The Pharmacokinetics and Pharmacodynamics of TV-1106, a Once Weekly Growth Hormone Supplement: Results from a Phase 2 Study of TV-1106 in Adults with GHD

INTRODUCTION and PURPOSE

TV-1106 (Teva Pharmaceuticals Ltd) a rhGH-albumin fusion protein and novel biological entity, is in development for the weekly treatment of growth hormone deficiency (GHD) in adult and pediatric patients. For patients with GHD, deficiency of growth hormone reduces production and release of insulin-like growth factor (IGF-I) with recognized clinical sequelae. IGF-I is accepted as the PD marker of GH activity. TV-1106 has an extended duration of action compared to daily GH treatment and thus can reduce the frequency of injections and improve compliance and quality of life for adults and children requiring growth hormone replacement therapy.

The pharmacokinetics and pharmacodynamics of TV-1106 were evaluated as part of an interim analysis at week 12 of the phase 2 study evaluating the effects of weekly TV-1106 in adults with GHD.

METHODS

Study Design

Adults with GHD (n = 93) on stable rhGH treatment (Gentropin) with IGF-I levels between -1.5 to +2.0 SDS were screened and entered a 4 to 8 week washout period from rhGH treatment; to be eligible for randomization they had to meet the additional criteria to exhibit a IGF-I reduction of at least 1 SDS during this washout period and demonstrate a IGF-I SDS < 0 post washout.

52 subjects of the 93 screened met inclusion/exclusion criteria and were randomized to receive treatment with TV-1106 or Genotropin in a 1:1 ratio.

TV-1106 was administered once weekly as a subcutaneous injection. A TV-1106 dose considered “comparable” to rhGH was calculated by multiplying the pre-washout rhGH dose by 28 (to account for molar ratio 7 x days between injections). For safety purposes, the initial dose of TV-1106 in this study was 60% of the converted “comparable” dose.

Of 41 patients randomized to TV-1106 treatment, 31 were included in the pharmacokinetic analyses (PK) (10 patients did not have detectable TV-1106 concentrations) and all 41 were included in the pharmacodynamic analyses (PD). These patients were divided into 1 of 4 quartiles based on TV-1106 dose at Week 12.

• Dose Group 1 = 3.36 to < 8.96 mg
• Dose Group 2 = 8.96 to 12.32 mg
• Dose Group 3 = ≥ 12.32 to 15.12 mg
• Dose Group 4 = ≥ 15.12 to 31.92 mg

11 patients who received daily injections of Genotropin were active control participants.

PK and PD Analyses

Non-compartmental analysis was performed on serum concentrations collected from patients treated with weekly doses of TV-1106. Serum samples were collected at pre-dose of the 12th dose (day 7 week 11) and at 24, 48, 72, 96 and 168 hours after the 12th dose.

The following pharmacokinetic (PK) parameters were calculated: TV-1106 pre-dose concentration D7/WK11 Cmin, Tmax and Cmax (maximum observed concentration) over the 12 week dosing interval, area under the drug concentration vs time curve from week 12 to last measurable observation (AUClast), area under the drug concentration vs time curve over the 12 week dosing interval (AUCtau), and half-life (t½).

The measurements of IGF-I was performed by Quest Diagnostics Clinical Trials (California) using a validated liquid chromatography tandem mass spectrometry method (for IGF-I). Serum IGF-I were also assessed as age-adjusted standard deviation score (SDS).

The following PK parameters for IGF-I were determined directly from the week 12 serum concentration: Cmin, Tmax, Cmax at week 12, Cmax pre-dose D7/WK 11, area under the effect-time curve (AUEC0-T), and mean IGF-I concentration profile (IGF-I SDS units). IGF-I was also expressed as age-adjusted standard deviation score (SDS).

CONCLUSIONS

• The overall TV-1106 treatment effect at 12 weeks as determined from IGF-I levels was similar between the TV-1106 dose quartiles and Genotropin treatment group with greater fluctuation between maximum and minimum values for all the TV-1106 doses as compared to Genotropin treatment.

REFERENCES:

DISCLOSURES: OCB, KB, AS, GA and KB are Teva Pharmaceutical employees. JSC reports having served on Teva’s advisory board and MB reports having received consultancy fees from Teva.

ACKNOWLEDGMENTS: Authors greatly appreciate the work conducted by Hussein Hallak PhD and William Tracewell PhD for the pharmacokinetic and pharmacodynamic analyses and the assistance of Pippa Loupe, PhD on development of this presentation.

RESULTS

Figure 1 displays the geometric mean serum concentrations vs time profile for all patients by 12 week dose quartiles.

There was wide variability in plasma concentrations of TV-1106 with the highest overall exposure observed in the highest dose quartile (Table 1).

Table 2A. Non-compartmental PK parameters for TV-1106

Table 2B. IGF-I PD parameters and IGF-I SDS units

Figure 2A. IGF-I levels for TV-1106 dose quartiles

Figure 2B. IGF-I SDS levels for TV-1106 dose quartiles and Genotropin groups