A multicenter, open-label, phase III study of Abcertin in Gaucher disease

Beom Hee Lee, MD, PhD, Ahmed Fathy Abdalla, MD, PhD, Jin-Ho Choi, MD, PhD, Amal El Beshlawy, MD, Gu-Hwan Kim, PhD, Gu-Hwa Han, MD, Sun Hee Heo, MS, Ahmed Megahed Hassan Megahed, MD, PhD, Mona Abdel Latif Elsayed, MD, PhD, Tarik El-Sayed Mohammad Barakat, MD, PhD, Khaled Mohamed Abd El-Azim Eid, MD, Mona Hassan El-Tagui, MD, Mona Mohamed Hamdy Mahmoud, MD, Ekram Fateen, MD, June-Young Park, PhD, Han-Wook Yoo, MD, PhD.

Abstract

Background: Gaucher disease (GD) is caused by a deficiency in the lysosomal enzyme glucocerebrosidase. Enzyme replacement therapy (ERT) is recommended for clinical improvement.

Methods: The efficacy and safety of a new imiglucerase, Abcertin, were assessed in 7 Egyptian patients with treatment-naive type 1 GD. Each patient was administered a biweekly 60 U/kg dose of Abcertin for 6 months. The primary endpoint was the change in hemoglobin concentration. The secondary endpoints were changes from baseline in platelet counts, spleen and liver volumes, biomarker levels, skeletal parameters, and bone mineral density.

Results: The hemoglobin concentration increased by a mean of 1.96±0.91 g/dL (range 1.11–2.80 g/dL) or 20.6% (p = .001). Statistically significant increases in the platelet count and decreases in the spleen volume and biomarker levels were also observed. There were no severe drug-related adverse events. One patient developed anti-imiglucerase antibodies without neutralizing activity.

Conclusion: Our study results demonstrate the efficacy and safety of Abcertin in patients with type 1 GD. This suggests that Abcertin can be an alternative ERT option for type 1 GD.

Abbreviations: ACE = angiotensin-converting enzyme, ACP = acid phosphatase, AUClast = last measurable concentration, BMD = bone mineral density, CCL-18 = chemokine ligand 18, CL = serum clearance, Cmax = maximum concentration of drug, ERT = enzyme replacement therapy, GD = Gaucher disease, MN = multiple of normal, MRI = magnetic resonance imaging, PK = pharmacokinetic, t1/2 = half-life, Tmax = time to Cmax, Vd = volume of distribution.

Keywords: enzyme replacement therapy, Gaucher disease, imiglucerase

1. Introduction

Gaucher disease (GD, OMIM #230800), the most prevalent glycolipid storage disorder, is caused by a deficiency in the lysosomal enzyme glucocerebrosidase (GBA). The overall incidence of GD is approximately 1 in 40,000 to 60,000 people depending on the ethnicity.[1,2]

Gaucher disease is an autosomal recessive disorder that presents in 3 clinical forms. Type 1 GD is characterized by anemia, thrombocytopenia, bone pain, hepatosplenomegaly, and growth retardation without neurological involvement. In contrast, neurological manifestations are observed in patients with types 2 and 3 GD. Type 2 GD is an acute and rapidly fatal form, whereas type 3 exhibits a more attenuated, chronic neurological course.[3–6]

Gaucher disease is a disease prototype for which enzyme replacement therapy (ERT) is recommended as the standard treatment in symptomatic patients. ERT effectively improves the clinical outcome of GD, particularly with regard to hepatosplenomegaly and hematological abnormalities.[7] Imiglucerase (Cerezyme; Genzyme Corp., Cambridge, MA), which was approved by the US Food and Drug Administration in 1994, is the most widely used recombinant human β-GBA.[8] The long-term safety and efficacy of Cerezyme have been well-validated.[8] and this agent is currently prescribed for patients with type 1 GD in over 50 countries. To date, 2 other forms of recombinant
β-GBA have been developed for the treatment of GD: velaglucerase alfa (VPRIV; Shire Human Genetic Therapies, Lexington, MA) and taliglucerase alfa (Elyso; Pfizer, New York, NY).[6,9] Recently, another form of imiglucerase, Abcertin (ISU Abxis, Seongnam, Korea), was developed. In a previous study, the short-term efficacy and safety of Abcertin were assessed in 5 Korean patients with type 1 GD who had been previously treated with Cerezyme.[11] In that study, the patients remained stable on Abcertin, with no serious side effects. In the current study, the efficacy and safety of Abcertin were assessed in 7 treatment-naïve patients with type 1 GD.

