Health System, Jacksonville, FL, USA, [6]Children´s Faculty Hospital Kosice, Kosice, Slovakia, [7]Pfizer Ltd, Tadworth, United Kingdom, [8]Pfizer, Inc., Collegeville, PA, USA, [9]Pfizer, Inc., New York, NY, USA, [10]UCL Great Ormond Street Institute of Child Health, London, United Kingdom, [11]Charles University in Prague, Prague, Czech Republic.

Background: Somatrogon is a long-acting recombinant human growth hormone (rhGH) comprised of the amino acid sequence of hGH and 3 copies of the carboxy-terminal peptide from human chorionic gonadotropin. Somatrogon is being developed as a once weekly subcutaneous (SC) injectable treatment for pediatric patients (pts) with GHD.
Aims: To evaluate patient and caregiver perceptions of the treatment burden associated with a once weekly somatrogon SC injection schedule compared with a once daily Genotropin SC injection schedule.
Methods: In this phase 3 (NCT03831880), open-label, crossover study, pediatric pts (3 to <18 years) with GHD on at least 3 months stable rhGH therapy were randomized 1:1 to receive treatment according to 1 of 2 sequences: Sequence #1, 12 weeks of Genotropin once daily followed by 12 weeks of somatrogon once weekly; Sequence #2, 12 weeks of somatrogon once weekly followed by 12 weeks of Genotropin once daily. The primary objective of the study was to evaluate treatment burden assessed as the difference between mean overall Life Interference (LI) total scores after each 12-week treatment period of weekly somatrogon and daily Genotropin. Secondary objectives further assessed treatment experience of pts and caregivers after each treatment period and their comparison of both treatments at the end of the study. A recently developed, validated dyad questionnaire (Turner-Bowker DM et al, 2020) was administered as an electronic Patient Reported Outcome to collect all assessments.
Results: Eighty-seven pts were randomized to Sequence #1 (n=43) or Sequence #2 (n=44) with 85 pts completing the study. Somatrogon administered as a once weekly injection had a lower (statistically significant) treatment burden than Genotropin administered as a once daily injection, based on the mean overall LI total scores after somatrogon (8.63) vs Genotropin (24.13) treatment (mean difference: -15.49; two-sided 95% CI: [-19.71, -11.27]; P <0.0001). Compared with once daily Genotropin, once weekly somatrogon was associated with greater convenience, higher satisfaction with treatment experience, and less life interference for the caregiver. A higher proportion of pts preferred once weekly somatrogon and demonstrated a greater intent to comply with treatment. The proportion of pts who experienced at least one treatment-emergent adverse event (TEAE) with Genotropin and somatrogon treatment were 44.2% and 54.0%, respectively. Injection site pain was the most common TEAE during the Genotropin (12.8%) and somatrogon (14.9%) treatment periods and was rated as mild in most cases. No severe or serious adverse events were reported.
Conclusions: In pediatric pts with GHD, compared with Genotropin administered once daily, somatrogon administered once weekly has a lower treatment burden as shown by less life interference, and is associated with a more favorable treatment experience.

Pediatric Endocrinology

GROWTH AND GROWTH HORMONE

Persistence of Use in Children Receiving Growth Hormone Therapy

Amalia Spataru, MSc[1], Paula van Dommelen, PhD[2], Lilian Arnaud, MSc[3], Quentin Le Masne, PhD[3], Silvia Quarteroni, PhD[1], Ekaterina B. Koledova, MD,PhD[4].
[1]Swiss Data Science Center, ETH Zurich and EPFL, Zurich, Switzerland, [2]TNO, Leiden, Netherlands, [3]Ares Trading SA, Eysins, Switzerland, [4]Merck KGaA, Germany, Darmstadt, Germany.

