



# Long-term effectiveness and safety of metreleptin in the treatment of patients with partial lipodystrophy

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## Abstract

**Purpose** To evaluate the effects of metreleptin in patients with partial lipodystrophy (PL).

**Methods** Patients aged  $\geq 6$  months with PL, circulating leptin  $< 12.0$  ng/mL, and diabetes mellitus, insulin resistance, or hypertriglyceridemia received metreleptin doses (once or twice daily) titrated to a mean of 0.124 mg/kg/day. Changes from baseline to month 12 in glycated hemoglobin (HbA1c) and fasting serum triglycerides (TGs; co-primary endpoints), fasting plasma glucose (FPG), and liver volume were evaluated. Additional assessments included the proportions of patients achieving target decreases in HbA1c or fasting TGs at month 12, long-term treatment effects, and treatment-emergent adverse events (TEAEs).

**Results** Significant ( $p < 0.05$ ) reductions in HbA1c ( $-0.6\%$ ), fasting TGs ( $-20.8\%$ ), FPG ( $-1.2$  mmol/L), and liver volume ( $-13.4\%$ ) were observed in the overall PL population at month 12. In a subgroup of patients with baseline HbA1c  $\geq 6.5\%$  or TGs  $\geq 5.65$  mmol/L, significant ( $p < 0.05$ ) reductions were seen in HbA1c ( $-0.9\%$ ), fasting TGs ( $-37.4\%$ ), FPG ( $-1.9$  mmol/L), and liver volume ( $-12.4\%$ ). In this subgroup, 67.9% of patients had a  $\geq 1\%$  decrease in HbA1c or  $\geq 30\%$  decrease in fasting TGs, and 42.9% had a  $\geq 2\%$  decrease in HbA1c or  $\geq 40\%$  decrease in fasting TGs. Long-term treatment in this subgroup led to significant ( $p < 0.05$ ) reductions at months 12, 24, and 36 in HbA1c, fasting TGs, and FPG. Metreleptin was well tolerated with no unexpected safety signals. The most common TEAEs were abdominal pain, hypoglycemia, and nausea.

**Conclusions** In patients with PL, treatment with metreleptin was well tolerated and resulted in improvements in glycemic control, hypertriglyceridemia, and liver volume.

**Keywords** Diabetes mellitus · Leptin · Lipodystrophy · Metreleptin · Partial lipodystrophy

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## Introduction

Lipodystrophy syndromes are rare, heterogeneous, and often life-threatening disorders of body fat deficiency [1]. There are four main subtypes, defined by the etiology (genetic or acquired) and extent of adipose tissue loss (generalized or partial): congenital generalized lipodystrophy (CGL), familial partial lipodystrophy (FPLD), acquired generalized lipodystrophy (AGL), and acquired partial lipodystrophy (APL) [1, 2].

FPLD encompasses a group of mostly autosomal dominant disorders characterized by fat loss in the select areas of the body [1]. Subcutaneous fat loss in FPLD is often observed in the limbs and gluteal region and may be associated with accumulation of excess fat in the face, neck, and intra-abdominal region [1, 3, 4]. The severity and prognosis of FPLD can vary on the basis of subtype and the

range of different organ manifestations [5, 6]. FPLD is often missed clinically in men because many unaffected men have a muscular physique [7] or truncal obesity, and men with FPLD appear to have less severe metabolic complications than women with FPLD [8]. There are many known genetic subtypes of FPLD. In addition, patients without an identifiable single gene are classified as having FPLD type 1.

Some patients with partial lipodystrophy (PL) present without any family history and may have been classified as having APL. Many are later reclassified as AGL if progressive fat loss occurs, or as FPLD type 1 if additional family history suggests familial inheritance. These patients are different than those with the distinctive APL syndrome also known as Barraquer–Simons syndrome or cephalocaudal lipodystrophy syndrome, who tend to progressively lose fat in the face, neck, arms, and trunk and accumulate fat in the lower extremities [1]. The etiology of Barraquer–Simons syndrome is unknown, but it has been associated with autoimmune diseases.

In patients with lipodystrophy, the lack of normal fat depots for storage of excess calories can result in lipid overflow, causing ectopic fat deposition in the liver and muscle [9, 10]. This leads to insulin resistance, diabetes mellitus, and hypertriglyceridemia [9]. In generalized lipodystrophy (GL), widespread deficiency of adipose tissue leads to low levels of circulating leptin, an adipokine that signals overall body energy availability [11, 12]. Because the extent of fat loss is variable in PL, leptin levels and body fat percentages are often within normal ranges [13]. Metabolic abnormalities in patients with PL, including diabetes, insulin resistance, hypertriglyceridemia, and hepatic steatosis, may not be as severe as those in GL syndromes [2, 6, 14]. However, some patients with PL have metabolic abnormalities, morbidity, and mortality as severe as those with GL. Occasionally, distinguishing between PL and GL may be challenging if fat loss in PL is extensive, and there is no obvious increased adiposity of the residual depots.