2. Methods

2.1. Determination of sample size

The sample size for this study was determined to ensure sufficient power for the detection of a clinically significant change in the hemoglobin concentration from baseline to week 24. A mean hemoglobin change of 1 g/dL over this period was determined to be clinically significant, according to the published report of a clinical study involving the use of Cerezyme and VPRIV.[10,12] The sample size was calculated using a mean hemoglobin change of 1.6 ± 1.0 g/dL, 2-sided alpha levels of 0.05, and a power of 90%.

The following equation was used to determine the sample size:

\[ H_0 : \mu - \mu_0 = 0 \text{ vs. } H_A : \mu - \mu_0 \neq 0 \]

\[ N = \frac{(z_{a/2} + z_\beta)^2 \sigma^2}{(\mu - \mu_0)^2} \]

\[ \mu - \mu_0 = \text{mean change in hemoglobin concentration from baseline to week 24} \]

\[ \sigma = \text{standard deviation (SD) of change} \]

The sample size was calculated to be seven patients. Assuming a 20% dropout rate, 9 patients were required for the study.

2.2. Subjects

The inclusion criteria for this study were as follows: diagnosis of type 1 GD; age > 2 years; GD-related anemia, defined as a hemoglobin concentration of ≥ 1 g/dL below the lower limit of normal for age and sex; the presence of moderate splenomegaly (2–3 cm below the left costal margin) by palpation, GD-related thrombocytopenia (platelet count < 90 × 10^9/L), or GD-related readily palpable enlarged liver; and lack of treatment for GD (eg, investigational products, miglustat, velaglucerase alfa, or imiglucerase) within 12 months before study enrolment. We excluded patients who met any of the following criteria: type 2 or type 3 GD; splenectomy; antibody positivity to Abcertin or imiglucerase during screening or an anaphylactic reaction to Abcertin or imiglucerase; treatment with any non-GD-related investigational drug or medical device within 30 days before study entry or during the study period; treatment with red blood cell growth factor (eg, erythropoietin) or chronic systemic corticosteroids within the previous 6 months; human immunodeficiency virus (HIV) and/or hepatitis B or C positivity; anemia at screening complicated by iron, folic acid, or vitamin B12 deficiency or an infectious/immune-mediated cause; significant comorbidity that could affect the study data or confound the study results (eg, malignancies, primary biliary cirrhosis, autoimmune liver disease); and pregnancy, lactation, and a lack of willingness to use a highly effective barrier or medical method of contraception. This study was approved by the Medical Research Ethics Committee of Mansoura University, Mansoura City, Egypt, and the Research Ethics Committee of Cairo University, Giza Governorate, Egypt. Written informed consent was obtained from all subjects or their parents. This study was registered at ClinicalTrials.gov in study no. NCT02770625.

2.3. Study design

This was a multicenter, open-label, phase III study designed to evaluate the pharmacokinetics, efficacy, and safety of a 60-U/kg dose of Abcertin every 2 weeks for 6 months in patients aged ≥ 2 years with type 1 GD. Patients were treatment-naïve or had not been treated for GD within 12 months before study enrolment. The study drug Abcertin is a recombinant protein produced by genetically engineered Chinese Hamster Ovary cells. Abcertin has the same amino acid sequence as human GBA except for 1 amino acid (arginine replaced with histidine at the 495th amino acid). The structural, physicochemical, immunological, and biological properties of imiglucerase have been well-characterized both in vivo and in vitro. Carbohydrate remodeling with neuraminidase, galactosidase, and N-acetylgalcosaminidase is applied in the manufacturing process to maximize mannose-6-phosphate exposure, which is critical for intracellular uptake and has a direct correlation with the efficacy of infusions.[11]

