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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-naïve, Pre-Pubertal, Growth-Hormone Deficient Children

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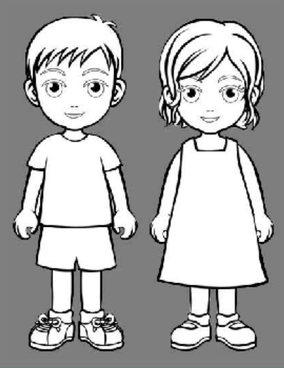
Screening

Treatment-naïve pre-pubertal (boys ≥ 3 to ≤ 11 yrs of age, girls ≥ 3 to ≤ 10 yrs of age) children diagnosed with idiopathic growth hormone insufficiency, GH insufficiency as part of multiple pituitary hormone deficiencies, or organic GH insufficiency (due to pituitary tumor, pituitary or brain surgery, or intracranial radiation therapy) were eligible to be screened for entry into study.



Inclusion Criteria

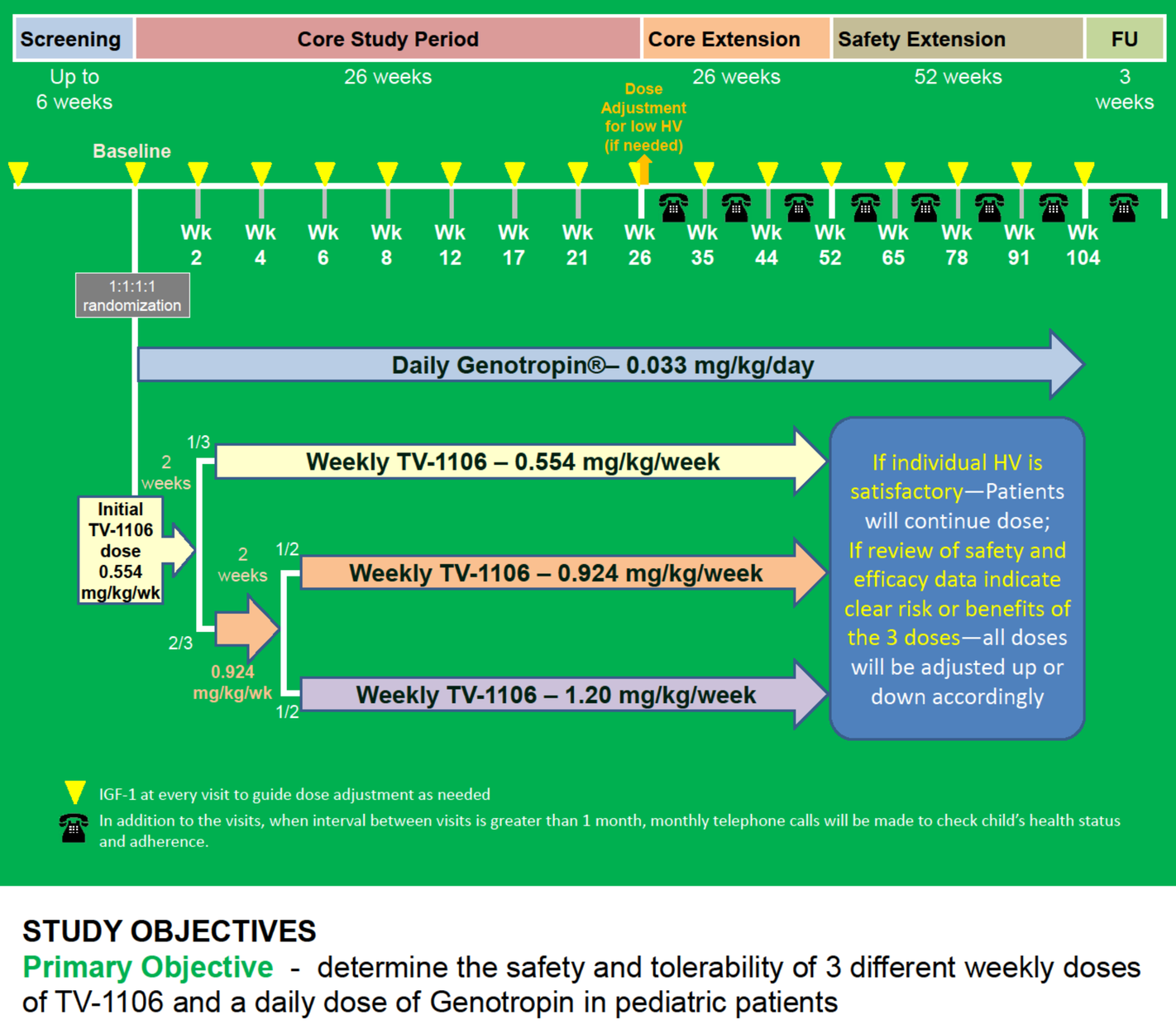
- GH concentration < 10 ng/mL
- H-SDS ≤ -2.0
- HV-SDS < 0
- IGF-I SDS < -1.0
- BMI ≤ 95%-of BMI for CA and gender according to CDC 2000 standard

Exclusion Criteria

- Any clinically significant abnormality
- Contraindications to rhGH treatment
- History or currently active malignancy
- Children with new diagnosis of pituitary/hypothalamic tumor or intracranial tumor within 12 months of baseline
- Children born small for gestational age (SGA)
- Growth altering medications, such as anabolic steroids or methylphenidate, except for pituitary replacement hormone therapy (thyroxine, hydrocortisone, desmopressin)
- Children requiring glucocorticoid therapy for asthma in excess of 400 µg/day

Study Design

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



▼ IGF-1 at every visit to guide dose adjustment as needed

☎ In addition to the visits, when interval between visits is greater than 1 month, monthly telephone calls will be made to check child's health status and adherence.

Measures

Efficacy

Primary Endpoint

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

Secondary Endpoints

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

Exploratory Endpoints

1) IGF-I SDS
2) TV-1106 PK concentrations at baseline , and day 3 of weeks 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, HV-SDS, change in H-SDS and BA/CA after 104 weeks of treatment
6) Patient adherence
7) Number and proportion of patients in each response category for the QOL questionnaires
8) Predicted adult height by Bayley-Pinneau method.[3]

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) IGF-SDS and IGF-I binding protein (IGFBP-3) at all timepoints
4) Physical examinations including fundoscopy, opthalmologic 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) IGF-I and IGFB-3 samples for TV-1106 and Genotropin patients will be collected at multiple timepoints throughout the study.
   - Peak IGF-I levels will be assessed on day 3, 72 hours after weekly TV-1106 at weeks 4, 6, 8, 35, 44, and 65.
   - Trough IGF-I levels will be measured day 7 after weekly TV-1106 at weeks 2, 12, 26, 52, and 104.
   - For Genotropin patients, peak and trough IGF-I will be collected at the same time as measured for TV-1106 patients.
2) TV-1106 pk concentrations will be measured weeks 4, 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 17 and 21.
3) Genotropin PK samples (prior to Genotropin administration) will be collected at baseline, day 7 week 2, 12, 26, 52, 78 and 104.
4) TV-1106 and Genotropin serum concentration will be measured using a validated ELISA method.

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-SDS).

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

DISCLOSURES: RGR has served as consultant for Teva and is a member of Teva's advisory board. JMW has served as consultant for Pfizer, Biopartners, OPKO, Versartis, Teva, Merck-Serono and Ammonett and has received speaker's honoraria from Pfizer, Versartis, Merck-Serono, Lilly and Sandoz. OM and EB have no disclosures to report. KB, AS, GA, MB and KB are Teva Pharmaceutical employees.

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Growth Hormone

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