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SYMPOSIUM

Application of Adaptive Design Methodology in Development of a Long-Acting Glucagon-Like Peptide-1 Analog (Dulaglutide): Statistical Design and Simulations

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Abstract

Background:

Dulaglutide (dula, LY2189265), a long-acting glucagon-like peptide-1 analog, is being developed to treat type 2 diabetes mellitus.

Methods:

To foster the development of dula, we designed a two-stage adaptive, dose-finding, inferentially seamless phase 2/3 study. The Bayesian theoretical framework is used to adaptively randomize patients in stage 1 to 7 dula doses and, at the decision point, to either stop for futility or to select up to 2 dula doses for stage 2. After dose selection, patients continue to be randomized to the selected dula doses or comparator arms. Data from patients assigned the selected doses will be pooled across both stages and analyzed with an analysis of covariance model, using baseline hemoglobin A1c and country as covariates. The operating characteristics of the trial were assessed by extensive simulation studies.

Results:

Simulations demonstrated that the adaptive design would identify the correct doses 88% of the time, compared to as low as 6% for a fixed-dose design (the latter value based on frequentist decision rules analogous to the Bayesian decision rules for adaptive design).

Conclusions:

This article discusses the decision rules used to select the dula dose(s); the mathematical details of the adaptive algorithm—including a description of the clinical utility index used to mathematically quantify the desirability of a dose based on safety and efficacy measurements; and a description of the simulation process and results that quantify the operating characteristics of the design.

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Abbreviations: (ASTIN) Acute Stroke Therapy by Inhibition of Neutrophils, (bpm) beats per minute, (CUI) clinical utility index, (DBP) diastolic blood pressure, (DMC) Data Monitoring Committee, (DP) decision point, (dula) dulaglutide, (GLP-1) glucagon-like peptide-1, (HbA1c) hemoglobin A1c, (HR) heart rate, (NDLM) normal dynamic linear model, (PD) pharmacodynamic, (T2DM) type 2 diabetes mellitus

Keywords: adaptive dose finding, dulaglutide, GLP-1, seamless design

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