



Safety and PK/PD correlation of TV-1106, a recombinant fused human albumin-growth hormone, following repeat dose administration to monkeys



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ABSTRACT

Purpose: TV-1106 is a recombinant human albumin genetically fused to growth hormone which is intended to reduce the frequency of injections for GH therapy users. We report the safety, tolerability, pharmacokinetics and pharmacodynamics of repeated subcutaneous injections of TV-1106 in Cynomolgus monkeys.

Method: Cynomolgus monkeys received four weekly subcutaneous injections of 0, 5, 10 or 20 mg/kg TV-1106 and were monitored for safety signals throughout the study. Serum levels of TV-1106 and insulin-like growth factor 1 (IGF-1) were assayed.

Results: Treated animals showed no adverse effects or histopathological changes. TV-1106 serum concentrations showed sustained exposure to the drug. Exposure increased in a dose-dependent manner with peak concentrations at approximately 24 h post-dosing and elimination half-lives in the range of 12 to 24 h. IGF-1 serum concentrations were elevated throughout the entire study duration, indicative of the pharmacological response. There was a clear correlation between change in IGF-1 levels and dose or exposure to TV-1106.

Conclusions: The safety, pharmacokinetic and pharmacodynamic findings support the further development of TV-1106 as a once-weekly administered treatment for patients with GHD.

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1. Introduction

The human growth hormone gene (hGH-N) encodes for the 22 kD human growth hormone protein. It is selectively expressed in pituitary somatotroph cells, and is essential for proper linear growth during childhood and adolescence and is also needed for important non-growth-related metabolic functions throughout adulthood [1]. Much of the anabolic action of GH is mediated by liver derived circulating insulin-like growth factor 1 (IGF1) and by tissue specific IGF1 [2]. Daily injections of recombinant human growth hormone (rhGH) have been primarily used in hypopituitary patients with GH deficiency (GHD) to achieve normal growth in children and adolescences and to correct GHD-caused metabolic abnormalities in adults. However, daily injections have serious compliance issues and indeed, compliance studies in patients with GHD have shown that approximately 25% of patients miss more than two injections per week [3]. To better ensure drug compliance, long acting rhGH are being developed and tested [4].

Teva Pharmaceuticals LTD is developing TV-1106, a long acting rhGH for treating both pediatric and adult GHD. TV-1106 is rhGH that is fused at its N-terminus to the C-terminus of mature human serum albumin (HSA) which confers the long acting characteristics of the fused molecule. TV-1106 is a single polypeptide chain with a molecular mass of approximately 88.5 kDa, in which residues 1–585 correspond to the mature form of HSA and residues 586–776 correspond to the mature form of rhGH. HSA is well distributed in the human body and is known to be a carrier for many proteins [5]. Studies have shown a longer half-life and decreased plasma clearance for therapeutic proteins fused to HSA [6,7]. It was therefore anticipated that TV-1106 will have a longer plasma elimination half-life, thereby enabling patients to reduce the number and frequency of injections and as a result, it is anticipated to improve compliance and quality of life.

TV-1106 (also called Albutropin), was originally developed by Human Genome Sciences (HGS, Rockville Maryland) where early stages of development were performed. Single dose studies in both rats and monkeys have established the extended residence time and duration of action [8].

Teva Pharmaceutical Ltd. acquired the rights for the drug, improved the formulation of TV-1106 and has continued the preclinical and

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clinical testing of the product. The following is an account of the preclinical safety, pharmacokinetics and pharmacodynamic effects of TV-1106 in Cynomolgus monkeys. The dosing regimen consisted of 4 once weekly subcutaneous injections in support of the clinical dosing regimen. Monkeys were selected as the testing model to minimize immunogenic responses to the introduced human material and due to their responsiveness to human GH.

2. Materials and methods

2.1. Animals

Sixteen male and 16 female captive-bred Cynomolgus monkeys (*Macaca fascicularis*), approximately 5 years old, were used for this study at the Laboratory of Pharmacology and Toxicology GmbH & Co. KG (LPT). All animal experimentations were compliant with the EU-directive L197 Commission Recommendation on Guidelines for the Accommodation and Care of Animals Used for Experimental and other Scientific Purposes. Their diet consisted of a certified monkey diet (ssniff Pri V3994 ssniff Spezialdiäten GmbH, Germany), 60 g/kg b.w., supplemented with fruits. Water was provided ad libitum.

2.2. Drug

TV-1106 (Teva Pharmaceuticals, Ltd) was supplied in vials containing 25 mg/mL active protein in the formulation buffer (10 mM Sodium Phosphate, 200 mM Mannitol, 60 mM Trehalose Dihydrate, 0.08% Polysorbate 80) and had a pH of 7.2. This stock solution was further diluted using the formulation buffer to the appropriate concentrations. The vehicle control consisted of the formulation buffer. The drug and vehicle control were administered via a subcutaneous bolus injection under the skin once weekly for a total of 4 injections per animal on test days 1, 8, 15 and 22. Injection site location was rotated across different sites of the lateral dorsum according to the following order: top right (first injection), top left (2nd injection), bottom right (3rd injection) and bottom left (4th injection).

