Efficacy of HS-10382 (TERN-701) in tumor xenograft models, a new investigational allosteric ABL1 kinase inhibitor as a potential treatment for CML

Y. Zhou1, B. Parsons2, D. Sun1, Y. Li1, G. Chen1, M. Luo1, C. Jones2, X. Lian3, X. Wang3, Y. Sun3, J. R. Jasper2, H. Niu1

1 Translational Medicine Center, Shanghai Hansoh Biomedical CO., Ltd., Shanghai, China; 2 Terns Pharmaceuticals, Inc., Foster City, CA, USA; 3 Jiangsu Hansoh Pharmaceutical Group Co., Ltd., Lianyungang, Jiangsu, China

1 BACKGROUND

• Chronic Myeloid Leukemia (CML) is a myeloproliferative disorder characterized by a reciprocal translocation between chromosomes 9 and 22, leading to the loss of myristoyl-directed autoregulation and constitutive activation of the BCR-ABL1 oncoprotein.1,2

• HS-10382 (TERN-701) is a novel allosteric inhibitor of BCR-ABL1, optimized for selectivity and pharmacokinetic parameters, that binds the myristate pocket.

• TERN-701 retains activity against the BCR-ABL1T315I resistance mutation which confers resistance to all approved active site inhibitors except for ponatinib.3

2 RESULTS

TERN-701 in vitro potency and selectivity

A) Inhibition of ABL1 kinase domain activity by TERN-701 and comparator tyrosine kinase inhibitors (TKIs) in a radioactive substrate phosphorylation assay (TERN-701 IC50 = 0.4 nM). B,C,D) Anti-proliferation concentration-response curve of KCL22-s, K562, and Ba/F3T315I cells treated with TERN-701 or comparator TKIs (TERN-701 IC50 = 2.28 nM, 5.25 nM, and 15.60 nM for panels B, C, and D respectively). TERN-701 demonstrated comparable potency to the control allosteric inhibitor asciminib. Cell viability was assessed using CellTiterGlo. E) TERN-701 was also assessed at 1 µM against a panel of 375 kinases; no kinase, including wild-type ABL1, was inhibited by >50%.

TERN-701 modulation of in vivo pharmacodynamic biomarkers

BALB/c nude mice were administered a single dose of TERN-701 p.o. following implantation with KCL22-s xenografts. Tumor tissue and plasma were then collected at the specified time points post-dose to establish a PK/PD relationship. TERN-701 inhibited both BCR-ABL1 autophosphorylation and Crkl (a BCR-ABL1 target protein) phosphorylation in a time-dependent manner.

3 CONCLUSIONS

• TERN-701 demonstrated low-nanomolar potency against BCR-ABL1 in biochemical and cell-based assays in vitro and showed minimal activity against a panel of 375 kinases, underscoring its selectivity.

• TERN-701 demonstrated time-dependent pharmacodynamic modulation of BCR-ABL1 autophosphorylation and Crkl phosphorylation in vivo.

• TERN-701 is an effective and well-tolerated anti-CML agent, outperforming asciminib in the K562 and Ba/F3T315I models at equivalent dosages and dosing schedules (including once-daily dosing).

• TERN-701 is currently in a multi-center Phase 1 dose escalation/expansion trial in the greater China region.

REFERENCES

