will perform an interim analysis for the first 23 patients. When at least 2 patients experience CR or PR or SD (SD≥6 month) 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 is 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 [60].

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.

10.5 Planned Analyses

10.5.1 Interim Analyses

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 assessment in Phase II. Any additional interim analyses can be conducted as requested by the sponsor for safety/efficacy monitoring while the study is ongoing.

A sponsor-led data review committee 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 assessment 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 to the sponsor, which can include employees and study investigators.

Any outcomes of these safety and efficacy reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the Institutional Review Boards/Ethics Committees (IRBs/ECs).

10.5.2 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 for each tumor type and each genetic mutation.

10.5.3 Final Analysis

The intended purpose of the final analysis is to provide the up-to-date information on the primary/secondary endpoints after patients have completed the follow-ups as described in the

protocol. The methods used in the final analyses will be similar as those used in the primary analyses.

10.6 Planned Methods of Analysis

10.6.1 General Considerations

The analysis methods used in the study will be mainly descriptive statistics.

Unless stated otherwise, the term "descriptive statistics" refers to the number of patients (n), mean, median, standard deviation (SD), minimum (min), and maximum (max) for continuous data and frequencies and percentages for categorical data. Min and max values will be rounded to the precision of the original value, means and medians will be rounded to 1 decimal place greater than the precision of the original value, and SDs will be rounded to 2 decimal places greater than the precision of the original value. 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.

Unless otherwise noted, all data collected during the study will be included in data listings and will be sorted by study (Phase I or Phase II), patient number, and then by date/time for each patient number. For Phase I expansion and phase II, patients will additionally be sorted by tumor types and genetic mutations.

Demographic and baseline characteristic data will be summarized with descriptive statistics by treatment group and overall for each study part using the All-treated and SS populations. The variables include, but not limited to, age (years), gender, race, weight (kg), height (cm), ECOG performance status, tumor type, genetic mutation, previous chemotherapy and previous immunotherapy.

All analyses will be conducted using SAS® version 9.2 or higher.

10.6.2 Primary Efficacy Endpoint

In Phase I, there is no primary efficacy endpoints.

In Phase II, the objective response rate (ORR) will be calculated and summarized for each tumor type and genetic mutation. If possible, a 95% of confidence interval should be provided for each ORR.

10.6.3 Secondary Efficacy Endpoint(s)

In Phase I, there is no secondary efficacy endpoints.

In Phase II, Kaplan-Meier method will be used to analyze the duration of response (DoR), the progression-free survival (PFS), time to response (TTR), time to progression (TTP) and 1-year overall survival (OS) rate for each tumor type and genetic mutation. If possible, a 95% of

confidence interval should be provided for each estimate. The point estimate and its 95% exact confidence interval (Clopper Pearson) will be used for analyzing DCR.

10.6.4 Pharmacokinetic Analysis

Samples for PK analysis of HH2710 and its metabolite will be obtained from all patients enrolled in Phase I dose escalation/expansion and Phase II trial.

Below is the list of PK parameters that will be calculated after single dose (C1D1) and steady State (C1D15).

Table 10-2 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_{0-24}	Area under the plasma concentration-time curve from 0 to 24 hours post-dose, calculated by linear/log trapezoidal method
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity after dosing calculated by linear/log trapezoidal method
%AUCextrap	Area under the plasma concentration-time curve extrapolated from time t to infinity as a percentage of total AUC (%)
Lambda_z (λz)	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 apparent 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, if possible, for each dose. Refer to the PK analysis plan for additional details regarding with the PK analyses.

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

10.6.5 Pharmacodynamics Analysis

Multiple biomarkers intended to demonstrate inhibition of the molecular target, and mechanism of action will be investigated (pRSK and total pRSK) from blood. Additional biomarkers, including peripheral blood mononuclear cells (PBMCs) and/or DNA sequence analysis, may be identified and measured as appropriate. Descriptive statistics will be provided for pharmacodynamics data in a summary table and a listing will present all data or a figure.

