TPS7081

A phase 1 multicenter, open-label, dose-escalation and dose-expansion study to evaluate the safety, tolerability, pharmacokinetics (PK), and efficacy of HS-10382 (TERN-701) in patients (pts) with chronic myeloid leukemia (CML)

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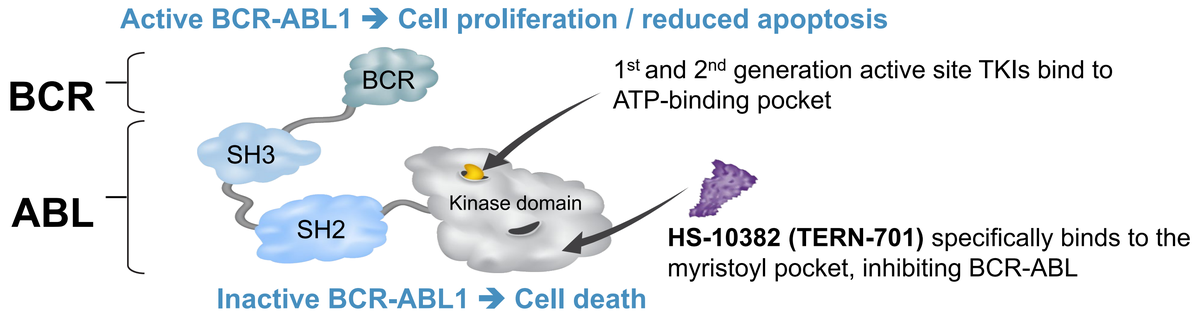
1 BACKGROUND

- Chronic myeloid leukemia (CML) is driven by the BCR-ABL1 fusion protein, formed by a translocation between chromosomes 9 and 22 that creates the Philadelphia chromosome[1]
- Tyrosine kinase inhibitors (TKIs) target the ATP binding site of ABL1 and have greatly improved the prognosis for CML, but many patients ultimately fail treatment because of resistance mutations[2-6]
- HS-10382 (TERN-701) is an allosteric TKI that specifically binds to the myristoyl pocket of ABL1 and is designed for simplified dosing and fewer drug-drug interactions compared to asciminib **(Figure 1)**[7]
- In nonclinical studies, HS-10382 (TERN-701)
  - was highly potent against wild-type BCR-ABL1 as well as the most common mutations occurring in patients treated with active site TKIs[7]
  - showed a potential for synergy with active site TKIs through stabilization of the inactive ABL1 conformation

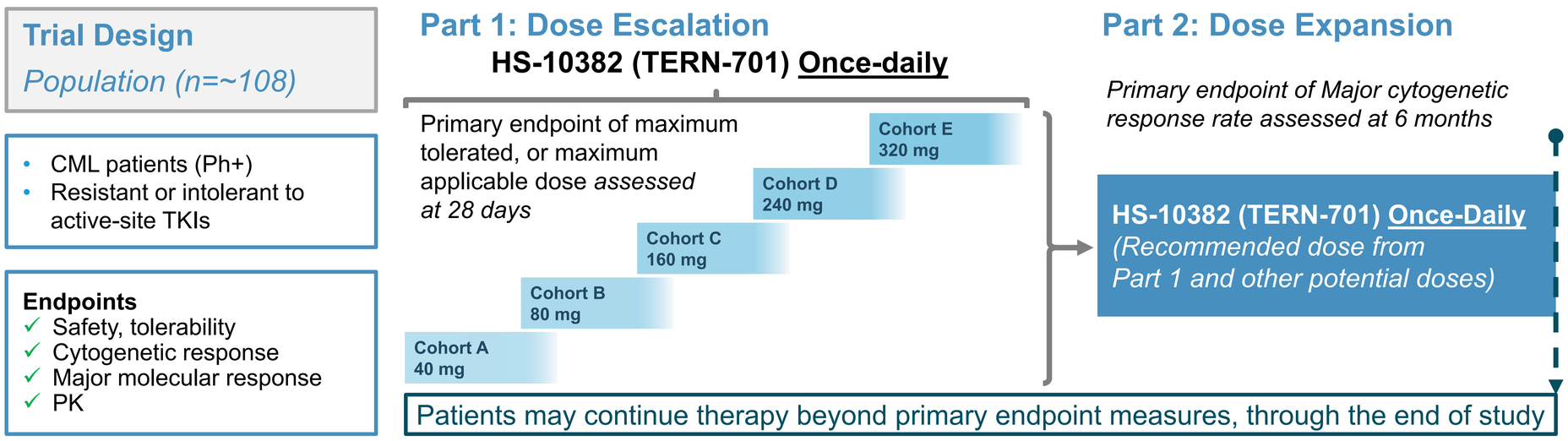
Figure 1. HS-10382 (TERN-701) allosterically binds to the myristoyl site of the BCR-ABL1 fusion protein, resulting in the inhibition of BCR-ABL1 kinase activity



2 STUDY DESIGN

- A phase 1 clinical study to evaluate the safety, tolerability, pharmacokinetics and efficacy of HS-10382 (TERN-701) in patients with chronic myeloid leukemia **(Figure 2)**
- In the dose-escalation phase, ~ 30 patients will receive HS-10382 (TERN-701) dosed once daily
  - Until the MTD is determined, successive cohorts of ~ 6 patients will receive ascending doses of HS-10382 (TERN-701)
- In the dose-expansion phase, ~ 60 patients will be enrolled across 1-3 dose cohorts of HS-10382 (TERN-701) dosed once daily
  - Patients will be treated until disease progression or unacceptable toxicity
- Study objectives are described in **Table 1**
- Key eligibility criteria are summarized in **Table 2**