2.4. Efficacy and safety variables

The primary efficacy variables included the change in hemoglobin concentration from baseline to week 24. Secondary efficacy variables included changes in the platelet count, spleen, and liver volumes, skeletal status, and bone mineral density (BMD) between baseline and week 24, and single-dose pharmacokinetic (PK) and biomarker (angiotensin-converting enzyme [ACE], acid phosphatase [ACP], chitotriosidase, and chemokine ligand 18 [CCL 18]) analyses. Liver and spleen volumes were measured by ultrasound and expressed as multiples of normal (MN). Skeletal status was evaluated using simple x-rays; osteosclerosis and osteonecrosis were assessed as none, mild, moderate, or severe, and assigned respective scores of 0, 1, 2, or 3 points.[13] BMD of the femur neck and lumbar spine (L2–4) were measured at 0 and 24 weeks (where applicable) using dual-energy radiography absorptiometry (Lunar Corp., Madison, WI).

Safety parameters included assessed adverse events, vital signs, physical examination, electrocardiography, laboratory test findings (hematology and coagulation, serum chemistry, and urinalysis), and a test for antibodies against Abcertin.

2.5. Efficacy and safety assessment

Fifteen study visits were scheduled: screening (visit 0), administration (biweekly visits 1–13; weeks 0–24), and follow-up (visit 14; week 26). Each treatment was intravenously infused for 90 minutes, and patients were monitored during the infusion. The infusion rate was adjusted as required depending on symptoms and adverse events. Vital signs were monitored during infusion. Patients remained at the clinic for 2 hours after the infusion and were discharged if no adverse events were observed.

For the PK analysis, blood samples were collected before infusion (0, before), at 15, 30, 60, and 90 minutes during the infusion, and at 100, 120, 150, and 180 minutes after the initiation of infusion. For each patient, GBA activity was
analyzed and used to calculate a PK profile comprising the following information: area under the concentration–time curve from the time of dosing to the last measurable concentration (AUClast), maximum drug concentration (Cmax), time to Cmax (Tmax), half-life (T1/2), serum clearance (CL), and volume of distribution (Vd).

2.6. Statistical analysis
All values are presented as means ± standard deviations (SDs). Paired t test was used to evaluate the parameters. All P values were 2-tailed, and a p value of ≤.05 was considered significant. SAS version 9.2 (SAS Institute, Cary, NC) or higher was used for all data analysis.

3. Results
3.1. Baseline characteristics of the subjects
A total of 8 Egyptian patients were enrolled in the study, and all 8 completed the study. However, only 7 patients were included in the analyses, because after study completion, the eighth patient was confirmed to have type 3 GD. The baseline characteristics are shown in Table 1. The mean age of the subjects was 6.3 ± 4.9 years (range 2–15 years). All patients were diagnosed with GD based on decreased GBA activity in peripheral leukocytes or on genetic testing.

3.2. Efficacy of Abcertin
Changes in the efficacy variables are summarized in Table 2. The mean hemoglobin concentration at baseline was 9.49 ± 0.86 g/dL (range 8.69–10.28 g/dL); it increased significantly to 11.44 ± 0.87 g/dL (range 10.64–12.25 g/dL) after 24 weeks of treatment, resulting in a mean increase from baseline of 1.96 ± 0.91 g/dL (range 1.11–2.80 g/dL), which is equivalent to a 20.6% increase (P = .001) (Fig. 1A). The mean platelet count also increased significantly from 132.60 ± 72.27 × 10^3/µL (range 65.73–199.41 × 10^3/µL) at baseline to 180.3 ± 47.10 × 10^3/µL (range 136.73–223.84 × 10^3/µL) after 24 weeks of treatment, resulting in a mean increase from baseline of 47.7 ± 47.43 × 10^3/µL, which is equivalent to a 36% increase (P = .037) (Fig. 1B). At baseline, the liver volume was 1.53 ± 0.61 MN (range 0.97–2.09 MN), and at week 24, the volume was 1.54 ± 0.51 MN (range 1.07–2.01 MN). The spleen volume decreased from 29.05 ± 18.91 MN (range 11.56–46.54 MN) at baseline to 15.21 ± 9.47 MN (range 6.45–23.97 MN) at week 24. The 47.6% (–13.84 ± 11.56) reduction in spleen volume was significant (P = .019); however, the reduction in liver volume was not (Table 2).