10.6.6 Safety Endpoints

All safety summaries will be provided for the safety population.

Summaries for safety variables (physical examinations, vital signs, clinical laboratory analyses, ECGs) will be given with descriptive statistics. In addition, all safety variables will be presented in by-patient listings, sorted by site and patient identifier.

Adverse events will be coded using the MedDRA coding dictionary and the severity will be graded according to the NCI-CTCAE V5.0. A listing of all events, with seriousness, severity, relationship, sequelae and begin and end times will be provided. Narratives for any serious adverse events will be provided. Deaths, serious adverse events (SAEs), and AEs leading to discontinuation of study medication will be summarized by primary system organ class (SOC) and preferred terms, along with the by-patient listing.

An isotonic regression will be used to estimate the MTD in Phase I.

10.6.7 Handling of missing values/censoring/discontinuations

10.6.7.1 Date Values

In cases of incomplete dates (e.g., pertaining to AE, concomitant medication, medical history, etc.), the missing component(s) will be assumed as the most conservative value(s) possible. For example, if the start date has a missing day value, the first day of the month will be imputed for study day computations (i.e., treatment-emergent status, etc.). If day is missing for an end date, the last day of the month will be imputed. Similar logic will be assumed for missing month and year components.

Date imputation will only be used for computational purposes e.g., treatment-emergent status, etc. Actual data values as they appear in the original CRFs will be shown in the data listings.

10.6.7.2 Non-Date Values

Every effort will be made to obtain the protocol-required data for all study assessments that are scheduled for each scheduled visit for all patients who have been enrolled. No data imputation will be applied to missing study data except for imputing date values.

10.6.8 Censoring Rules for Duration of Response (DoR)

In general, DoR will be censored as described below:

- Patients who do not have documented tumor progression and are still on study at the time of analysis will be censored at the date of the last disease assessment documenting absence of progressive disease.
- Patients who are removed from study prior to documentation of tumor progression will be censored at the date of disease assessment documenting absence of progressive disease.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Haihe monitors, auditors, Haihe Clinical Quality Assurance representatives, designated agents of Haihe, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

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

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

documented in the patient source documents. The date when a patient's Informed Consent was actually obtained will be captured in their CRFs.

Haihe will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Haihe before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Haihe monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

Additional consent form

Sub-studies and studies with an optional Exploratory Biomarker component will have a separate consent form covering those studies. This form will be adapted for each Study based on a standard template used globally for all Studies. These informed consent forms will be submitted for ethical approval together with the Study Protocol and the main informed consent form of the Study. If a patient opts not to participate in the optional assessments, this in no way affects the patient's ability to participate in the main research study.

11.4 Discontinuation of the study

Haihe reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in **Section 4.4**

11.5 Publication of study protocol and results

Upon study completion and finalization of the study report the results of this study will be submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this study, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients. As part of participating in a Haihe-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and patient files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical study.

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the study documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Study unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Haihe. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Haihe or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel (according to the local regulation) who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Haihe or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Haihe and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the Clinical study report.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Haihe, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Haihe should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. FDA requires the notification of urgent safety measures as soon as possible, but within 15 days) but not later than 10 working days.

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14 Appendices

14.1 Appendix 1 RECIST v1.1

Statement: this appendix is internal translation material only for reference. Actual operation should be based on English version.

Interpretation

At baseline, tumour lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable lesions

Tumor lesions: must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable lesions

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10mmto <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: meningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by pharmacological exam that is not measurable by reproducible imaging techniques, and cystic lesions.

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions;
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above;
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts;
- "Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumour lesions situated in a previously irradiated area, or in an area patiented to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Specifications by methods of measurements

Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of assessment

The same method of assessment and the same technique should be used to characterize each reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and P10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung. CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next). If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumour markers: Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumour markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumour assessment for use in at least first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Tumour response evaluation

Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumour burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumour progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

Baseline documentation of target and non-target lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm×30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference of baseline diseases.