Background: Long-term persistence of use and starting at the earliest possible age are associated with attainment of near-normal adult or final height in children who are treated with growth hormone therapy. However, there are many factors associated with a lack of persistence. Our aim was to study persistence of use in children with growth disorders using the easypod™ connected autoinjector e-device, which automatically records adherence data and can transmit them via an online portal (easypod™ connect). We investigated persistence of use, defined indicators of a long persistence of use, and developed a model to predict and identify children at risk of discontinuing treatment in the following 6 months. **Data and Methods:** Anonymized data from children transmitting over 10 injections between January 2007 and April 2020 were analyzed. A child was considered to discontinue the use if they had no injection in the last 6 months (before April 2020) or had an injection pause of at least 6 consecutive months. Persistence was estimated by Kaplan-Meier analyses and Weibull accelerated failure time modeling. To predict the individual risk of discontinuing the use in the following 6 months, individual survival probabilities curves were estimated for each patient still using the system, and the survival probabilities were then recalculated such that they were conditional on the fact that a child had already used the device for a certain time. The Harrell's c-index was used to assess the algorithm performance. **Results:** Data were available for 17,651 children of whom 11,056 discontinued the use and 6,595 were still persistent in April 2020. Median persistence of use for all patients using the device was 2.1 years. There was a highly significant difference in median persistence of use between the regions: 1.0, 1.5 and 2.8 years in the available countries in the Asia-Pacific, America and Europe regions, respectively. Other indicators that had a significant positive impact on persistence of use were: at least one dose change a year, having auxological measurements recorded in the system (and if 'Yes', height standard deviation < -2 at start of use had an additional effect), starting treatment at an early age, adherence ≥85%, customized injection speed setting and being male. For the individual prediction, random survival forests showed the best performance (Harrell's c-index=0.72). **Conclusions:** Data from the connected autoinjector e-device showed that the persistence of use was approximately 2 years in children with growth disorders. We were able to define 8 indicators that had a positive impact on persistence of use of which several indicators were related to patient management. Our prediction model can be used to identify children needing

Downloaded from https://academic.oup.com/jes/article/5/Supplement_1/A681/6241937 by guest on 12 May 2021

support to reach longer persistence of use and subsequently optimal clinical outcomes.

Pediatric Endocrinology
GROWTH AND GROWTH HORMONE

Pharmacokinetics and Pharmacodynamics of Macimorelin Acetate (AEZS-130) in Paediatric Patients With Suspected Growth Hormone Deficiency (GHD)

Violetta Csákváry, MD[1], Agota Muzsnai, MD[2], Dmitri Raduk, MD, PhD[3], Tetyana Chaychenko, MD, PhD[4], Birgitte Bentz Damholt, PhD[5], Nicky Kelepouris, MD[6], Michael Teifel, PhD[7], Nicola Ammer, MD, MSc PM[8].

[1]Department of Paediatrics, Markusovszky Teaching Hospital, Szombathely, Hungary, [2]Buda Children's Hospital, Budapest, Hungary, [3]HCI [2]nd Children's City Clinical Hospital, Minsk, Belarus, [4]Department of Paediatrics № [1] and Neonatology, Kharkiv National Medical University, Kharkiv, Ukraine, [5]Novo Nordisk A/S, Global Development (current affiliation: Novo Nordisk A/S, Stem Cell Development, Måløv, Denmark), Søborg, Denmark, [6]Novo Nordisk Inc., Plainsboro, NJ, USA, [7]Aeterna Zentaris GmbH (current affiliation: Cleara Biotech BV, Utrecht, The Netherlands), Frankfurt, Germany, [8]Aeterna Zentaris GmbH, Frankfurt, Germany.

Growth hormone deficiency (GHD) in children is a rare, aetiologically diverse condition that results in growth failure and short stature. Inadequate response to two different growth hormone stimulation tests (GHST) is required for the diagnosis of GHD. Macimorelin acetate, a potent, orally administered growth hormone (GH) secretagogue, is approved by the FDA and EMA for the diagnosis of adult GHD. Study AEZS-130-P01 is the first of two studies to investigate macimorelin acetate as a diagnostic test in children with suspected GHD.

This was an open-label, group comparison, dose escalation trial to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of single-dose 0.25, 0.5 and 1 mg/kg oral macimorelin acetate in paediatric subjects with suspected GHD. The macimorelin GHST was administered between two standard GHST, conducted as per local clinical practice, with a recovery period of 7-28 days between tests. Blood samples were collected pre-dose (±15 min) and 15, 30, 45, 60, 90, 120 and 360 minutes after macimorelin acetate intake.

