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

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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-naïve 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, AUC_{last} = last measurable concentration, BMD = bone mineral density, CCL-18 = chemokine ligand 18, CL = serum clearance, C_{max} = maximum concentration of drug, ERT = enzyme replacement therapy, GD = Gaucher disease, MN = multiple of normal, MRI = magnetic resonance imaging, PK = pharmacokinetic, $t_{1/2}$ = half-life, T_{max} = time to C_{max}, V_d = 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.[2] 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

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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).[9,10] 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:

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

$$N = \frac{(z_{\alpha/2} + z_\beta)^2 \sigma^2}{(\mu - \mu_0)^2} + \frac{(z_{\alpha/2})^2}{2}$$

$\mu - \mu_0$= mean change in hemoglobin concentration from baseline to week 24

σ= 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 $<90 \times 10^9$/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-acetylglucosaminidase is applied in the manufacturing process to maximize mannose-6-phospate 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

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, $\times 10^3/\mu L$	Spleen volume, MN	Liver volume, MN	Genotype	Enzyme activity (1–5 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 (3rd P)	25 (<3rd P)	10.1	120	12.24	0.69	NA	0.42*
3	Male	Egyptian	6	108 (10th P)	17 (5th 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	17.26	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 (25th P)	14 (50th–75th P)	8.1	74	45.04	2.09	L444P/N370S	1.6†
Mean ± SD (range)	Male	Egyptian	6.3 ± 4.86 (2–15)	103.6 ± 03.61 (79–137)	18.7 ± 8.7 (10–31)	9.5 ± 0.5 (8.1–10.3)	132.6 ± 32.6 (44–258)	29.0 ± 9.0 (7.2–56.32)	1.5 ± .52 (0.69–2.25)		

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.

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 (AUC_{last}), maximum drug concentration (C_{max}), time to C_{max} (T_{max}), half-life ($t_{1/2}$), serum clearance (CL), and volume of distribution (V_d).

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 $132.60 \pm 72.27 \times 10^3/\mu L$ (range 65.73–$199.41 \times 10^3/\mu L$) at baseline to $180.3 \pm 47.10 \times 10^3/\mu L$ (range 136.73–$223.84 \times 10^3/\mu L$) after 24 weeks of treatment, resulting in a mean increase from baseline of $47.7 \pm 47.43 \times 10^3/\mu L$, 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 2

Efficacy of the per protocol population.

	Baseline	24 wks	Percentage change at 24 wks	*P*
Hemoglobin, g/dL	9.5 ± 0.86	11.4 ± 0.87	20.6	.001
Platelets, $\times 10^3/\mu L$	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	29.0 ± 18.91	15.2 ± 9.47	−47.6	.019
ACE, U/L	195.7 ± 109.0	159.3 ± 58.25	−18.6	.372
ACP, IU/L	25.4 ± 7.52	15.4 ± 4.31	−39.3	.003
Chitotriosidase*, nmol/mL/h	15529.48 ± 8644.95	4770.0 ± 2519.23	−69.3	.078
CCL-18, ng/mL	927.1 ± 595.46	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).