With regard to the skeletal status, all patients were negative for both osteosclerosis and osteonecrosis at baseline and week 24. The mean BMD Z-score of the L-spine was −0.95 ± 1.59 (range −2.43 to 0.52) at baseline and −0.10 ± 2.46 (range −2.38 to 2.17) at week 24 (P = .377).

The levels of biomarkers, including ACE, ACP, CCL-18, and chitotriosidase, were measured at baseline and week 24. Among

### Table 1
Demographics and baseline clinical characteristics of the per protocol population.

| No. | Sex | Ethnicity | Age at enrollment, y | Height, cm | Weight, kg | Hemoglobin, g/dL | Platelet, x 10^7/µL | Spleen volume, MN | Liver volume, MN | Genotype | Enzyme activity (I–5 µmol/g/h) |
|-----|-----|-----------|---------------------|-----------|-----------|-----------------|-----------------|------------------|--------------|----------|-------------------------------|
| 1   | Male | Egyptian | 15                  | 137 (<3rd P) | 31 (<3rd P) | 8.9              | 129             | 56.32            | 1.23         | NA       | 0.34*                          |
| 2   | Male | Egyptian | 9                   | 122 (5th P) | 25 (<3rd P) | 10.1             | 120             | 12.24            | 0.69         | NA       | 0.42*                          |
| 3   | Male | Egyptian | 6                   | 108 (10th P) | 17 (6th P) | 8.9              | 44              | 43.18            | 2.08         | NA       | 0.2*                           |
| 4   | Male | Egyptian | 8                   | 114.2 (<3rd P) | 23 (25th P) | 10.3             | 193             | 17.28            | 1.03         | NA       | 0.5*                           |
| 5   | Male | Egyptian | 2                   | 79 (<3rd P) | 10 (<3rd P) | 9.8              | 258             | 7.2              | 1.34         | L444P/L444P | 0.49*                          |
| 6   | Male | Egyptian | 2                   | 82 (5th P) | 11 (3rd P) | 10.3             | 110             | 22.09            | 2.25         | L444P/N370S | 0.49*                          |
| 7   | Male | Egyptian | 2                   | 83 (30th P) | 14 (50th–70th P) | 8.1          | 140             | 45.04            | 0.79         | L444P13393 | 1.6*                           |

Mean ± SD (range)

1 Male, Human

NA = not available; P = percentile; SD = standard deviation.

Normal range of GBA activity in peripheral leukocytes: 1–5 µmol/g/h and ≥ 9.3 µmol/g/h.

### Table 2
Efficacy of the per protocol population.

|                | Baseline | Percentage change at 24 wks | P     |
|----------------|----------|-----------------------------|-------|
| Hemoglobin, g/dL | 9.5 ± 0.86 | 11.4 ± 0.87                 | 20.6  | .001 |
| Platelets, x 10^7/µL | 132.6 ± 72.27 | 180.3 ± 47.10               | 36    | .037 |
| Liver volume, MN   | 1.5 ± 0.61 | 1.5 ± 0.51                  | 0.5   | .949 |
| Spleen volume, MN   | 20.0 ± 18.91 | 15.2 ± 9.47                 | −47.6 | .019 |
| ACE, U/L            | 190.7 ± 100.0 | 159.3 ± 58.25               | −18.6 | .372 |
| ACP, IU/L           | 25.4 ± 7.52  | 15.4 ± 4.31                 | −39.3 | .003 |
| Chitotriosidase, nmol/mL | 15529.48 ± 8644.95 | 4770.2 ± 2515.23         | −69.3 | .078 |
| CCL-18, ng/mL       | 927.1 ± 506.45 | 577.3 ± 310.05              | −37.7 | .037 |
| L-spine BMD Z-score | −1.0 ± 1.60   | −0.1 ± 2.46                 | −89.1 | .377 |

ACE = angiotensin converting enzyme, ACP = acid phosphatase.

