Reported outcomes of 453 pregnancies in patients with Gaucher disease: An analysis from the Gaucher outcome survey

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A B S T R A C T

Gaucher disease (GD) may worsen during pregnancy, leading to the discussion of continuing treatment during pregnancy. We examined fetal outcomes of pregnancies reported in the Gaucher Outcome Survey, an international GD-specific registry established in 2010. A total of 453 pregnancies were reported. Most pregnancies (336/453, 74.2%) were in women who did not receive GD-specific treatment during pregnancy, while enzyme replacement therapy (ERT) was received during 117/453 (25.8%) pregnancies. No pregnancies exposed to substrate reduction therapy were reported. The percentage of normal outcomes (live birth delivered at term with no congenital abnormalities) was similar in untreated and treated pregnancies (92.9% vs. 91.4%). The percentage of spontaneous abortions in untreated pregnancies was 3.6% (95% CI, 1.9–6.2%) compared with 6.9% (95% CI, 3.0–13.1%) in treated pregnancies (p = 0.1866). In women who received velaglucerase alfa 1 month prior to conception and/or during pregnancy, 34/36 (94.4%) pregnancies had normal outcomes and 2 (5.6%) ended in spontaneous abortion. Normal outcomes were observed in the 20 pregnancies with velaglucerase alfa exposure starting < 1 month prior to conception and continuing through all trimesters. These observations, in addition to information in the literature, suggest that continuation of ERT during pregnancy may be appropriate for GD patients.

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1. Introduction

The lysosomal storage disorder Gaucher disease (GD), is caused by a deficiency of the enzyme β-glucocerebrosidase. Signs and symptoms of the disease result from accumulation of the enzyme’s glycolipid substrate in the cells of the monocyte-macrophage system. Type 1 GD is the most common form of the disease, predominantly affecting the hematologic, visceral, and skeletal systems. The acute (type 2) and chronic (type 3) neuromopathic forms of the disease affect a minority of GD patients [1]. Pregnancy has been reported to exacerbate disease manifestations in women with GD and patients may be at higher risk of experiencing complications such as bleeding during delivery and postpartum [2,3].

Enzyme replacement therapy (ERT) with recombinant β-glucocerebrosidase is available for patients with symptomatic type 1 and type 3 GD and is effective for improving hematological and visceral disease manifestations [4,5]. The first ERT for GD, alglucerase, became available in 1991, and those currently available are imiglucerase, velaglucerase alfa and taliglucerase alfa.

The use of alglucerase or imiglucerase during pregnancy in symptomatic patients with GD has been associated with a reduced incidence
of spontaneous abortions and GD-related complications during delivery and postpartum compared with untreated patients [2]. A study of women with GD who were exposed to velaglucerase alfa during pregnancy, some of whom may be included in the analysis presented here, reported normal outcomes for 21 of 25 pregnancies (the remaining 4 ended in early first trimester missed abortions), and postpartum complications in only 1 of 21 pregnancies (placental tear and bleeding, which resolved without intervention) [6].

Oral substrate reduction therapies (SRTs) with glucosylceramide synthase inhibitors have also demonstrated efficacy for the treatment of type 1 GD. The two approved SRTs, miglustat and eliglustat, have similar mechanisms of action but are structurally different and have distinct side-effect profiles. Eliglustat is the only SRT approved as a first-line therapy for adults with type 1 GD. There are limited data on the use of SRT in human pregnancy. In animal studies, maternal death has been observed with miglustat and fetal harm has been shown with both eliglustat and miglustat [7,8].

Risk summaries and guidance provided in product labeling on the use of GD-specific ERTs and SRTs during pregnancy in the United States and the European Union vary (Table 1).

Recommendations published in 2011 by a panel of GD experts propose that asymptomatic patients should not be advised to start ERT before pregnancy, and that the initiation of ERT during pregnancy should only be considered if there is a clear worsening of several disease parameters [9]. For symptomatic patients not receiving treatment, starting ERT before pregnancy may help prevent worsening of disease parameters and GD-related complications during pregnancy. Patients already on treatment should be encouraged to remain on treatment during pregnancy at their pre-pregnancy dose, though dose adjustments during pregnancy could be considered if disease parameters worsen. The decision to start or continue treatment during pregnancy is based on a patient's informed decision, which must be respected.