Metreleptin, a recombinant analogue of human leptin, is the only drug approved for the management of metabolic complications associated with lipodystrophy [1]. In the United States, metreleptin is approved specifically as an adjunct to diet as replacement therapy to treat complications of leptin deficiency in patients with generalized forms of lipodystrophy (CGL or AGL) [15]. In the European Union, metreleptin was approved in 2018 as an adjunct to diet as replacement therapy to treat complications of leptin deficiency in adults and children aged  $\geq 2$  years with confirmed CGL or AGL or in adults and children aged  $\geq 12$  years with confirmed FPLD or APL for whom standard treatments have not achieved adequate metabolic control [16].

An open-label pilot study at the National Institutes of Health (NIH) (NIH 991265 [ClinicalTrials.gov identifier:

NCT00005905]) and its long-term extension (NIH 20010769 [NCT00025883]) were integrated to analyze the long-term efficacy and safety of metreleptin treatment in patients with GL or PL. Interim data from these studies have been previously reported [13, 17–22], as well as the final data in patients with GL [23]. Here, we report the final data of the long-term efficacy and safety of metreleptin in patients with PL from the combined study, including subgroups with significant metabolic abnormalities.

## Patients and methods

### Study design and participants

Two prospective, non-randomized, open-label clinical trials of metreleptin in lipodystrophy were conducted. The pilot study was conducted from 2000 to 2003, and the long-term study was initiated in 2001 and continued through 2014. Because the studies used similar protocols and almost all patients in the pilot study continued into the long-term study, these are considered 1 study. Detailed study designs have been published previously [23]. Inclusion criteria were age  $\geq 6$  months with clinically significant PL, circulating leptin  $< 12.0$  ng/mL (female patients) or  $< 8.0$  ng/mL (male patients), and  $\geq 1$  of the following metabolic abnormalities: presence of diabetes according to the 1997 American Diabetes Association's (ADA) criteria, fasting insulin  $> 208.4$  pmol/L or fasting triglycerides (TGs)  $> 2.26$  mmol/L ( $> 200$  mg/dL).

Informed consent was obtained from all patients or their legal guardians. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice and was approved by the National Institute of Diabetes and Digestive and Kidney Diseases and the National Institute of Arthritis and Musculoskeletal and Skin Diseases institutional review boards.

All patients were admitted to the NIH Clinical Center for screening and baseline assessments. Patients or caregivers administered metreleptin subcutaneously. Metreleptin dosing was weight-, sex-, and age-dependent (Table 1). Doses were titrated per protocol in the pilot study and were based on clinician judgment and clinical response in the long-term study.

Vital signs and laboratory assessments were recorded at baseline and at scheduled post-baseline visits. All patients were followed up at the NIH. However, because of the wide geographic distribution of patients both within and outside the United States, some patients were unable to attend all protocol-scheduled visits. Therefore, patients could undergo clinical laboratory testing at their primary care physician's office as needed. Visits were scheduled more frequently

