To the Editor:

Gaucher disease (GD) is a lysosomal storage disorder for which safe and effective intravenous enzyme replacement therapy (ERT) has been available for more than 25 years. The safety of the several ERTs for GD has also afforded the possibility of home infusions, reported by patients to be less stressful than those received in the hospital setting. ERT is usually a life-long commitment to infusions, and many patients find the every-other-week (EOW) hourly infusions onerous, impacting aspects of their quality of life, including time taken off school/work. Over the past 2 decades, we became aware of several anecdotal reports from patients who while responsible for their infusions at home, decreased the infusion duration from the standard 60 min to as little as 2-5 min without apparent untoward effect.

Previous experience with a rapid intravenous infusion of biological materials, in particular, monoclonal antibodies, have defined a variable potential for reactions ranging from mild local irritations at the access site, various inflammatory and immunological responses to life-threatening hypersensitivities and anaphylactoid reactions. These reactions could conceivably occur too quickly for an effective response by a medical team, particularly in the home environment. Even in patients previously exposed to a particular drug without a reaction when infused at a standard rate, such concern is never trivial. Thus, in designing a study protocol to assess the safety of decreased infusion time of velaglucerase alfa from 60 to 10 min using a step-wise reduction in time and allowing for home infusions in the final phase.

Figure 1 shows the timeline of the study design. The volume for each infusion in the study was set at 100 mL, controlled with an infusion pump (hospital) and by gravity (home). This study was a prospective study. The protocol guaranteed the safety of the patient by measuring blood pressure, heart rate and temperature at four time points during the hospital clinic setting (ie, 10 min prior, at the start, at the end of infusion and 1 h after the start of the infusion) and at the home setting (ie, blood pressure was measured before and after the infusion).

Inclusion criteria for the study were: age ≥ 18 years, nonsplenectomized, ≥ 3 months exposure to velaglucerase alfa at a stable dose with no infusion-related or drug-related adverse events (AEs) and no clinically significant comorbidities. Safety was the primary end-point as determined by AEs during or directly after infusions as monitored by an experienced nurse. Efficacy parameters included hemoglobin concentration and platelet counts, spleen and liver volume estimation by ultrasound and determination of the biomarker glucosylsphingosine (lyso-Gb1) (Centogene, Rostock, Germany). Drug concentration was assessed in plasma samples taken at time 0-90 min posttransfusion at study baseline, that is, 60-min transfusion, and at end-of-study (EOS), that is, 10-min transfusion. Nonvalidated questionnaire of 7 visual analog scales in Hebrew was used to assess disease impact. These were continua of 0-10 points, worst case to best case scenarios regarding: (1) dependence, (2) constant fatigue, (3) unremitting bone pain, (4) depression related to GD, (5) dissatisfaction with treatment, (6) family severely impacted by GD, and (7) pessimistic about future. Local institutional review board approval was granted for the study, and all participating patients provided written informed consent before commencing study procedures.

Descriptive statistics were employed. Baseline and 9 months hematologic parameters, spleen, and liver volume estimation and lyso-Gb1 levels were compared using the paired t test for normally distributed data. Statistical analysis was performed with SPSS statistical package (version 22 for Windows). A P value < .05 was considered significant.

Fifteen patients, mean age 32 (range 22-44) years, genotype N370S homozygous (N = 7) or heterozygous, were recruited (Supporting Information Table S1). No patient had AEs while receiving velaglucerase alfa infusions for a mean of 9.6 (range: 2.5-17) years. All patients were maintained on prestudy dosages (15-60 units/kg body weight)/infusion EOW.

There were no severe AEs associated with the 10-min infusions, in the clinic or at home; the only mild AE was a single female patient who experienced discomfort (feeling cold) in the infused arm during two 10-min infusions. This patient subsequently became pregnant and was withdrawn from the trial. A second patient withdrew for personal reasons.

All the patients maintained stability in the key disease features including the hematological parameters, organ volumes, and lyso-Gb1 levels (Supporting Information Table S1; P > .1). The drug concentration/time curves differed in peak levels (higher for 10-min infusion) and width (longer for the 60-min infusion) (Supporting Information Table S2).
The timeline of the study consisted of three parts, starting with 3 months at the standard infusion time of 60 min EOW in the home setting. Next was an accelerated infusion rate phase of 3 months with 1 infusion at 30 min, 1 infusion at 20 min, and then 4 infusions over 10 min, all in the hospital clinic setting. The final stage of 3 months duration was 5 infusions over 10 min at home and an EOS infusion plus study evaluations in the clinic. Arrows denote biweekly infusions, the wide arrow show infusions given in the hospital setting (SZMC) and the thin arrows show infusions given in the home setting. AE, adverse event; EOS, end of study clinic evaluation [Color figure can be viewed at wileyonlinelibrary.com]

Figure S2). Of the 13 patients who completed the questionnaire at baseline and at EOS, scores across scales remained stable over time with only the pregnant patient mean scores are decreasing from 9.2 to 3.5. The remaining mean scores ranged from 5.3–9.4 at baseline and 7.6–9.7 at EOS. Similarly, mean responses to the specific questions were not significantly altered over the study period, remaining in the 6.2–9.7 range. No patient developed antibodies. In total 12 patients have continued into a 15-month extension phase of the study which is ongoing (MOH_2017-10-19_001865).

With this study protocol, we established that step-wise shortening of infusion duration, from 1 h to 10 min in 3 stages over 6 months and as home infusions, did not compromise the safety or efficacy of treatment in adult patients with type 1 GD receiving velaglucerase alfa EOW at dosages ranging from 15 to 60 units/kg body weight. Return to the home setting was uneventful and was achieved by the known safety profile of this ERT. The pharmacodynamics differences seen when shortening infusion duration to 10 min are expected, however future studies, such as our pending trial in naïve patients are required to explore the potential ramification with regard to efficacy.

Regarding the impact on some features of disease-related psychosocial issues, all but one patient indicated no change over time when asked to complete scales of some basic health-related quality of life queries. Disease-specific clinical parameters and the biomarker lysoGb1 were maintained over the course of the study among all patients. Anecdotal reports and willingness of most patients to continue in an extension phase confirm the value of convenience, specifically decreased infusion duration, to patients for whom ERT infusions are currently envisioned to be a life-long commitment. Thus, as the impetus for reducing infusion times for ERT was also initially driven by patients (some with decades-long exposure to intravenous ERT), it is not unlikely that patients with comparable medical profiles might be encouraged to attempt this “change in practice” protocol.

Moreover, this approach may also have broader implications for healthcare providers and payers because of the possibility of reducing the considerable costs engendered by both prolonged intravenous administrations and the reliance on a hospital setting. For many patients, the safety of velaglucerase alfa allows for shorter home infusion durations.

We conclude that this study provides evidence to consider more rapid infusion of velaglucerase alfa in patients with type 1 GD stable on infusion therapy without prior infusion-related toxicities and is equally applicable in the clinic setting and for home therapy.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conceived the study and helped design the protocol, analyzed the results, and reviewed all versions of the article: Zimran

Involved in data analysis, article writing, and reviewed all versions of the article: Revel-Vilk

Assisted in the various technical and logistic aspects of the trial and reviewed all versions of the article: Becker-Cohen

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REFERENCES

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.