*The chitotriosidase values of 2 patients had the null chitotriosidase activity were excluded for the analysis (patient #5: baseline 1.5 nmol/mL/h→week 24 2.4 nmol/mL/h; patient #7: baseline 6.8 nmol/mL/h→15 nmol/mL/h).
these, reductions in ACP (from 25.44 ± 7.52 to 15.44 ± 4.31 U/L) and CCL-18 levels (from 927.05 ± 595.46 to 577.33 ± 310.05 ng/mL) were significant \((P = .003 \text{ and } P = .037, \text{ respectively})\).

Although the chitotriosidase level decreased in most of the subjects, its activity was null at baseline in subjects 5 and 7. The changes in ACE and chitotriosidase levels were not significant (Table 2, Fig. 1).

### 3.3. Pharmacokinetics of Abcertin

After a single intravenous infusion of Abcertin 60 U/kg over 90 minutes, the plasma GBA concentration, which represents the plasma activity of Abcertin, tended to continuously increase until the infusion. The \(C_{\text{max}}\), \(AUC_{\text{last}}\), \(t_{1/2}\), and CL were 47.70 ± 48.45 mU/mL, 38.65 ± 35.37 h·mU/mL, 0.20 ± 0.12 hours, and 45.34 ± 34.95 U/(h·mU/mL), respectively. The time to \(C_{\text{max}}\) ranged from 1 to 1.67 hours after the intravenous infusion of Abcertin, and the \(t_{1/2}\) ranged from 0.1 to 0.42 hours (Fig. 2).

### 3.4. Safety

No life-threatening event was reported during this study. A total of 26 adverse events were reported in 6 (85.7%) patients (Table 3). No severe or study drug-related adverse events or effects leading to treatment discontinuation were reported. Among the reported adverse events, infections (5 [71.4%]...
patients) were most common, followed by gastrointestinal disorders (4 [57.1%] patients). Two serious adverse events (Ludwig angina and viral pneumonia in 1 patient each) were reported in this study; these were of moderate intensity, unrelated to Abcertin, and resolved without sequelae and did not lead to treatment discontinuation.

Anti-Abcertin antibodies (anti-drug antibodies [ADAs]) were analyzed by ADA confirmation assay and neutralizing activity test. In ADA confirmation assay, Abcertin and ADA complex is generated by preincubation of ADA in human serum sample with Abcertin. Then, this complex could not bind to Abcertin-coated immunoplate. Sequentially, signal is reduced. This procedure can confirm the signal is induced by specifically binding to Abcertin or not. Also, for neutralizing activity test, the principle that enzyme activity of Abcertin is inhibited by neutralizing antibodies is utilized. The activity of Abcertin is measured by the determination of amount of fluorophore, 4-methylumbelliferone (4MU) released from the substrate which has a fluorophore function, 4-methylumbelliferyl-b-D-galactoside (4MUG) after the reaction with Abcertin. One (14.3%) patient developed anti-Abcertin antibodies without neutralizing activity at week 24 (Table 4).

4. Discussion
This was a multicenter, open-label, phase III study to evaluate the safety and efficacy of Abcertin in patients with type 1 GD who were previously treated with Cerezyme[11]. In that study, several limitations were noted, including the small number of enrolled patients (n = 5), the ethnically homogeneous patient background (Korean), non-ERT-naïve patients, a short study period (6–12 months), and lack of a standard dose among the study subjects (doses ranged from 30 to 55 U/kg every other week).

Therefore, we conducted this phase III clinical trial of Abcertin as a standalone study designed to evaluate the efficacy and safety of a biweekly 60 U/kg dose during a 6-month period in ERT-naïve Egyptian patients with type 1 GD. The calculated sample size for this study (7 patients) was important to ensure the efficacy of Abcertin.

