Model-Based Drug Development (MBDD) of Pegylated Growth Hormone (PEG-hGH) in the Treatment of Adult Growth Hormone Deficient (AGHD)

Rujia Xie[1], Tracy Higgins[1] and Jaap Mandema[2]
1 Pfizer, Sandwich, United Kingdom; 2 Quantitative Solutions Inc. CA, USA

Objectives

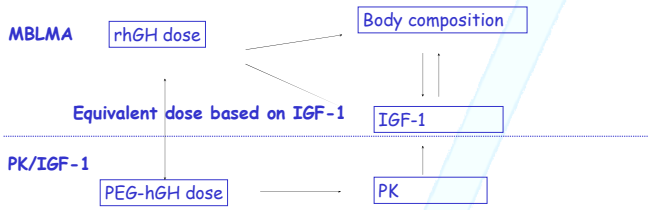
This presentation overviews the major MBDD activities and their influence on the early development of PEG-hGH and the inception of an expedited late development strategy.

Methods

There were three key influential MBDD activities undertaken in the early development of PEG-hGH (Figure 1):

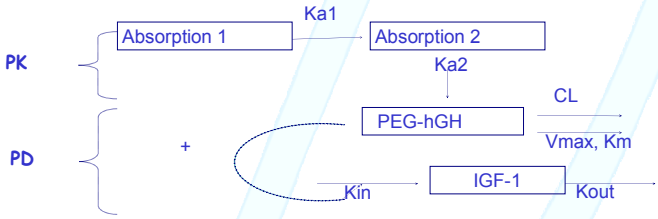
A model-based literature meta-analysis (MBLMA) was conducted across the extensive prior literature available on the treatment of AGHD with recombinant human growth hormone (rhGH) (Genotropin). Summary level data was available on 135 trials (354 unique treatment arms) presenting 6395 patients and patient level data was available on 3 trials. A nonlinear mixed effect regression method (NLME in Splus) was used to analyse the data. The dose response relationships for the biomarker insulin growth factor-1 (IGF-1) [1] and outcome measures of body composition were characterised. The relationship between change in IGF-1 and change in body composition was established. An Emax model was used to describe these relationships. Patients' characteristics were captured in the meta-database [1].

Figure 1. Diagram of MBDD activates



A semi-mechanistic PK/IGF-1 model to describe IGF-1 vs. time profiles after administration of PEG-hGH was developed [2], applied and updated across Phase 1 (56 males) and Phase 2a (7 males). The data were analysed by a nonlinear mixed effects modelling approach using NONMEM. The diagram of PK/PD models for AGHD patients is shown in Figure 2. PEG-hGH stimulating IGF-1 production rate (kin) was described by an Emax model.

Figure 2. Diagram of PK/PD models for PEG-hGH



$$Kin * (1 + \frac{E_{max} * C_{PEG-hGH}}{EC_{50} + C_{PEG-hGH}})$$

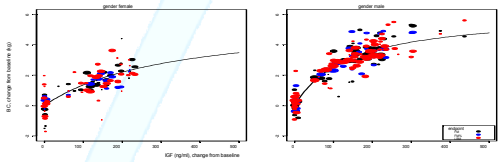
Ka: 1st order absorption rate; **CL: clearance**
Vmax: maximal elimination capacity; **EC50: PEH-hGH conc reaching 50% Emax**
Kin: IGF-1 production rate; **Kout: IGF-1 elimination rate**

The computer added trial design (CATD) was performed to assist Phase 2a/b PEG-hGH study designs using PK/IGF-1 models developed from Phase 1 and 2 data, including variability and parameter uncertainty. Gender difference obtained from MBLMA for rhGH was incorporated into the simulations under the assumption of similar gender effect on both drugs; rhGH and PEG-hGH. IGF-1 responses were simulated at the various scenarios to optimise study design and assist dose selection and sample size estimation.

Results

Dose/IGF-1 [1] and dose/body composition responses for rhGH were well described. The MBLMA approach allowed the relationship between IGF-1 and body composition for rhGH to be fully quantified (Figure 3). This result supported the rationale to use IGF-1 as a biomarker for the early development of PEG-hGH and provided the confidence to select Phase 3 dose(s) based on the Phase 2 IGF-1 response; saving a dose body composition Phase 2 study. Females were less sensitive than males and this relationship was well quantified for all endpoints for rhGH based on MBLMA (Figure 3).

Figure 3: Impact of gender on predicted and observed IGF-1 and body composition



PEG-hGH and IGF-1 data were well described by proposed models (Figure 2). IGF-1 responses were simulated utilising dose/IGF-1 model for rhGH [1] and PKPD model for PEG-hGH (Figure 2). The equivalent clinical efficacious doses for PEG-hGH to rhGH were predicted based on simulated IGF-1 response (Figure 4). This approach was used to optimise the dose regimen for PEG-hGH and supported the early investment in the dose strength for Phase 3 (Figure 5).

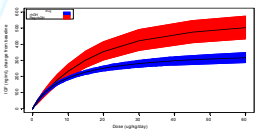


Figure 4. Predicted IGF-1 dose response for rhGH and PEG-hGH in a typical population

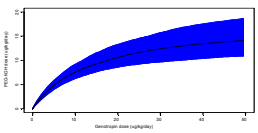


Figure 5. Equivalent dose of PEG-hGH to rhGH based on an equivalent IGF-1 response

For Phase 2b trial, clinical trial simulation (CTS) was performed to provide a quantitative assessment of the likelihood of trial success and likely study outcomes of proposal study design, taking into account different sub-populations. The results from CTS were used to estimate sample size using a dose-response approach. Compared to conventional sample size calculation, the number of subjects were reduced by 70%. The duration were reduced to 6 weeks with less arms and more efficient crossover type study design.

Conclusions:

The application of MBDD has supported the efficient and cost-effective clinical drug development of PEG-hGH. The established quantitative linkage between IGF-1 and body composition has the potential to improve routine clinical practice with rhGH.

Acknowledgements:
We thank Eric Didier, Gwyn D'Souza, Mats Karlsson, Peter Milligan and Scott Marshall for their valuable contributions to the studies and modelling work.

References:
[1]. Relationship between the Dose of Recombinant Human Growth Hormone (rhGH) and Insulin Growth Factor-1 (IGF-1) in Adult Patients with Growth Hormone Deficiency (AGHD). Poster for PAGE, Marseille, 2008
[2]. Population Pharmacokinetic/Pharmacodynamic Analysis for Pegylated Recombinant Human Growth Hormone (PHA-794428) in Male Healthy Volunteers. Abstract for Endocrine Society Meeting, Boston June 24-27, 2006