The overall objective of this study was to assist pregnant women with GD and their physicians in their consideration of treatment during pregnancy. We sought to obtain evidence by evaluating the fetal outcomes of pregnancies in GD patients using real-life data from the Gaucher Outcome Survey (GOS). GOS is an international observational GD-specific registry established in 2010. Patients with a confirmed diagnosis of GD can be enrolled in GOS regardless of their GD type or treatment status. The registry is designed to document the clinical outcome of patients over time and collects real-world information on many aspects of GD, such as key disease features, treatment patterns, and medical history. In collaboration with GD experts at 34 medical centers in 11 countries, GOS has 1094 patients enrolled as of July 2016. Here we report on the pregnancy events in patients enrolled in GOS at the time of the July 30, 2015 data extract.

2. Patients and methods

2.1. Pregnancy data collected

Data on pregnancy events were collected via the GOS electronic case report form (Supplementary Table 1). The form was completed for pregnancies of enrolled females and may include pregnancies that occurred before enrollment into GOS.

Data on patients’ GBA1 genotype was provided via selection from a prespecified list or entered as free text. Free-text entries were manually reclassified into one of eight categories following review by a GOS study medical monitor.

Information on GD-specific treatment status and treatment received during pregnancy was collected. GD-specific treatments were defined as the ERTs alglucerase, imiglucerase, velaglucerase alfa, and taliglucerase alfa, and the SRTs, miglustat and eliglustat. If a patient received velaglucerase alfa, additional information on the dose received and timing of treatment during pregnancy was obtained (the timing of treatment during pregnancy could only be entered for velaglucerase alfa as it was not requested for other treatments received during pregnancy [Supplementary Table 1]).

Information on fetal outcomes was provided via selection from a pre-specified list. Outcomes in the list were: normal, spontaneous abortion, elective abortion, neonatal death, intrauterine stillbirth, stillbirth during delivery, and congenital abnormality. A normal pregnancy outcome indicates a delivery at term resulting in a live birth with no congenital abnormalities.

2.2. Analysis

Pregnancy data were analyzed for the overall cohort and in subgroups based on GD-specific treatment status during pregnancy: 1) patients who received velaglucerase alfa; 2) patients who received GD-specific treatment other than velaglucerase alfa (imiglucerase, alglucerase or taliglucerase alfa; no pregnancies exposed to SRT were reported); and 3) patients who did not receive any GD-specific treatment.

For comparison of pregnancy outcomes in untreated pregnancies and those exposed to GD-specific treatment, the percentage of pregnancies with a normal outcome or ending in spontaneous abortion and 95% exact confidence interval (CI) for percentages were calculated. A p-value for the Fisher exact test of no difference in probability of a specific pregnancy outcome (normal or spontaneous abortion) was also calculated, assuming independence between pregnancies occurring in the same patient. Calculated p-values are results of exploratory analysis and should be interpreted descriptively; p-values over a prespecified significance level (5%) cannot be interpreted as evidence of no difference between groups.

2.3. Adverse events

No data on pregnancy-related or GD-related complications during pregnancy were collected in the pregnancy form. Information on any adverse events that occurred at any time in women in the pregnancy cohort were extracted and reviewed by a GOS medical monitor. The start and stop dates of the events and the end date of pregnancy were used to determine whether an adverse event occurred during pregnancy.

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Table 1

| Treatment name | United States Prescribing Information | European Medicines Agency Summary of Product Characteristics |
|----------------|--------------------------------------|----------------------------------------------------------|
| Imiglucerase (Cerezyme®) | “Cerezyme should not be administered during pregnancy except when the indication and need are clear and the potential benefit is judged by the physician to substantially justify the risk” [18]. | “Treatment naïve women should be advised to consider commencing therapy prior to conception in order to attain optimal health”. “In women receiving Cerezyme treatment continuation throughout pregnancy should be considered” [14]. |
| Velaglucerase alfa (VPRIV®) | “VPRIV should be used during pregnancy only if clearly needed” [17]. | “Caution should be exercised when prescribing to pregnant women” [23]. |
| Miglustat (Zavesca®) | “Zavesca should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus” [7]. | “Miglustat crosses the placenta and should not be used during pregnancy” [19]. |
| Elaglutat (Cerdenga®) | “Cerdenga should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus” [6]. | “As a precautionary measure, it is recommended to avoid the use of Cerdelga during pregnancy” [24]. |

* Refer to referenced prescribing information and summaries of product characteristics for complete risk summaries and labeling regarding use of these treatments in pregnancy.
3. Results

3.1. Baseline demographics

Pregnancies were reported for 189 women enrolled in GOS (Table 2). The women had a median (interquartile range [IQR]) age at GD symptom onset of 17.3 (8.6–26.9) years and a median (IQR) age at time of GD diagnosis of 19.4 (9.3–28.4) years. The most common GBA1 genotype in the women with available data was N370S/N370S (93/162, 57.4%).