All other lesions including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’. In addition, it is possible to record multiple target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

Response Criteria

This section provides the definitions of the criteria used to determine objective tumour response for target lesions.

Evaluation of target lesions

Complete response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have short axis <10 mm.
Partial response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression)
Stable disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions:

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure': While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retro peritoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5mmshould be assigned in this circumstance as well.) This default value is derived from the 5mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement

error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5mm.

Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

The table below provides the definitions of the criteria used to determine the tumour response for the group of non-target lesions.

Evaluation of non-target lesions	
Complete response (CR):	Disappearance of all non-target lesions and normalization of tumour marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
Progressive disease (PD):	Unequivocal progression (see comments below) of existing non-target lesions. Notes: the appearance of one or more new lesions is also considered progression).

Special notes on assessment of progression of non-target disease:

The concept of progression of non-target disease requires additional explanation as follows: When the patient also has measurable disease to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. furthermore, depending on the nature of the study, the protocol requirements and confirmatory measurement standard of

results. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the best overall response.

Time point response

The table below provides evaluation for patients with target lesions and patients with non-target lesions only (no target lesion).

Time point response: patients with target (+/- non-target) lesions

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = non-evaluable.

Time point response: patients with non-target lesions only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	Not evaluated
Equivocal PD	Yes or No	PD
Any	Yes	PD

Note: 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease. Since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category

when no lesions can be measured is not advised. For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Missing assessments and non-evaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements is made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

Best overall response

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered not evaluable.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). See the following table for further information.

Best Overall Response when Confirmation of CR and PR Required

Overall response First time point	**Overall response Subsequent time point**	**Best overall response**
CR	CR	CR
CR	PR	SD, PD or PR[a]

CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

Note: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable. a: If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

14.2 Appendix 2 ECOG performance status score

Grade	Performance Status
0	Asymptomatic, fully active, able to carry on all pre-disease activities without restriction.
1	Symptomatic but completely ambulatory, restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work.
2	Symptomatic, ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours, < 50% in bed during the day.
3	Symptomatic, capable of only limited self-care, confined to bed or chair 50% or more of waking hours, but not bedbound.
4	Completely disabled, cannot carry on any self-care, bedbound.
5	Death.

References: Am. J. Clin. Oncol.:Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

14.3 Appendix 3 Cockcroft-Gault formula and calculation formula of body surface area

Serum creatinine concentration (mg/dL):

$$\text{Creatinine clearance rate of males (mL/min)} = \frac{(140-\text{Age})\times(\text{Body weight})a}{(72)\times(\text{Serum creatinine})}$$

$$\text{Creatinine clearance rate of females (mL/min)} = \frac{(0.85)(140-\text{Age})\times(\text{Body weight})a}{(72)\times(\text{Serum creatinine})}$$

Serum creatinine concentration (μmol/L):

$$\text{Creatinine clearance rate of males (mL/min)} = \frac{(140-\text{Age})\times(\text{Body weight})a}{(0.81)\times(\text{Serum creatinine})}$$

$$\text{Creatinine clearance rate of females (mL/min)} = \frac{(0.85)(140-\text{Age})\times(\text{Body weight})a}{(0.81)\times(\text{Serum creatinine})}$$

[a] The unit of age is year and that of body weight is kilogram.

14.4 Appendix 4 Women of child-bearing age and contraceptive measures

Women of child-bearing age refer to any women who have experienced menarche, not experienced surgical sterilization (hysterectomy or bilateral ovariectomy) and not yet reached menopause. Menopause refers to 12-month menostasis of women aged over 45 years in circumstance of lacking other biological or physiological causes. In addition, menopause can be confirmed only serum follicle-stimulating hormone (FSH) level in women aged below 55 years > 40 mIU/mL.

