P2-415

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

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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.[1] 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 level 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 4:1 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 (4 to account for molar ratio x 7 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/WK 11 minimum serum concentration (D7/WK11 C_{min}), C_{min} and C_{max} (maximum observed concentration) over the week 12 dosing interval, area under the drug concentration vs time curve from week 12 to last measurable observation (AUC_{0-t}), area under the drug concentration vs time curve over the week 12 dosing interval (AUC_{0-7}(AUC_{tau})) and half-life ($t_{1/2}$).
- The measurements of IGF-I was performed by Quest Diagnostics Clinical Trials (Valencia, California) using a validated liquid chromatography tandem mass spectrometry method (for IGF-I). Serum IGF-I were also expressed as age-adjusted standard deviation score (SDS).
- The following PD parameters for IGF-I were determined directly from the week 12 serum concentrations: C_{max}, T_{max}, C_{min} at week 12, C_{min} pre-dose D7/WK 11, area under the effect-time curve $AUEC_{0-T}$, and $AUEC_{0-168}$.

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:
1. Ooi GT, Boisclair YR. Molecular biology of the IGF binding proteins. In: Rosenfeld RG, Roberts CT, editors. *The IGF System*. Totowa, NJ: Humana Press, 1999:111–39.

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RESULTS

Serum Concentrations of TV-1106

- **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 based on C_{max} and AUC_{0-t} observed for highest dose quartile and substantially less for the 3 lower dose quartiles **(Table 1)**.

Figure 1. Geometric means of Week 12 TV-1106 serum concentrations per TV-1106 dose quartile

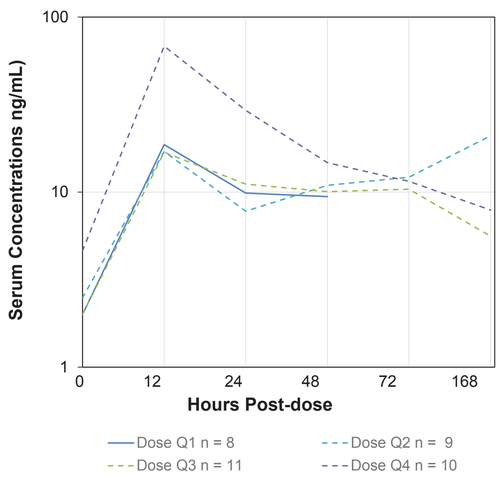

Table 1. Non-compartmental PK parameters for TV-1106

PK parameter Geometric mean [n] (min and max)	Overall	Dose quartile 1	2	3	4
D7/WK11 C_{min} (ng/mL)	BLQ [30] (BLQ, 325.1)	BLQ [2]	BLQ [7] (BLQ, 14.30)	BLQ [10]	4.62 [9] (BLQ, 325.1)
C_{max} (ng/mL)[a]	33.46 [31] (5.20, 937.9)	25.42 [2] (9.30, 69.5)	18.07 [7] (5.2, 50.0)	18.23 [10] (5.80, 73.8)	83.58 [10] (11.3, 937.9)
C_{min} (ng/mL)[b]	BLQ [31] (BLQ, 22.5)	BLQ [2]	BLQ [7] (BLQ, 14.3)	BLQ [10]	BLQ [10] (BLQ, 22.5)
AUC_{0-t} (ng*h/mL)	1237 [31] (62.0, 22253)	954.9 [2]	576.9 [7] (62.0, 3970)	746.1 [10] (188, 4033)	3213 [10] (813, 22253)
AUC_{0-7} (ng*h/mL)	3691 [12] (1259, 22657)	NC	2235 [2] (1259, 3969)	2387 [5] (1354, 4060)	6973 [5] (16600, 22657)
$t_{1/2}$ (h)[c]	34.65 [11] (17.52, 70.21)	NC	44.04 [1]	41.52 [5] (24.89, 70.21)	27.56 [5] (17.52, 39.00)

BLQ = below the level of quantification; [a]apparent value since no PK samples were collected during the first 24 hours after dosing when the true C_{max} is most likely to occur; [b]arithmetric mean values presented; [c] $t_{1/2}$ were calculated for 11 patients. Due to the limited serum concentration data collected during the elimination phase, $t_{1/2}$ estimates may not reflect the true terminal half-life of TV-1106.

Pharmacodynamic Properties of TV-1106

- **Figure 2A** displays the IGF-I levels during week 12 by the dose quartiles. Overall, mean IGF-I levels C_{max} values were highest for highest dose quartile and lowest for the lowest dose quartile.
- The mean IGF-I concentration profile (**in SDS units**) showed a greater fluctuation between peak and trough values over the 1-week TV-1106 dosing interval than the Genotropin treatment group, although the IGF-I levels stay within the appropriate range of -1.5 to +2.0 SDS (**Figure 2B**).
- Similar ranges of T_{max} between dose quartiles were observed. Mean C_{min} values were the lowest for Dose Group 4 consistent with a greater observed fluctuation between peak and trough concentrations for this highest TV-1106 dose quartile. The mean AUEC values varied less than 7% between all the dose quartiles. Mean values for each dose quartile were less than 8% lower than the Genotropin treatment group (**Table 2**).
- Mean peak levels between all TV-1106 dose quartiles (0.8 to 0.9 SDS) and the Genotropin treatment group (0.9 SDS) were similar. However, the mean trough values were consistently lower for each TV-1106 dose quartile (-1.0 to -0.2 SDS) than the Genotropin treatment group (0.0 SDS) **(Table 2)**.