To compare historically its clinical effectiveness with Cerezyme, we have used the published phase III data (Protocol No. RC91–0110) of effectiveness with Cerezyme. Since there were several practical limitations for comparative studies, for example,

### Table 3
All adverse events documented in the per protocol population.

| System organ class preferred term | Incidence, n |Patients, n (%) |
|----------------------------------|-------------|----------------|
| Any adverse event | 26 | 6 (85.7%) |
| Blood and lymphatic system disorders | 2 | 2 (28.6%) |
| Iron deficiency anemia | 1 | 1 (14.3%) |
| Microcytic anemia | 1 | 1 (14.3%) |
| Endocrine disorders | 1 | 1 (14.3%) |
| Cushingoid | 1 | 1 (14.3%) |
| Gastrointestinal disorders | 4 | 4 (57.1%) |
| Diarrhea | 1 | 1 (14.3%) |
| Abdominal pain | 1 | 1 (14.3%) |
| Anal pruritus | 1 | 1 (14.3%) |
| Dental caries | 1 | 1 (14.3%) |
| Hepatobiliary disorders | 1 | 1 (14.3%) |
| Hepatitis | 1 | 1 (14.3%) |
| Infections and infestations | 16 | 5 (71.4%) |
| Bronchitis | 3 | 3 (42.9%) |
| Nasopharyngitis | 4 | 2 (28.6%) |
| Acute tonsillitis | 1 | 1 (14.3%) |
| Ascariaasis | 1 | 1 (14.3%) |
| Enterobiasis | 1 | 1 (14.3%) |
| Gastroenteritis | 1 | 1 (14.3%) |
| Gastroenteritis viral | 1 | 1 (14.3%) |
| Giardiasis | 1 | 1 (14.3%) |
| Ludwig angina | 1 | 1 (14.3%) |
| Pneumonia viral | 1 | 1 (14.3%) |
| Urinary tract infection | 1 | 1 (14.3%) |
| Respiratory, thoracic and mediastinal disorders | 1 | 1 (14.3%) |
| Nasal dryness | 1 | 1 (14.3%) |
| Skin and subcutaneous tissue disorders | 1 | 1 (14.3%) |
| Heat rash | 1 | 1 (14.3%) |

### Table 4
Anti-Abcertin antibodies.

| Parameter   | Visit | Result  | Abcertin (60 U/kg) (N = 7) |
|-------------|-------|---------|----------------------------|
| Anti-Abcertin | Baseline | Negative | 7 (100.0%) |
|             |       | Positive | 0 (0.0%) |
|             | Week 24 | Negative | 6 (85.7%) |
|             |       | Positive | 1* (14.3%) |

* Antibody without neutralizing activity.
in acquiring the reference drug and recruiting the treatment-naive patients. As, overall, these studies have similar parameters including selection criteria for patients, dose regimen (60 U/kg administered every 2 weeks as an intravenous infusion), efficacy measurements (changes in hemoglobin, platelet counts, and spleen and liver volumes), and safety measurements, it seems reasonable to compare 2 independent studies, although it was not head-to-head comparison. One-sample t-test was utilized to show no difference during the 6-month treatment periods, respectively, in each group of Abcertin and Cerezyme, which was statistically significant \( (P < .05) \). The primary efficacy analysis evaluated whether Abcertin was similar to Cerezyme based on the change of hemoglobin concentration between baseline and month 6. One-sample t-test was utilized to compare the 2 groups in between. Abcertin was considered to be similar to Cerezyme in case of \( P > .05 \). For the secondary efficacy parameters, Student t-test was conducted between mean changes of parameters in between group of Abcertin and Cerezyme. A P value of smaller than .05 was statistically significant. A 95% confidence interval (CI) was presented for the difference in the mean change between the 2 groups. Safety was evaluated through assessment of adverse events/SAEs, laboratory parameters (hematology, serum chemistry, coagulation, and urinalysis), anti-imiglucerase antibody formation test, vital signs, physical examinations, and ECG findings. Among signs and symptoms in GD, the commonest clinical sign is low hemoglobin counts (anemia) and it has been aimed to treat anemia hence hemoglobin counts has been assessed as the primary efficacy endpoint.\(^{14}\) Also, the primary efficacy endpoint in both clinical trials was the difference in hemoglobin concentration between baseline and month 6.