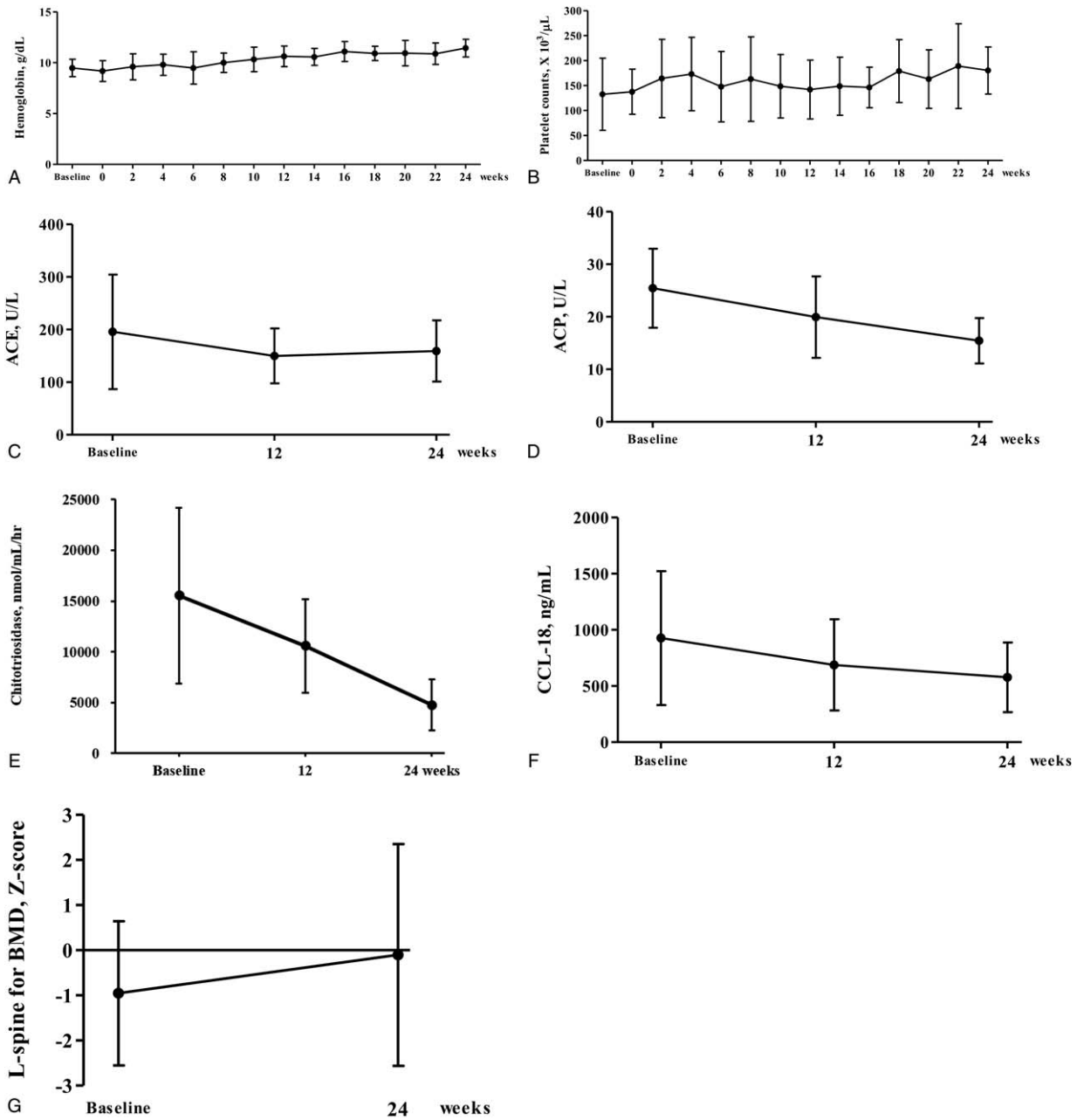

Figure 1. Efficacy of Abcertin for Gaucher disease in the per protocol population. Mean changes in hemoglobin concentrations (A), platelet counts (B), angiotensin-converting enzyme (ACE) levels (C), acid phosphatase (ACP) levels (D), chitotriosidase levels (E), chemokine ligand 18 (CCL-18) levels (F), and L-spine bone densitometry (BMD) (G). Baseline refers to data obtained during the screening visit. Data are expressed as means ± standard deviations.