3.2. Pregnancy events, overall cohort of treated and untreated patients

A total of 453 pregnancies with delivery or end dates from January 1959 to July 2015 were reported (Fig. 1). Most pregnancies were reported from Israel (368/453, 81.2%; Supplementary Fig. 1). For patients with GD type provided (188/189, 99.5%), all pregnancies were in patients with type 1 GD, except for two in one woman with type 3 GD. Both of the type 3 GD patient’s pregnancies occurred in the late 1970s before ERT was available. Her first pregnancy, at age 19, resulted in a spontaneous abortion, while her second pregnancy, at age 21, had a normal outcome.

Of the 452 outcomes reported for 453 pregnancies, 418 (92.5%) had normal outcomes (delivery at term resulting in a live birth with no congenital abnormalities). The median (IQR) age of patients at delivery for pregnancies with normal outcomes was 29.5 (25.3, 33.1) years (Supplementary Table 2). For the remainder of pregnancies with specified outcomes, 20 (4.4%) resulted in spontaneous abortion, 13 (2.9%) in elective abortion, and 1 (0.2%) in neonatal death (Table 3).

3.3. Pregnancies in patients receiving velaglucerase alfa

There were 36 pregnancies with exposure to velaglucerase alfa <1 month before conception or at some time during pregnancy, 34 (94.4%) of which had normal outcomes (Table 4). For the pregnancies with dose information (33 dose entries for 30 pregnancies), velaglucerase alfa was received at ≥20 U/kg in 14 entries and ≥20 U/kg in 19 entries.

Two (2/36, 5.6%) pregnancies with exposure to velaglucerase alfa and ending in spontaneous abortion were reported in one patient. In both instances, the patient received velaglucerase alfa (15 U/kg every other week) prior to conception, but not during pregnancy. She subsequently had a pregnancy with a normal outcome where she received the same dose of velaglucerase alfa before conception and during her first and second trimesters.

Of the 36 pregnancies with exposure to velaglucerase alfa, there were 20 during which treatment was received before conception and in all trimesters (Table 5). All 20 of these pregnancies had normal outcomes.

3.4. Pregnancies in patients receiving GD-specific treatment other than velaglucerase alfa

There were 81 pregnancies with exposure to GD-specific treatment other than velaglucerase alfa, namely alglucerase (n = 6), imiglucerase (n = 63), or taliglucerase alfa (n = 6, treatment not specified in six; Table 4).

In pregnancies with exposure to alglucerase, all six had normal outcomes. In pregnancies with exposure to taliglucerase alfa, four of six had normal outcomes, one ended in spontaneous abortion and one in elective abortion.

In women who received imiglucerase, 56 of 62 pregnancies (90.3%; outcome not specified for one) had normal outcomes and one ended in elective abortion. Five events of spontaneous abortion were reported in three patients, including one patient who had three normal outcomes before the loss and three after with exposure to imiglucerase.

3.5. Pregnancies in untreated patients

Most pregnancies in GOS were not exposed to any GD-specific treatment (356/453, 74.2%). For pregnancies with end dates available (n = 324), 135 occurred prior to 1991, before ERT was available. Of the 336 untreated pregnancies, 312 (92.9%) had normal outcomes (Table 4). Twelve (3.6%) ended in spontaneous abortion, 11 (3.3%) in elective abortion, and one in neonatal death (0.3%).

The patient whose pregnancy resulted in neonatal death had normal pregnancy outcomes approximately 2.5 years before the event and 1 year after the event, both without receiving GD-specific treatment. She subsequently had a third normal outcome while receiving velaglucerase alfa before conception and throughout pregnancy. One patient experienced a spontaneous abortion when not receiving treatment during pregnancy; approximately 2 years later she had a normal pregnancy outcome while receiving velaglucerase alfa before conception and throughout pregnancy.