The mean observed hemoglobin level in trial medication group (n = 7) increased from 9.49 ± 0.324 g/dL (mean ± SE) at baseline to 11.44 ± 0.329 g/dL (mean ± SE) at month 6. The mean change from baseline was 1.96 ± 0.345 g/dL (mean ± SE) with a 20.6% change (Fig. 1A). The mean hemoglobin level in historical group (n = 15) increased from 10.71 g/dL at baseline to 12.53 g/dL after administration for 6 months. The mean change from baseline was 1.82 g/dL with a 17.0% change. When comparing the trials by means of 1-sample t test, the result \( (P = .704) \) alludes that Abcertin shows similar clinical effectiveness with effectiveness with Cerezyme, in GD patients, and also the observed change from baseline is equivalent to their increasing height and weight during their growth. The L-spine BMD was found to normalize, achieving the peak mineral bone mass after 6.6 years of Cerezyme treatment.\(^{17}\) Therefore, the absence of statistically significant changes in some secondary endpoints could be attributed to the small number of patients enrolled in our study, their young age, and short observation period of the study.

During the study period, Abcertin was well-tolerated by all 7 patients, without reports of severe drug-related adverse events. The common adverse events were transient infections and gastrointestinal illnesses. One case each of moderately intense Ludwig angina and viral pneumonia was resolved without sequelae and did not lead to treatment discontinuation. Furthermore, only 1 patient developed anti-Abcertin antibodies, which showed no neutralizing activity.

With regard to PK, in most patients, the plasma GBA concentration increased with an intravenous single infusion of Abcertin 60 U/kg until the end of the 90-minute infusion period. However, variable 1\(_{1/2}\) and C\(_{max}\) values were observed among patients. It is difficult to determine the cause of the variations in Abcertin PK characteristics observed in this study because few studies of imiglucerase PK in pediatric patients with GD are available for comparison. Indeed, little is known about the PK of infused recombinant β-GBA in humans.\(^{18,19}\) Because it is taken up into cells by mannose/mannose-dependent receptors, a substantial proportion of infused enzymes may be absorbed into tissues other than the reticuloendothelial system.\(^{20}\)

Individual differences in the distribution of mannose/mannose-dependent receptors among various cell types might account for differences in PK among patients. Another possible explanation would be individual differences in intracellular/intralysosomal metabolism of infused enzymes.

All the subjects enrolled in the study were pediatric patients. Currently, ERT is recommended for symptomatic pediatric patients, including those with type 3 GD, and also those with type 1 disease.\(^{16}\) Initiating ERT early in the disease helps to prevent or stabilize the devastating complications and improve the patient’s quality of life. Although the safety and efficacy of Abcertin in our study was analyzed only in patients with type 1 GD, ERT should be considered for type 3 GD as well.

Some genotype and phenotype correlations in GD are known. In particular, 2 common GBA mutations, p.F370S and p.L444P, are representative mutations for types 1 and 3 GD, respectively.\(^{21}\) Unfortunately, the analysis of GBA mutations was available only for 3 patients included in our study. Nevertheless,
close observation is required for the development of neurological manifestations in these 3 patients because they all showed either a heterozygous or homozygous p.L444P mutation.

5. Conclusions
In conclusion, our Abcertin phase III study demonstrated that Abcertin achieved the clinical endpoints, including improvements in the hemoglobin concentration and other efficacy endpoints (eg, platelet count, spleen volume, and biomarkers). In addition, we did not observe any adverse events related to Abcertin. Therefore, we suggest that although the dose equivalence with other ERTs has not been established, Abcertin is effective and safe for patients with type 1 GD and should be considered as an alternative ERT option for patients with non-neuropathic GD.

Acknowledgments
We thank the patients and their families for participating in this study.