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

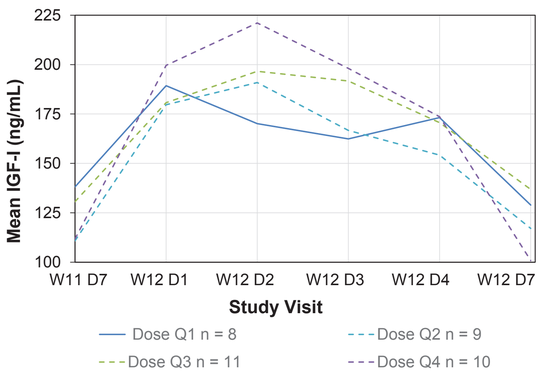

Figure 2B. IGF-I SDS levels for TV-1106 and Genotropin groups

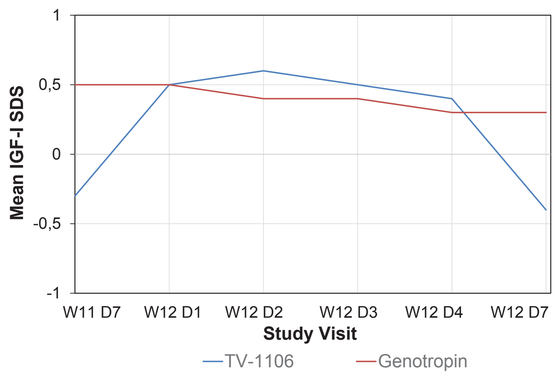

Table 2. IGF-I PD parameters and IGF-I SDS units

		TV-1106 [n = 41] Overall	Dose quartile 1	2	3	4	Genotropin [n = 11]
PD parameters week 12 mean SD [n]	D7/WK11 C_{min} (ng/mL)	122.9 (40.51) [40]	137.8 (29.19) [8]	110.8 (32.48) [9]	128.0 (35.62) [11]	111.8 (58.29) [9]	176.0 (31.58) [10]
	C_{min} (ng/mL) Week 12[a]	110.0 (36.39) [41]	126.3 (44.22) [8]	102.8 (28.46) [9]	116.8 (35.83) [11]	92.5 (38.21) [10]	145.4 (46.66) [11]
	C_{max} (ng/mL)	211.0 (81.72) [41]	195.8 (44.22) [8]	196.7 (61.62) [9]	204.7 (55.15) [11]	242.0 (138.45) [10]	215.8 (52.42) [11]
	T_{max} (day)[b]	2.0 (1.0, 4.0) [41]	1.0 (1.0, 4.0) [8]	2.0 (1.0, 3.0) [9]	2.0 (1.0, 4.0) [11]	2.0 (1.0, 4.0) [10]	2.0 (1.0, 7.0) [11]
	$AUEC_{0-T}$ (ngxh/mL)	26992 (8595) [38]	26527 (8505)[7]	26120 (5757) [9]	27844 (8259) [10]	26659 (13170) [9]	28301 (7158) [10]
	$AUEC_{0-168}$ (ngxh/mL)	231885 (3804) [12]	20246 (8458) [2]	23582 (2597) [5]	23681 (2432) [2]	22766 (4674) [2]	25288 (8382) [3]
IGF-I SDS mean (SD) [n]	Pre- washout: screening	0.3 (0.62) [41]	0.3 (0.44) [8]	0.3 (0.64) [9]	0.5 (0.53) [11]	0.2 (0.88) [10]	0.7 (0.59) [11]
	Post-washout : baseline	-1.5 (0.88) [41]	-0.9 (0.79) [8]	-1.4 (0.94) [9]	-1.5 (0.76) [11]	-2.2 (0.65) [10]	-1.1 (1.7) [11]
	D7/WK11	-0.3 (0.75) [40]	0.0 (0.74) [8]	-0.4 (0.72) [9]	-0.2 (0.61) [11]	-0.7 (1.00) [9]	0.5 (0.44) [9]
	C_{max} week 12	0.8 (0.78) [41]	0.8 (0.65) [8]	0.8 (0.66) [9]	0.8 (0.63) [11]	0.9 (1.22) [10]	0.9 (0.65) [11]
	Trough week 12	-0.4 (0.74) [41]	-0.2 (0.83) [41]	-0.3 (0.49) [9]	-0.2 (0.77) [11]	-1.0 (0.74) [10]	0.0 (0.82) [11]

[a]C_{min} at week 12 was calculated during the interval from pre-dose week 12 (D7/WK11) through pre-dose week 13 (day 7 week 12); [b]Median (minimum, maximum) [n]

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