For pregnancies with end dates available, the percentage of spontaneous abortions in untreated pregnancies before 1991 (5/135, 3.7%) was similar to that reported after 1991 (6/189, 3.2%). The percentage of normal outcomes in untreated pregnancies was 92.9% (95% CI, 89.6%–95.4%) compared with 91.4% (95% CI, 84.7%–95.8%) in those exposed to GD-specific treatment (p = 0.6830; Table 4). The percentage of spontaneous abortions in untreated pregnancies was 3.6% (95% CI, 1.9%–6.2%), compared with 6.9% (95% CI, 3.0%–13.1%) in those exposed to GD-specific treatment (p = 0.1866). The median (IQR) age of patients at the end of treated pregnancies was 31.9 (28.6, 35.0) years compared with 28.8 (24.2, 32.2) years for untreated pregnancies (Supplementary Table 2).

3.6. Adverse events

An adverse event of gestational diabetes was reported for one woman who received velaglucerase alfa during the second trimester of a pregnancy with a normal outcome. Also reported was an event of congenital abnormalities (polydactyly and possible microprosopus) in a baby with trisomy 13 born to a woman whose pregnancy was recorded as having a normal outcome. The woman had GBA1 genotype N370S/L444P and received imiglucerase at 30 U/kg every other week for the second half of her pregnancy. Both adverse events were deemed unrelated to treatment.

An adverse event of monoclonal gammopathy of undetermined significance (MGUS) was reported in a woman who had two untreated

Table 2
Demographics of women with pregnancies reported in GOS (n = 189).

| Characteristics | Patients (n = 189) |
|-----------------|-------------------|
| GD type, n (%)  |                   |
| Type 1          | 187 (99.5)        |
| Type 3          | 1 (0.5)           |
| Missing information | 1                 |
| GBA1 genotype, n (%)ab |         |
| [c.1226A > G] + [c.1226A > G] [N370S/N370S] | 93 (57.4) |
| [c.1226A > G] + [c.144T > C] [N370S/L444P] | 14 (8.6) |
| [c.1226A > G] + [c.84dupG] [N370S/84GG] | 12 (7.4) |
| [c.1226A > G] + Other [N370S/other] | 31 (19.1) |
| [c.1226A > G] + Unknown [N370S/unknown] | 8 (4.9) |
| [c.144T > C] + Other [L444P/other] | 1 (0.6) |
| Other/other     | 3 (1.9)           |
| Missing information | 27                |
| Age at GD symptom onset, median (IQR) years | 17.3 (8.6, 26.9) |
| Age at GD diagnosis, median (IQR) years | 19.4 (9.3, 28.4) |
| Age at end of pregnancy, median (IQR) years | 29.5 (25.2, 33.0) |

a Percentages determined from number of patients with available data.

b GBA1 genotype numbers obtained following reclassification that occurred outside the database entry (manual reclassification of free-text entries), which must be considered.

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pregnancies with normal outcomes. Her MGUS was diagnosed approximately 5 years after her second pregnancy.

4. Discussion

We report fetal outcomes for 189 GD patients enrolled in GOS, which includes outcomes from the largest cohort of velaglucerase alfa-treated pregnant women published to date. Most pregnancies resulted in reported normal outcomes. Although the percentage of normal outcomes in untreated pregnancies was similar to that in pregnancies exposed to ERT, it is possible that untreated women may have had milder GD than those who received ERT during pregnancy after it became available in 1991[2]. Women in the untreated pregnancy group may also have been receiving treatment prior to pregnancy (then discontinued treatment during pregnancy), thereby affording amelioration of disease burden before pregnancy[9]. Furthermore, more than