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 ($P = .003$ and $P = .037$, 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_{max}, AUC_{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_{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%]

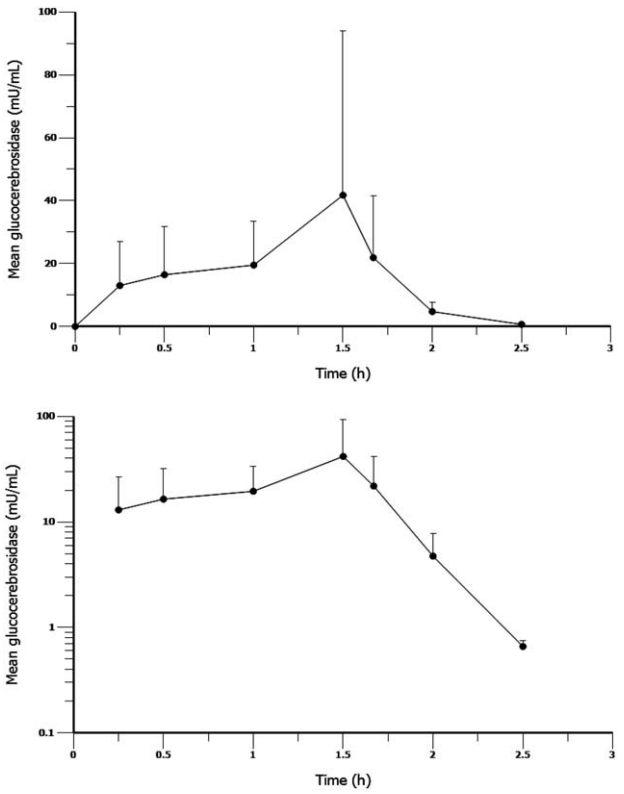

Figure 2. Mean plasma glucocerebrosidase concentration–time profile in the per protocol population (n = 7) after a single intravenous infusion of Abcertin 60 U/kg (top: linear, bottom: semi-log). Error bars represent standard deviations.

Table 3

All adverse events documented in the per protocol population.

	Abcertin (60 U/kg) (N = 7)	
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%)
Ascariasis	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%)

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. In our previous study, we reported the results of a phase II multicenter, open-label, switchover trial to assess 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 4

Anti-Abcertin antibodies.

Parameter	Visit	Result	Abcertin (60 U/kg) (N = 7) n (%)
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-naïve 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 hemolgobin 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 considered to be clinically meaningful in the 60-U/kg dose based on the previous study as defined an increase in hemoglobin of 1 g/dL was considered clinically significant after administration for 6 months. Therefore, Abcertin may have its therapeutic utility comparable with Cerezyme.

With regard to secondary endpoints, significant improvements were also noted in platelet counts, spleen volumes, and biomarker levels. The significant increase in platelet count is important to the therapeutic efficacy of ERT, and the 36% increase from baseline in this study (Fig. 1B) was comparable with a 21.5% increase in a previous study (Fig. 1C–F).[15] Patients with GD exhibit increased plasma levels of several proinflammatory and/or anti-inflammatory cytokines, chemokines, and hydrolases, such as ACP, CCL-18, ACE, and chitotriosidase.[16] These biomarker levels were elevated before ERT in our patients as well, but they decreased with the use of Abcertin (with a decrease ranging from 18.6% to 69.3% from baseline), although the decrease was statistically significant only for ACP and CCL-18, but not for ACE and chitotriosidase. We believe that high variability of the values among subjects limited the statistical power in this small subset of patients. Of note, 2 of 7 subjects had no chitotriosidase activity. In addition, because these biomarkers reflect the activation of macrophages, their levels can be affected not only by GD but also by other inflammatory conditions.

Currently, it is recommended that the measurement of liver and spleen volumes be obtained using volumetric computed tomography or magnetic resonance imaging (MRI).[16] The bone marrow burden score using MRI provides more detailed information about the skeletal status.[17] Unfortunately, these methods were unavailable in our study. Instead, liver and spleen volumes were measured using ultrasound and BMD by dual-energy x-ray absorptiometry. Compared with a significant decrease in the spleen volume, the liver volume did not significantly change 6 months after the administration of Abcertin. Previous studies have reported marked reductions in the liver volume after 2 years of ERT.[17] A mean reduction of 0.9 MN in the liver volume was achieved after 8 years of ERT in 884 children (https://www.gauchercare.com/healthcare/registry.aspx). It should also be kept in mind that liver volumes consistently increase in children not receiving ERT at rate 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 $t_{1/2}$ 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.N370S 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.

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