ABSTRACT

Title
Prevalence of immunology testing in patients treated with alglucosidase alfa with significant hypersensitivity/anaphylactic reactions.

Keywords
Immunology testing, alglucosidase alfa, hypersensitivity, anaphylactic reactions

Rationale and background
Myozyme (alglucosidase alfa) is indicated for long-term enzyme replacement therapy (ERT) in patients of all ages with Pompe disease (acid α-glucosidase deficiency). As a therapeutic protein, Myozyme has the potential to trigger an immunologic response, involving the formation of antibodies against recombinant human acid α-glucosidase. In clinical studies, the majority of patients developed IgG antibodies to alglucosidase alfa, typically within 3 months of treatment. Some patients treated with Myozyme in clinical trials and the post-marketing setting who were evaluated, tested positive for presence of alglucosidase alfa-specific IgE antibodies, some of whom reported events of anaphylaxis. The clinical relevance of the development of inhibitory antibodies in patients treated with Myozyme is unknown. Immunological testing will help to further characterize infusion-associated reactions (IARs) and hypersensitivity reactions.

As part of the Risk Management Plain (RMP) for Myozyme, a Safety Information Packet (SIP) was developed to serve as an educational resource for treating physicians. The SIP was designed to educate physicians toward minimizing the identified risks associated with Myozyme, which included suggested IAR management guidelines, adverse event reporting guidelines and immunological testing procedures. The European Medicines Agency (EMA) and the Pharmacovigilance Risk Assessment Committee (PRAC) requested that Sanofi Genzyme revise the original version of the SIP to improve the readability and contents, and to assess the effectiveness of the revised material in terms of the evaluation of the process and the outcomes. This study is focused on the evaluation of the outcomes, through the evaluation of the prevalence of immunology testing in patients experiencing significant hypersensitivity/anaphylactic reactions.

Research question and objectives
The objective of the study was to determine the prevalence of immunology testing in patients treated with alglucosidase alfa with significant hypersensitivity/anaphylactic reactions. The difference in the prevalence of testing between the two periods of 3 years before and after the implementation of the revised SIP (version 8.2) was assessed as a measure of the effectiveness of the risk minimization measures.

Study design
Cross-sectional study; repeated analyses using pre-existing data from pre- and post-implementation of the revised SIP.

Setting
This study was conducted using existing data sources (1) Sanofi Genzyme Pharmacovigilance adverse event database, a spontaneous reporting system, (2) Genzyme Clinical Specialty Laboratory database which captures routine performance of immunology testing since treatment start.

The population included all patients treated with alglucosidase alfa with a spontaneously reported significant hypersensitivity/anaphylactic reaction to the Sanofi Genzyme Pharmacovigilance adverse event database during the study period within European countries in which the revised SIP had been distributed by March 31, 2016. Two groups were defined based on the SIP distribution date:
3 year pre-implementation period: defined as the 3 year period prior to the distribution of the revised SIP (ending 1 month prior to the effective distribution). For example, if the SIP was distributed in September 30, 2015, the pre-implementation period would be from Sept 1, 2012 to Aug 31, 2015.
3 year post-implementation period: defined as the 3 year period after the distribution of the revised SIP (beginning the month after the effective distribution date). For example, if the SIP was distributed September 30, 2015, the post-implementation period would be from November 1, 2015 to October 31, 2018.