Overall, 24 paediatric subjects (8 per cohort [C1, C2, C3]) were included in the pharmacokinetic/pharmacodynamic (PK/PD) analysis. Five males and 3 females were observed in C1 and C2, 7 males and 1 female in C3. In all three cohorts, at least 3 subjects represented Tanner stages I or II. All 24 subjects (100%) were white, with a median age of 9.8, 9.0 and 10.5 years (range 4-15 years) and a median body-mass index of 16.1 kg/m^2 (12.4-21.4 kg/m^2) at screening. Overall, 88 adverse events were reported, many related to the standard GHST; none were considered related to the macimorelin test. Maximum plasma concentrations for macimorelin were mainly observed between 30-45 min. The mean C_{max} values were 3.46, 8.13 and 12.87 ng/ml for C1, C2, and C3, respectively. The AUCs increased with dose; the mean AUC_{0-6} values were 6.69, 18.02 and 30.92 h*ng/mL. The mean elimination half-lives were 1.22, 1.61 and 1.71 h, respectively. PK and PD profiles for all three cohorts were comparable, with peak GH levels mainly observed within 30-60 min following macimorelin intake.

Macimorelin acetate was safe and well tolerated in all dosing cohorts. A dose-dependent increase in macimorelin C_{max} and AUC in children and adolescents correlated well with data from adult subjects. A robust dose-proportional GH response was also achieved. PD results showed that GH response was comparable in all dose groups, with a slight shift to earlier t_{max} at higher macimorelin doses.

Pediatric Endocrinology
GROWTH AND GROWTH HORMONE

Phase 3 Study Evaluating Once Weekly Somatrogon Compared to Daily Genotropin in Japanese Patients With Pediatric Growth Hormone Deficiency (pGHD)

Reiko Horikawa, PhD,MD[1], Toshiaki Tanaka, MD, PhD[2], Yukihiro Hasegawa, MD[3], Tohru Yorifuji, MD[4], David Ng, PhD[5], Ron G. Rosenfeld, MD[6], Yuko Hoshino, MSc[7], Akifumi Okayama, M. Eng[7], Daisuke Shima, PhD[7], Roy Gomez, MS, PhD[8], Aleksandra Pastrak, MD, PhD[9], Orlando Castellanos, MD[10].

[1]National Center for Child Health & Development, Tokyo, Japan, [2]Tanaka Growth Clinic, Tokyo, Japan, [3]Tokyo Metropolitan Children's Medical Center, Tokyo, Japan, [4]Division of Pediatric Endocrinology and Metabolism, Children's Medical Center, Osaka City General Hospital, Osaka, Japan, [5]WuXi Clinical, Austin, TX, USA, [6]Oregon Health and Science University, Portland, OR, USA, [7]Pfizer R&D Japan, Tokyo, Japan, [8]Pfizer, Ixelles, Belgium, [9]OPKO Health, Toronto, ON, Canada, [10]OPKO Health, Miami, FL, USA.

Objectives: Somatrogon is a long-acting recombinant human growth hormone consisting of the amino acid sequence of human growth hormone and three copies of the carboxy-terminal peptide of human chorionic gonadotropin. Somatrogon is being developed as a once weekly treatment for children with pGHD. A Phase 3 trial was designed to compare the efficacy and safety of somatrogon administered once weekly with Genotropin administered once daily in Japanese patients with pGHD (ClinicalTrials.gov: NCT03874013).

Methods: 44 Japanese pGHD patients (age 3-11 years) were randomized in a 1:1 ratio to receive either once weekly somatrogon (0.66 mg/kg/week) or once daily Genotropin (0.025 mg/kg/day) subcutaneously for 12 months. Somatrogon-treated patients had a pharmacokinetic assessment in the first 6 weeks with dose escalation occurring in 3 steps, at 0.25, 0.48, and 0.66 mg/kg/week, for 2 weeks at each dose. For the remaining 46 weeks, patients in the somatrogon treatment group continued to receive somatrogon at a dose of 0.66 mg/kg/week. The primary endpoint of the study was annualized height velocity (HV) at 12 months.

Results: Baseline characteristics were balanced and comparable between the two treatment groups. The least square means of HV at month 12 were 9.65 cm/year in the somatrogon group (n=22) and 7.87 cm/year in the Genotropin group (n=22), with a point estimate treatment difference of 1.79 cm/year (95% confidence interval: 0.97, 2.60) in favour of somatrogon. The point estimate was greater than the pre-established mean treatment difference

Downloaded from https://academic.oup.com/jes/article/5/Supplement_1/A681/6241937 by guest on 12 May 2021