2.3. Observations

The animals were monitored for clinical signs during the acclimation period, the treatment period and the treatment-free period as follows: on the days of treatment, the monkeys were observed before and after dosing for any signs of behavioral changes, reaction to treatment or illness.

Daily cage-side observations included examination of skin/fur orifices, somatomotor activity and behavior patterns. Special attention was paid to the local tolerance at the injection site. Body weights and food consumption were recorded pre-dose, at study initiation and thereafter at weekly intervals. Reflex testing was carried out before the first drug administration and on test days 2 and 23. Examinations were conducted in a quiet room, away from the general animal housing noise. The following reflexes were checked for presence or absence: cerebral nerve reflex, pupillary reflex (PuR), corneal and eyelid reflex (CR/LP). Other cerebral reflexes (mimicking and chewing) and reflexes in the limb region (grasp reflex) were observed outside the cage.

The body temperature was measured with an anal probe before the first administration and on test days 2 and 23. The respiratory rate and electrocardiogram (ECG) recordings were carried out in all animals before the first administration and on test days 2 and 23. Recordings were made with a CARDIOVIT AT-1 (Schiller, Ottobrunn, Germany) using the standard limb leads I, II and III and augmented limb leads aVR, aVL and aVF. The recordings were examined visually for any abnormalities of the electrical complexes. Peripheral arterial systolic and diastolic blood pressure was measured after the completion of each ECG recording on the shaven tail of the conscious animal using a blood pressure monitor (series 3000, TSE Technical & Scientific Equipment GmbH, Homburg,

Germany). Ophthalmological and auditory examinations were performed on all animals, once pre-dose and once at the end of the in-life period (test day 29). The eyes were examined with a HEINE ophthalmoscope (Heine Optotechnik, Herrsching Germany). The following ocular structures were examined: adnexa oculi, conjunctiva, cornea, anterior chamber, iris (pupil dilated), lens, vitreous body and fundus. The auditory acuity was checked by a simple noise test.

2.4. Urinalysis

Urine was collected for 3 h from the overnight fasted animals before the first drug administration and on test days 3, 17 and 28. The following tests were performed using qualitative indicators (Combur 9 Test, Roche Diagnostics GmbH, Mannheim, Germany): protein, glucose, bilirubin, urobilinogen, ketones, hemoglobin and nitrite. Measurements of pH and specific gravity were also made. Microscopic examinations of urine samples were carried out by centrifuging samples and spreading the resulting deposit on a microscopic slide. The color and turbidity of the urine were visually examined.

2.5. Blood and tissue analyses

Blood samples were taken from the monkeys' femoral veins after fasting overnight. Blood samples were taken at the following time-points: before the first drug administration, on test days 2 and 16 and on the day of dissection (test day 29). On test day 29 (7 days after the last administration) the animals were dissected following a randomization scheme. The animals were sacrificed (150 mg pentobarbital/kg b.w., i.v.) and exsanguinated by carotid dissection, weighed, dissected and inspected macroscopically. All superficial tissues were examined visually and by palpation. The gastro-intestinal tract was examined as a whole and the stomach and caecum were incised and examined. The lungs were removed and all pleural surfaces were examined under suitable illumination. The liver, kidneys, gonads, adrenal glands, uterus, intra-abdominal lymph nodes and accessory reproductive organs were examined.

2.6. Histopathology

Tissue samples from all animals were taken and preserved in neutral buffered 10% formalin. All organs of all animals were examined histologically following preparation of paraffin sections and haematoxylin-eosin staining.

2.7. Toxicokinetics

Blood sampling for toxicokinetics: blood for toxicokinetic analysis was collected for 168 h (0.5, 1, 4, 8, 24, 72 and 168 h) after the first and last (4th) injections, and once before the third and fourth injections. At each time point, a sufficient volume of blood was collected from the vena cephalica or saphena magna (not from the arm used for administration) of all the animals. Serum was separated from the whole blood, frozen at -80°C and stored until assayed. TV-1106 concentrations were measured using a validated ELISA with a mouse monoclonal hGH antibody (Fitzgerald Industries International, Acton MA) as a coating antibody and a goat anti-HSA HRP-conjugated polyclonal antibody as a detection antibody. Toxicokinetic evaluation of the serum data was performed using TopFit 2.11 [9]. A non-compartmental model for subcutaneous injection was employed and the following parameters were determined: C_{max} (maximum concentration, $\mu\text{g}/\text{mL}$), t_{max} (time of maximum concentration, h), $\text{AUC}_{(0-168\text{h})}$ (area under the observed serum concentration time curve from the start of injection to 168 h after last dose $\mu\text{g} \cdot \text{h}/\text{mL}$), $\text{AUC}_{(0-t)}$ (area under the observed serum concentration time curve from the start of administration to the last measurable concentration at time t, $\mu\text{g} \cdot \text{h}/\text{mL}$), $t_{1/2}$ (terminal elimination half-life, h), $\text{AUC}_{(0-\infty)}$ (area under the observed serum concentration

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