Figure 2. Phase 1 dose-escalation and dose-expansion study design of HS-10382 (TERN-701) in patients with chronic myeloid leukemia



3 STUDY OBJECTIVES

Table 1

Primary Objective
Part 1 (Dose escalation): Maximum tolerated dose[a] (MTD) for HS-10382 (TERN-701)
Part 2 (Dose expansion): Major cytogenetic response[b] (MCyR) rate at 6 months
Secondary Objectives
Evaluate the safety profile of HS-10382 (TERN-701) from baseline until 28 days after last dose
Assess the pharmacokinetics profile of HS-10382 (TERN-701)
Estimate hematologic, molecular, and cytogenetic response by specific time points
Assess event-free, progression-free survival and overall survival up to 24 months

[a] Time Frame: From the single dose to the last dose of the first cycle as 28 days of multiple dosing (35days). MTD was defined as the previous dose level at which 2 out of 3 subjects or 2 out of 6 subjects experienced a DLT.

[b] Time Frame: 6 months. MCyR is the proportion of patients achieving Complete cytogenetic response (CCyR: defined as 0% Philadelphia chromosome-positive [Ph+] metaphases by cytogenetic analysis of bone marrow) and Partial Cytogenetic Response (PCyR: defined as >0% to 35% Ph+ metaphases by cytogenetic analysis of bone marrow).

4 ELIGIBILITY CRITERIA

Table 2

Key inclusion criteria	Key exclusion criteria
✓ 18 - 74 years of age	x CML-AP patients who have progressed to blast phase (BP)
✓ CML-chronic phase (CP)/advanced phase (AP) patients with the Ph chromosome or BCR-ABL1 fusion genes	x Previous treatment with a BCR-ABL1 TKI allosteric inhibitor
✓ Prior treatment with ≥2 ATP-competitive TKIs in patients without the T315I mutation or ≥1 ATP-competitive TKI in patients with the T315I mutation	x Impaired cardiac function[a]
✓ CML-CP/AP patients who are resistant to or intolerant to previous TKI therapy	x History of acute pancreatitis within one year or past medical history or chronic pancreatitis
✓ ECOG PS 0-2	x Uncontrolled hypertension/diabetes
✓ Life expectancy >12 weeks as determined by the Investigator	x Clinically severe gastrointestinal (GI) dysfunction that may significantly alter absorption of study drug
	x Inadequate bone marrow reserve or liver and kidney organ function, with unacceptable laboratory values at screening[b,c]

[a]Any one of the following: resting corrected QT interval (QTc) > 470 ms, clinically important abnormalities in rhythm, conduction, or morphology of the resting ECG, factors that increase the risk of QTc prolongation or risk of arrhythmic events, left ventricular ejection fraction (LVEF) ＜50%, Myocardial heart failure or congestive heart failure within 6 months prior to the 1st scheduled HS-10382 (TERN-701) dose, uncontrollable angina

[b]without corrective treatment within 1 week before blood collection for laboratory tests

[c]Absolute neutrophil count < 0.5 × 10^9/L; Platelet count < 50 × 10^9/L; Hemoglobin < 70 g/L; Total bilirubin > 1.5 × upper limit of normal (ULN); If any evidence of Gilbert syndrome (unconjugated hyperbilirubinemia), total bilirubin > 3.0 × ULN or direct bilirubin > 1.5 × ULN; Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 2.5 × ULN; Creatinine > 1.5 × ULN and creatinine clearance < 50 mL/min (calculated by the Cockcroft-Gault formula in Appendix F); confirmation of creatinine clearance is required only if creatinine is > 1.5 × ULN; International normalized ratio (INR) > 1.5, and activated partial thromboplastin time (APTT) > 1.5 × ULN; Serum albumin (ALB) < 28 g/L; Serum lipase or amylase > 1.5 × ULN; Alkaline phosphatase > 2.5 × ULN.

5 STATUS

- This study is currently being conducted in 7 sites in China
- Dose escalation portion (Part 1) has completed enrollment with Cohort 5 (320 mg) being fully enrolled as of April 2023
- Next step is to complete data analysis to determine whether higher dose escalation is required or to initiate the dose expansion (Part 2) with 1-3 doses of HS-10382 (TERN-701)
- Please visit ClinicalTrials.gov and search for NCT05367700 to find out the latest information on this study

ACKNOWLEDGEMENTS

This study is funded by Hansoh Pharmaceutical Group Co. Ltd, Shanghai, China. The study was approved by the institutional review board of each participating site and informed consent is obtained from all patients.

ABBREVIATIONS

TKIs, tyrosine kinase inhibitors; CML, chronic myeloid leukemia; Ph+ CML, Philadelphia chromosome–positive CML; CP, chronic phase; QD, once daily; MMR, major molecular response; AEs, adverse events; ABL, Abelson tyrosine kinase; ATP, adenosine triphosphate; BCR, breakpoint cluster region; CHR, complete hematologic response; BP, blast phase; AP, accelerated phase; ECOG, Eastern Cooperative Oncology Group; GI, gastrointestinal

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