In vitro and in vivo pharmacodynamic activity of TG-1601

**TG-1601** is a novel BET inhibitor with strong binding affinity and long-lasting effect in preclinical models.

**Background**

- BET (Bromodomain and extra-terminal) proteins bind to acetylated lysine residues on chromatin and participate in the regulation of gene transcription. Inhibition of BET protein binding to chromatin with small molecules selectively suppresses the transcription of a set of oncogenes, including MYC and BCL-2.
- **TG-1601** (also known as **CK-253**), a novel, selective and potent small molecule inhibitor of BET (bromodomain) proteins, exhibits efficacious activity against BET proteins with Kd values ranging from 0.5 nM to 9.1 nM. MYC transcription is inhibited with an EC50 of 5 nM, with GI50 comprised between 15 nM and 85 nM in a variety of leukemia and myeloma cancer cell lines, indicating potent inhibition of cell proliferation.
- Time course and dose-response studies conducted in vitro in 22 leukemia cell lines have shown that TG-1601 xenografts reported an effective BET protein binding was undetectable 3 hours following a single 25 mg/kg oral dose, with a TG-1601 tumor concentration of 5 µM achieved. Interestingly, at 24h post-dose, while TG-1601 is cleared from the tumor, MYC protein level remains below 40% of its initial level, indicating a long-lasting effect of pharmacological activity of TG-1601, potentially attributable to binding affinity compared to earlier generated molecules.
- In vivo, the long-lasting effect, efficacy studies in MV-4-11 tumor-bearing mice, dosed with a 20 mg/kg/day PO regimen interrupted by 20 mg/kg/day PO regimen, showed that drug holidays of 2, 3 and 4 days per week only modestly affected efficacy (2%, 17% and 52% TGI, respectively), suggesting discontinuous dosing of TG-1601 may not significantly impact efficacy.

**Methods**

- The objective of this study was to characterize, **in vitro**, the 72 members of the BET family.
- Discovery. The assay includes trace bromodomain concentrations (<0.1 nM), with a detection limit of 1 nM.
- Using the assay presented above, the binding affinity of TG-1601 was determined on the members of the BET family.
- Results: The growth of two normal (transformed) cell lines (Beas2B and WT9-BRD4, and BRDT, with Kd values ranging from 0.5 nM to 9.1 nM. MYC transcription. Inhibition of BET protein binding to chromatin with small BET (bromodomain and extra-terminal) proteins bind to acetylated lysine residues on chromatin and participate in the regulation of gene transcription. Inhibition of BET protein binding to chromatin with small molecules selectively suppresses the transcription of a set of oncogenes, including MYC and BCL-2.
- Objective: The objective of this study was to characterize, **in vitro**, the 72 members of the BET family.
- Results: The growth of two normal (transformed) cell lines (Beas2B and WT9-BRD4, and BRDT, with Kd values ranging from 0.5 nM to 9.1 nM. MYC transcription.
- Inhibition of BET protein binding to chromatin with small BET (bromodomain and extra-terminal) proteins bind to acetylated lysine residues on chromatin and participate in the regulation of gene transcription. Inhibition of BET protein binding to chromatin with small BET (bromodomain and extra-terminal) proteins bind to acetylated lysine residues on chromatin and participate in the regulation of gene transcription.