References
[1] Grabowski GA. Recent clinical progress in Gaucher disease. Curr Opin Pediatr 2005;17:519–24.
[2] Zimran A, Elstein D, Levy-Lahad E, et al. Replacement therapy with imiglucerase for type 1 Gaucher’s disease. Lancet 1995;345:1479–80.
[3] Cox TM, Schofield JP. Gaucher’s disease: clinical features and natural history. Baillieres Clin Haematol 1997;10:657–89.
[4] Kim JW, Liou BB, Lai MY, et al. Gaucher disease: identification of three new mutations in the Korean and Chinese (Taiwanese) populations. Hum Mutat 1996;7:214–8.
[5] Beutler E. Enzyme replacement in Gaucher disease. PLoS Med 2004;1:e21.
[6] Schiffermann R, Mankin H, Dambrosia JM, et al. Decreased bone density in splenectomized Gaucher patients receiving enzyme replacement therapy. Blood Cells Mol Dis 2002;28:288–96.
[7] Starzyk K, Richards S, Yee J, et al. The long-term international safety experience of imiglucerase therapy for Gaucher disease. Mol Genet Metab 2007;90:157–63.
[8] Xu YH, Sun Y, Barnes S, et al. Comparative therapeutic effects of velaglucerase alfa and imiglucerase in a Gaucher disease mouse model. PLoS One 2010;5:e10750.
[9] Zimran A, Brill-Almon E, Cherkoff R, et al. Pivotal trial with plant cell-expressed recombinant glucocerebrosidase, taliglucerase alfa, a novel enzyme replacement therapy for Gaucher disease. Blood 2011;118:5767–73.
[10] Zimran A, Altarascu G, Philips M, et al. Phase 1/2 and extension study of velaglucerase alfa replacement therapy in adults with type 1 Gaucher disease: 48-month experience. Blood 2010;115:4651–6.
[11] Chos JH, Lee BH, Ko JM, et al. A phase 2 multi-center, open-label, switch-over trial to evaluate the safety and efficacy of Abcertin(R) in patients with type 1 Gaucher disease. J Korean Med Sci 2015;30:378–84.
[12] Barton NW, Brady RO, Dambrosia JM, et al. Replacement therapy for inherited enzyme deficiency-macrophage-targeted glucocerebrosidase for Gaucher’s disease. N Engl J Med 1991;324:1464–70.
[13] Di Rocco M, Giona F, Carabbi F, et al. A new severity score index for phenotypic classification and evaluation of responses to treatment in type I Gaucher disease. Haematologica 2008;93:1211–8.
[14] Wemreh NJ, Goldblatt J, Villalobos J, et al. Long-term clinical outcomes in type 1 Gaucher disease following 10 years of imiglucerase treatment. J Inherit Metab Dis 2013;36:543–53.
[15] Grabowski GA, Barton NW, Pastores G, et al. Enzyme therapy in type 1 Gaucher disease: comparative efficacy of mannose-terminated glucocerebrosidase from natural and recombinant sources. Ann Intern Med 1995;122:33–9.
[16] Kaplan P, Baris H, De Meirleir L, et al. Revised recommendations for the management of Gaucher disease in children. Eur J Pediatr 2013;172:447–58.
[17] Robertson PL, Maas M, Goldblatt J. Semiquantitative assessment of skeletal response to enzyme replacement therapy for Gaucher’s disease using the bone marrow burden score. AJR Am J Roentgenol 2007;188:1521–8.
[18] Anderson HC, Charrow J, Kaplan P, et al. Individualization of long-term enzyme replacement therapy for Gaucher disease. Genet Med 2005;7:105–10.
[19] Charrow J. Enzyme replacement therapy for Gaucher disease. Expert Opin Biol Ther 2009;9:321–31.
[20] Sato Y, Beutler E. Binding, internalization, and degradation of mannose-terminated glucocerebrosidase by macrophages. J Clin Invest 1993;91:1909–17.
[21] Koprivica V, Stone DL, Park JK, et al. Analysis and classification of 304 mutant alleles in patients with type 1 and type 3 Gaucher disease. Am J Hum Genet 2000;66:1777–86.