| Patient | GBA1 genotype | Age at pregnancy loss (years) | Type of pregnancy loss | Treatment received during pregnancy |
|---------|---------------|------------------------------|------------------------|------------------------------------|
| 1       | N370S/N370S   | 31.2                         | Spontaneous abortion   | Velaglucerase alfa 15 U/kg EOW     |
| 3       | N370S/N370S   | 30.6                         | Spontaneous abortion   | Velaglucerase alfa 15 U/kg EOW     |
| 5       | N370S/N370S   | 23.9                         | Spontaneous abortion   | Taliglucerase 15 U/kg EOW          |
| 8       | N370S/N370S   | 29.5                         | Spontaneous abortion   | Untreated                          |
| 9       | N370S/N370S   | 25.5                         | Spontaneous abortion   | Untreated                          |
| 10      | N370S/N370S   | 29.6                         | Spontaneous abortion   | Untreated                          |
| 11      | N370S/N370S   | 20.5                         | Spontaneous abortion   | Untreated                          |
| 13      | N370S/V433 L  | 23.3                         | Spontaneous abortion   | Untreated                          |
| 15      | N370S/R496H   | 22.4                         | Spontaneous abortion   | Untreated                          |
| 16      | Missing       | 19.9                         | Spontaneous abortion   | Untreated                          |
| 17      | Missing       | 30.5                         | Spontaneous abortion   | Untreated                          |
| 18      | N370S/N370S   | 29.5                         | Spontaneous abortion   | Untreated                          |
| 19      | N370S/N370S   | 33.6                         | Elective abortion      | Untreated                          |
| 20      | N370S/N370S   | 31.3                         | Elective abortion      | Untreated                          |
| 21      | N370S/N370S   | 32.2                         | Elective abortion      | Untreated                          |
| 22      | N370S/N370S   | 22.1                         | Elective abortion      | Untreated                          |
| 23      | N370S/N370S   | 23.7                         | Elective abortion      | Untreated                          |
| 24      | N370S/N370S   | 31.9                         | Elective abortion      | Untreated                          |
| 25      | N370S/L444P   | 30.3                         | Elective abortion      | Untreated                          |
| 26      | N370S/RecTL   | 24.3                         | Elective abortion      | Untreated                          |
| 27      | Missing       | 23.4                         | Elective abortion      | Untreated                          |
| 28      | N370S/N370S   | 28.9                         | Neonatal death         | Untreated                          |

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The use of ERT during pregnancy in patients with GD has been associated with normal pregnancy outcomes while receiving velaglucerase alfa during pregnancy. While there is no evidence that ERT has a teratogenic effect on pregnancies in GD patients, its use can cause hypersensitivity or infusion-related reactions that could potentially be associated with unfavorable maternal or fetal outcomes during pregnancy. The ERTs for GD have generally acceptable tolerability profiles, but hypersensitivity reactions, including anaphylaxis, have been reported for imiglucerase, velaglucerase alfa, and taliglucerase alfa [16–18].

Velaglucerase alfa has been shown to have an acceptable tolerability profile in clinical trials in which assessment of safety was a primary objective (in patients who were not pregnant) [4,19,20]. Of 54 patients naïve to ERT who participated in velaglucerase alfa clinical trials, 28 (52%) experienced hypersensitivity reactions, the majority of which were mild and occurred during the first 6 months of treatment [17]. In our analysis, there was only one adverse event of gestational diabetes reported in a woman who received velaglucerase alfa during the second trimester of her pregnancy. The event was deemed unrelated to treatment and her pregnancy had a normal outcome. No infusion-related reactions or drug-related adverse events attributed to velaglucerase alfa were reported in this cohort of women during their pregnancies.

All 20 patients who received velaglucerase alfa prior to conception and in all three trimesters of their pregnancies had normal pregnancy outcomes. A further 14 of 16 pregnancies in patients who received velaglucerase alfa at some point prior to conception and/or during pregnancy also had normal outcomes. For nearly half of dose entries reported, velaglucerase alfa was received during pregnancy at <20 U/kg. This result likely reflects the high proportion of pregnancies with exposure to velaglucerase alfa reported from Israel [26/36, 72.2%], where ERT is generally administered at lower doses compared with other countries [21].

The analysis presented here is limited because GOS collects patient data from real-world clinical settings and is not designed specifically to investigate the effect of treatment on pregnancy outcome. The registry also does not have strict inclusion and exclusion criteria such as those in clinical trials, and may be subject to selection bias. Except for live birth, congenital abnormality, and neonatal death, no data on neonatal outcomes are collected in GOS. No adverse neonatal outcomes related to treatment have been suggested in studies of pregnancies in ERT-treated GD patients in which neonates were followed after birth [12,22]. Furthermore, no information on the postpartum period was collected for GOS patients. This period is important to assess as patients may experience GD-related complications following a pregnancy with a normal outcome. Additional evidence is needed to better understand how treatment during pregnancy influences complications and disease course postpartum.