- Women receiving hormone replacement therapy (HRT) may have artificially inhibited FSH levels. Therefore, a wash-out period may be required to reach the physiological FSH level. The duration of wash-out period is associated with the functions of HRT. Wash-out duration recommended by the guideline is as follows. An investigator shall inspect serum FSH level at his or her discretion. If serum FSH level at any time of the whole wash-out period > 40 mIU/ml, the woman will be regarded as menopause:
- At least one week of using vaginal hormone products (pessulum, ointment, gel)
- At least four weeks of using transdermal products
- At least eight weeks of using products for oral administration

Patients (including sexual partners of male patients) of child-bearing potential shall take full contraceptive measures and avoid donating eggs and sperms between the date of signing an informed consent form and month 6 after the last dose. Contraceptive measures acceptable in the study include: absolutely asexual life; intrauterine device (IUDs, e.g. Copper T); cervical cap (adding spermicidal cream or gel) plus male condom; diaphragm (adding spermicidal cream or gel) plus male condom or other two or more contraceptive measures. Patients will be provided with information on relevant acceptable contraceptive measures during patients' inform consent process.

14.5 Appendix 5 New York Heart Association (NYHA) Functional Classification

I	Patients have heart disease, but no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or angina pectoris.
II	Patients have heart disease and slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in undue fatigue, palpitation, dyspnea or angina pectoris.
III	Patients have heart disease leading to marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes undue fatigue, palpitation, dyspnea or angina pectoris.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

14.6 Appendix 6 QTc Fridericia's formula

$$\mathbf{QTcF} = \frac{\mathbf{QT}}{\sqrt[3]{RR}}$$

QT refers to the interval from the start of the Q wave to the end of the T wave.

RR refers to the interval from the occurrence of QRS wave group to the occurrence of the next QRS wave.

14.7 Appendix 7 CYP3A4 inhibitor and inducer

CYP3A4 inhibitor	CYP3A4 inducer
Potent: - Protease inhibitor - Ritonavir Crizotinib - Indinavir Darunavir - Nelfinavir Delavirdine - Saquinavir Dronedarone - Danoprevir Elvitegravir - Fosamprenavir Amprenavir - Macrolides antibiotics - Clarithromycin - Telithromycin - Chloramphenicol (antibiotics) - Azole antifungals - Ketoconazole - Itraconazole - Nefazodone (antidepressant) Intermediate: - Aprepitant (antemetic) - Calcium channel blockers - Verapamil - Diltiazem - Macrolides antibiotics - Erythromycin - Azole antifungals - Fluconazole - Bergamottin (grapefruit juice) - Valerian Weak: - Fluoxetine/norfluoxetine - Cimetidine (H2-antagonist)	- Anticonvulsants, mood stabilizer - Carbamazepine - Phenytoin (anticonvulsants) - Oxcarbazepine - Barbiturate - Phenobarbital Modafinil - Butalbital Nafcillin - Bosentan Nevirapine - Enzalutamide Primidone - Etravirine Rifabutin - Fosphenytoin Semagacestat - Mephenytoin Talviraline - Methylphenobarbital Thioridazine - Mitotane Vemurafenib - St John's wort (hypericum perforatum) - Bactericide - Rifampicin - Rifabutin - Non-nucleoside reverse transcriptase inhibitor - Efavirenz - Nevirapine - Hypoglycemic agents - Pioglitazone - Troglitazone - Glucocorticoid (glucose increased, immunosuppression) - Modafinil (stimulant)

CYP3A4 inhibitor	CYP3A4 inducer
− Buprenorphine (analgesic) − Cafestol (unfiltered coffee) − Orphenadrine	

Sensitive Substrates of CYP2C8, CYP2C9, and CYP2C19

CYP2C8	CYP2C9	CYP2C19
Repaglinide	Tolbutamide, warfarin	Lansoprazole, omeprazole

14.8 Appendix 8 Examples of P-gp inhibitor

Amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil

Source: http//www.fda.gov/drug/drug-interactions-labeling