

**Pharmacokinetic / Pharmacodynamic (PK/PD) Simulations Guide Selection of the Dose for Administration of Efgartigimod Subcutaneously in a Phase 3 Clinical Trial in Patients with Primary Immune Thrombocytopenia**

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**Disclosures**

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## Abstract

### Introduction

Efgartigimod (ARGX-113) is a human IgG1-derived Fc fragment that binds with high affinity to FcRn in a pH dependent way, resulting in a blockade of FcRn-mediated recycling of IgGs. This leads to rapid degradation of all IgGs, including disease associated autoantibodies.

The efficacy, safety, tolerability, and pharmacokinetic (PK) and pharmacodynamic (PD) profile of intravenously (IV) administered efgartigimod have been assessed during a Phase 1 study in healthy subjects (Ulrichts P. *JCI*. 2018;128), Phase 2 studies in patients with Myasthenia gravis (MG) (Howard JF. *Neurol*. 2019;92) and Immune Thrombocytopenia (ITP) (Newland AC. *Am J Hematol*. 2020;95:178-187), and a Phase 3 study in MG (Howard JF. *Lancet Neurol*. 2021;20). These studies have demonstrated that a dose of 10 mg/kg efgartigimod, administered in four weekly (qw) IV infusions, achieves close to maximal immunoglobulin G (IgG) reduction and a significant reduction of pathogenic autoantibodies in patients with ITP and MG. Furthermore, this dose was well-tolerated in all populations. Based on the results of the Phase 2 study in Primary ITP, a Phase 3 study was designed for IV administration in patients with persistent or chronic primary ITP (ADVANCE NCT04188379).

To allow for a convenient SC administration of efgartigimod at a dose that achieves a similar PD effect comparable to IV 10 mg/kg, a co-formulation with rHuPH20 SC was developed (recombinant human hyaluronidase PH20, an enzyme used to increase the dispersion and absorption of co-administered substances when administered subcutaneously). Here we describe the dose selection process for the SC dose to be used in a Phase 3 study of patients with persistent or chronic ITP.

## Methods

PK and PD data from a Phase 1 study, including 32 healthy adult male subjects receiving 750 mg, 1250 mg, 1750 mg, or 10 mg/kg single SC injections of efgartigimod co-mixed with rHuPH20 (8 subjects/dose group), were used for a PK/PD analysis to predict the efgartigimod PH20 SC dose that would result in a similar PD effect compared to the benchmark dose from previous studies of 10 mg/kg IV (1 hour infusion and body weight of 70 kg).

## Results

Weekly SC administration of 1000 mg efgartigimod co-mixed with 2000 U/mL rHuPH20 was predicted to result in comparable maximum total IgG reduction after the 4<sup>th</sup> SC injection (days 22-29) as after the 4<sup>th</sup> IV infusion of 10 mg/kg administered qw (**Figure 1**). Additionally, the area under the curve for total IgG concentration after the 4<sup>th</sup> dose (days 22-29) and trough IgG reduction (measured prior to dose on day 29) were predicted to be comparable between weekly 1000 mg SC and the weekly 10 mg/kg IV benchmark dose.

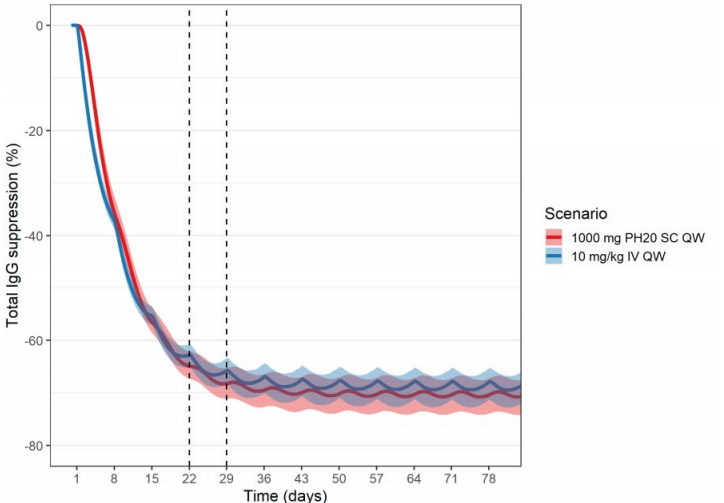
No statistically significant effect of body weight on the PK and PD of efgartigimod PH20 SC was found.

## Discussion

These results informed the weekly SC dose administration schedule in ADVANCE SC, a Phase 3, multicenter, randomized, double-blinded, placebo-controlled trial (NCT04687072) for evaluation of efficacy and safety of efgartigimod PH20 SC in adults with persistent or chronic primary ITP. Efgartigimod PH20 SC or placebo PH20 SC will be given weekly on visits 1-4 and then either weekly or every other week from visits 5 to 16, as determined by platelet counts. The frequency of administration will remain unchanged for the last 7 weeks (visits 17 to 24) to evaluate the sustainable platelet count improvement as the primary objective. Secondary objectives include extent of disease control (overall platelet count response, use of rescue treatment, and changes in concurrent ITP therapy), bleeding events, and quality of life assessments. ADVANCE SC recruitment is currently ongoing across approximately 70 sites in Asia-Pacific, Europe, Japan, Latin America, Middle East, Africa, and USA.

**Figure 1.** Simulation Profiles of total IgG suppression after 1000 mg Efgartigimod SC qw and 10 mg/kg IV qw

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Solid lines and areas: median, 5<sup>th</sup> and 95<sup>th</sup> percentiles of total IgG suppression; vertical dashed lines: Day 22 and Day 29.