### Table 4

| Pregnancy outcome                  | Untreated | Treated (all) | Velaglucerase alfa | Other GD treatment |
|------------------------------------|-----------|---------------|--------------------|-------------------|
|                                    | n = 336   | n = 143       | n = 117            | n = 68            |
| Normal                             | 312 (92.9%) | 139          | 106 (91.4)         | 67                |
| Spontaneous abortion               | 12 (3.6%)  | 11            | 8 (6.9%)           | 5                 |
| Elective abortion                  | 11 (3.3%)  | 10            | 2 (1.7%)           | 2                 |
| Neonatal death                     | 1 (0.3%)   | 0             | 0                  | 0                 |
| Unknown                            | 0          | 0             | 0                  | 0                 |

GD, Gaucher disease; GOS, Gaucher Outcome Survey.

* Other GD-specific treatments specified were alglucerase (n = 6), imiglucerase (n = 63), and taliglucerase alfa (n = 6); treatment type was unspecified in six pregnancies.

* Percentages determined from total number of pregnancies with specified outcomes.

* Patient subsequently had a normal pregnancy outcome while receiving velaglucerase alfa before conception and during her first and second trimesters.

### Table 5

| Timing of exposure to velaglucerase alfa during pregnancy |
|----------------------------------------------------------|
| **< 1 month before conception** | First trimester | Second trimester | Third trimester | Number of patients n = 32 | Number of pregnancies n = 36 |
|✓ | ✓ | ✓ | ✓ | 19 | 20 |
|✓ | ✓ | ✓ | ✓ | 1 | 1 |
|✓ | ✓ | ✓ | ✓ | 1 | 1 |
|✓ | ✓ | ✓ | ✓ | 3 | 4 |
|✓ | ✓ | ✓ | ✓ | 2 | 2 |
|✓ | ✓ | ✓ | ✓ | 1 | 1 |
|✓ | ✓ | ✓ | ✓ | 5 | 6 |

GOS, Gaucher Outcome Survey.
5. Conclusions

Our results provide evidence that may aid GD treatment decisions so that asymptomatic patients are not started on treatment unnecessarily during pregnancy, and provide guidance for symptomatic patients who may become pregnant during treatment. The normal outcomes reported for the 20 pregnancies exposed to velaglucerase alfa throughout, adds to information in the literature suggesting that continuation of ERT during pregnancy may be appropriate for GD patients.

Authorship contributions

HL, NB, PD, OG-A, IVDS, SPS and AZ are investigators involved in GOS. ZP is the GOs medical monitor. All authors contributed to the development of the manuscript, critically reviewed the manuscript during development, and approved the final draft prior to submission.

Conflicts of interest disclosures

HL receives consulting fees from Genzyme and Pfizer; is a member on the advisory board or similar committee of Shire; has participated in clinical trials sponsored by Amicus, Biomarin, GlaxoSmithKline, Genzyme/Sanoﬁ, Shire, Pfizer, and Ultragenyx; has participated in clinical studies using products manufactured by Amicus, Biomarin, Genzyme/Sanoﬁ, Pfizer, Shire, and Ultragenyx; and conducts research supported by Genzyme/Sanoﬁ. NB receives consulting fees from Genzyme and Shire; is a member on the advisory board or similar committee of Genzyme and Shire; has participated in clinical studies using products manufactured by Genzyme; and has conducted research supported by Genzyme and Shire. PD receives consulting fees from Genzyme, Shire, Amicus, and Alexion; has participated in clinical trials sponsored by Genzyme, Amicus, Protalix, and Shire; and has conducted research supported by Genzyme and Shire. OG-A receives consulting fees from Actelion, Pfizer, Shire, and Genzyme; has participated in clinical trials sponsored by Amicus, Genzyme, Shire, Alexion, and Protalix; and has conducted research supported by Genzyme, Shire, and Pfizer. IVDS is a member on the advisory board or similar committee of Shire; has participated in clinical trials sponsored by Genzyme, Shire, and Protalix; is a primary investigator in clinical trials and has received research support and educational grants sponsored by Genzyme, Biomarin, Shire, Protalix, Actelion, and Amicus. ZP is an employee of Shire. AZ receives honoraria from Shire, Genzyme/Sanoﬁ, and Pfizer; has participated in clinical trials sponsored by Shire; and his institution receives support from Genzyme, Shire, and Pfizer for participation in their respective registries.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.bcmd.2016.10.003.

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