An Open-label Phase 2 Dose-Finding Study Comparing 3 Different Doses of Weekly TV-1106 and Daily Recombinant Human Growth Hormone (Genotropin) in Treatment-naive, Pre-Pubertal, Growth-Hormone Deficient Children

Ron G. Rosenfeld, Jan M. Wit, Oleg Malievsky, Elena Bolchova, Kurt Brown, Anat Sakov, Gaya Anschutz, Merav Bassan, and Kathleen Butler MD

1 STATs Consulting, LLC, Professor Emeritus of Pediatrics, Oregon Health and Science University Portland Oregon USA. 2 Department of Pediatrics, Leiden University Medical Center, Leiden The Netherlands. 3 State Medical University, Russia. 4 Institute of Endocrinology and Metabolism, Kiev Ukraine. 5 Clinical Development Teva Pharmaceuticals Frazer PA USA. 6 Biostatistics Teva Pharmaceuticals, Netanya Israel. 7 Biostatistics Teva Pharmaceuticals West Chester PA USA. Research and Development Teva Pharmaceuticals, Netanya Israel

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STUDY OBJECTIVES

Primary Objective - determine the safety and tolerability of 3 different weekly doses of TV-1106 and a daily dose of Genotropin in pediatric patients

Secondary Objectives - evaluate the efficacy of 3 different weekly doses of TV-1106 and a daily dose of Genotropin as demonstrated by height velocity (HV), height velocity standard deviation score (HV-SDS) and delta height standard deviation score (H-HDSS).

Exploratory Objectives - pharmacokinetics and pharmacodynamic relationships between TV-1106, IGFI, and HV in children with GHD, continued safety assessments, bone maturation, and quality of life measures.

EXCLUSION CRITERIA

All patients have been screened for IGFI, and Genotropin will be administered to patients who are IGFI deficient.

STUDY DESIGN

60 children will be randomized 1:1:1 to one of three doses of weekly TV-1106 or daily Genotropin.

Efficacy

Primary Endpoint
Height Velocity (HV) after 26 weeks (6 months) of treatment

Secondary Endpoints
1) HV at 6.25 weeks of treatment
2) HV at 26 weeks and at 52 weeks of treatment. HV-SDS will be calculated using Swiss growth reference standards.
3) Change in HV-SDS from baseline to 26 weeks and 52 weeks of treatment. HV-SDS will be calculated using the CDC 2000 growth reference standards.

Exploratory Endpoints
1) IGFI-SDS
2) TV-1106 PK concentrations at day 3 of 4, 6, 44, 65, and 91.
3) TV-1106 PK trough values on day 7 of weeks 2, 12, 26, 52, 78, and 104.
4) Bone age/chronological age ratio (BA/CA) after 52 weeks of treatment
5) HV-SDS change in H-HDSS and BACCA after 104 weeks of treatment.
6) Patient adherence
7) Number and proportion of patients in each response category for the OOL questionnaires
8) Predicted adult height by Bayley-Pinneau method.

SAFETY

1) Adverse event reports, vital signs and concomitant medication use throughout the study
2) Clinical lab tests, hormone, ACTH stimulation, fasting glucose and insulin assessments
3) IGFI-SDS and IGFI-binding protein (IGFBP-3) at all timepoints
4) Physical examinations including anthropometry, orthopaedic consultations and additional examinations if symptoms of intracranial pressure are evident
5) Electrocardiography (ECG) will be performed at screening, weeks 26, 52, and 104.
6) MRI or CT (for patients with a previously treated pituitary tumor) at screening, weeks 52 and 104.

TOLERABILITY

Number and percent of patients who discontinue early from the study for any reason or whose dose is decreased or suspended temporarily due to an AE.

Pharmacodynamics and Pharmacokinetics

1) IGFI and IGFI-SDS for 3 samples of TV-1106 and Genotropin patients will be collected at multiple timepoints throughout the study
2) Trough IGFI levels will be measured on day 7 after weekly TV-1106 at weeks 2, 12, 26, 52, and 104.
3) For Genotropin patients, peak and trough IGFI will be collected at the same time as measurements for TV-1106 patients.
4) TV-1106 pk concentrations will be measured weeks 44, 65, and 91. For trough values, day 7 after weekly TV-1106 at weeks 2, 12, 26, 52, and 104. Additional timepoints days 1 and 5 after weekly TV-1106 at weeks 26, 52, and 104.
5) Genotropin PK samples (prior to Genotropin administration) will be collected at baseline, day 7 after weekly TV-1106 at weeks 2, 26, 52, 78, and 104.
6) TV-1106 and Genotropin serum concentration will be measured using a validated ELISA method.