Subjects
Patients with a spontaneously reported significant hypersensitivity/anaphylactic reaction occurring during alglucosidase alfa treatment course within European countries in which the revised SIP was distributed by March 31, 2016 were identified utilizing a two-step process. First, spontaneous case reports were identified by the Standardized MedDRA Queries “anaphylactic reaction” and “hypersensitivity” occurring during alglucosidase alfa treatment course within the study time frame. Identified case reports (also simply referred to as ‘cases’) were adjudicated in a second step with the following criteria applied to further identify significant hypersensitivity/anaphylactic reactions:

1. All cases of anaphylactic reaction were considered potentially ‘significant’. After adjudication, cases identified that did not meet the definition of a true anaphylaxis case, because they were non-serious, were excluded.
2. All serious cases of hypersensitivity were considered potentially ‘significant’. In addition, non-serious cases of hypersensitivity determined to be NCI Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher were considered potentially ‘significant’.
3. Potentially ‘significant’ hypersensitivity/anaphylactic reactions that were not excluded in criteria 1 and 2 were medically reviewed and excluded if there was evidence documenting a clearly-stated alternative medical diagnosis/explanation provided by the reporting party. In the absence of a clearly-stated alternative medical diagnosis/explanation, cases in which the onset of *all* corresponding events occurred >48 hours from start of infusion also were excluded.

Variables and data sources
The outcome was the history of immunology testing as recorded in Genzyme Clinical Specialty Laboratory database, including testing for alglucosidase alfa IgE antibody, complement activation, serum tryptase, or alglucosidase alfa IgG antibody since treatment start performed in patients with

a reported significant hypersensitivity/anaphylactic reaction. Specific subtypes of testing (alglucosidase alfa IgE antibody, complement activation, serum tryptase, and alglucosidase alfa IgG antibody) also were analyzed separately. The absence of a record of testing for a patient in this study was considered as not having an immunology test performed, and therefore, there were no missing data for this endpoint.
The following data sources were used:

1. Sanofi Genzyme's Pharmacovigilance adverse event database,
2. Sanofi Genzyme Clinical Specialty Laboratory database (capturing records and/or results of immunology testing conducted in these laboratories).

Data pertaining to the same patients were linked across these two databases using date of birth, initials and country of origin.

Sample Size
After inclusion/exclusion criteria were applied, the analysis included 48 patients in the pre-SIP period and 46 patients in the post-SIP period with a spontaneously reported significant hypersensitivity/anaphylactic reaction during their country-specific pre- or post-SIP implementation period within the time period from July 22, 2012, to April 30, 2019 (data lock point (DLP) of this final report).

Prevalence calculation
The prevalence of immunology testing in patients treated with alglucosidase alfa with significant hypersensitivity/anaphylactic reactions was calculated by dividing the number of patients with a history of immunology testing among Groups 1 and 2 by the number of patients with significant anaphylactic/hypersensitivity reactions in Groups 1 and 2, respectively.

Results
A total of 92 unique patients with reported significant hypersensitivity/anaphylaxis reactions from 9 European countries were included in this study, with 2 patients contributing data to each period. Patient characteristics were generally similar between those included in the pre-SIP (Group 1) and post-SIP (Group 2) periods. Of the 48 patients included in the pre-SIP period, 58% had a record of immunology testing. In contrast, of the 46 patients included in the post-SIP period, 28% had a record of immunology testing for an absolute difference of 30% (95% CI 11% to 49%) between periods. The difference in the prevalence of testing between Groups 1 and 2 was consistent across subgroup analyses stratified by patient characteristics and significant hypersensitivity/anaphylaxis reaction types.

Discussion
The 30% decrease in the prevalence of testing between the two periods of 3 years before and after the implementation of the revised SIP (version 8.2) went in a direction opposite of what may have been intuitively expected after implementing risk minimization measures, that is that an improved SIP with a recommendation to test patients might increase the number of tests requested. In retrospect, it could be that a consequence of this clarifying update could have been that the testing approach was clearer and therefore fewer "unnecessary" samples could have been drawn. With the limitations of the data collected, it is not possible to differentiate routine immunological testing that may have been performed from any for-cause testing. The manual efforts to accurately link data sources and the consistency of the prevalence difference across subgroup analyses suggest the result may not be a technical artifact. A limitation of the pre-post study design is

historical bias, which may have played a role in the observed difference in prevalence testing that was independent of the implementation of the revised SIP.