**Table 1** Metreleptin dosing in the pilot and long-term studies

Pilot study: NIH 991265 (ClinicalTrials.gov identifier: NCT00005905)	Long-term extension: NIH 20010769 (ClinicalTrials.gov identifier: NCT00025883)
<ul style="list-style-type: none"> <li>• Weight-based dosing (sex and age dependent)</li> <li>• Total daily dose was divided into morning and evening administrations</li> <li>• Regimen               <ul style="list-style-type: none"> <li>◦ Month 1 (50% target dose)                   <ul style="list-style-type: none"> <li>0.02 mg/kg/day in female patients aged <math>\geq 18</math> years</li> <li>0.015 mg/kg/day in female patients aged <math>&lt; 18</math> years</li> <li>0.01 mg/kg in male patients</li> </ul> </li> <li>◦ Month 2 (100% target dose)                   <ul style="list-style-type: none"> <li>0.04 mg/kg/day in female patients aged <math>\geq 18</math> years</li> <li>0.03 mg/kg/day in female patients aged <math>&lt; 18</math> years</li> <li>0.02 mg/kg in male patients</li> </ul> </li> <li>◦ Months 3–4 (200% target dose)                   <ul style="list-style-type: none"> <li>0.08 mg/kg/day in female patients aged <math>\geq 18</math> years</li> <li>0.06 mg/kg/day in female patients aged <math>&lt; 18</math> years</li> <li>0.04 mg/kg in male patients</li> </ul> </li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Weight-based dosing (sex and age dependent)</li> <li>• Total daily dose could be given once or twice daily</li> <li>• Regimen               <ul style="list-style-type: none"> <li>◦ Starting dose was initially the same as in the pilot study</li> <li>◦ Dose was later modified to                   <ul style="list-style-type: none"> <li>0.08–0.10 mg/kg/day in female patients <math>\geq 5</math> years of age</li> <li>0.06 mg/kg/day in female patients aged <math>&lt; 5</math> years and in all male patients</li> </ul> </li> <li>◦ Dose escalations                   <ul style="list-style-type: none"> <li>◦ Based on clinical response and clinician judgment</li> <li>◦ Could be initiated after the 6-month follow-up visit</li> <li>◦ Performed in increments of 0.02 mg/kg/day in female patients aged <math>\geq 10</math> years and 0.01 mg/kg/day in all other patients</li> <li>◦ Capped at 0.24 mg/kg/day</li> <li>◦ Dose was not to be increased above 0.12 mg/kg/day in patients aged <math>&gt; 5</math> years without a clear decline in metabolic status without explanations for the change (e.g. infection, nonadherence, dietary indiscretion)</li> </ul> </li> </ul> </li> </ul>

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during the first year of treatment (every 4 months until 2003, then every 6 months after 2003) and then every 12 months after month 12.

The analysis populations are shown in Table 2. The safety analysis set comprised all enrolled patients who received  $\geq 1$  dose of study drug. The full analysis set included all patients in the safety analysis set who had measurements for either of the co-primary efficacy variables at baseline and at  $\geq 1$  post-baseline visit. The controlled concomitant medication full analysis set comprised all patients in the full analysis set with controlled concomitant medication use (i.e. no change or a decrease in baseline concomitant medications [glucose-lowering or lipid-lowering therapies]) before month 12.

In addition to the overall PL population, all efficacy and safety endpoints were evaluated in a subgroup of patients with glycated hemoglobin (HbA1c)  $\geq 6.5\%$  or TGs  $\geq 5.65$  mmol/L ( $\geq 500$  mg/dL) (PL subgroup 1). The co-primary efficacy endpoints were also evaluated in a subgroup of patients exceeding the ADA glycemic target recommendations with HbA1c  $\geq 8.0\%$  or TGs  $\geq 5.65$  mmol/L at baseline (PL subgroup 2).

## Endpoints

The co-primary efficacy endpoints were the actual change from baseline in HbA1c at month 12 and the percent change from baseline in fasting serum TGs at month 12. Key secondary endpoints were the proportions of patients achieving target decreases in HbA1c or fasting serum TGs from baseline (HbA1c  $\geq 1\%$  or TGs  $\geq 30\%$ , HbA1c  $\geq 1.5\%$  or TGs  $\geq 35\%$ , and HbA1c  $\geq 2\%$  or TGs  $\geq 40\%$ ) and actual and percent changes in fasting plasma glucose (FPG) from

**Table 2** Study analysis populations

	Overall PL population	PL subgroup 1 <sup>a</sup>
Safety analysis set <sup>b</sup>	41	31
Full analysis set <sup>c</sup>	40	30
Controlled concomitant medication full analysis set <sup>d</sup>	31	23

HbA1c glycated hemoglobin, PL partial lipodystrophy, TG triglycerides

<sup>a</sup>Patients with significant metabolic abnormalities associated with their disease as evidenced by baseline HbA1c  $\geq 6.5\%$  or TGs  $\geq 5.65$  mmol/L

<sup>b</sup>All enrolled patients who received  $\geq 1$  dose of study drug

<sup>c</sup>All patients in the safety analysis set who had either of the co-primary efficacy variables measured at baseline and  $\geq 1$  post-baseline visit

<sup>d</sup>All patients in the full analysis set with controlled concomitant medication use (i.e. no change or a decrease in baseline antidiabetic or lipid-lowering therapies) before month 12

baseline at month 12. Additional secondary endpoints included the proportion of patients with baseline HbA1c  $\geq 7\%$  who achieved HbA1c  $< 7\%$  or a  $\geq 1\%$  decrease from baseline, the proportion of patients with baseline TGs  $\geq 2.26$  mmol/L who achieved TGs  $< 2.26$  mmol/L or a  $\geq 30\%$  decrease from baseline, and the proportion of patients with baseline TGs  $\geq 5.65$  mmol/L who achieved TGs  $< 5.65$  mmol/L or a  $\geq 30\%$  decrease from baseline. Changes from baseline to month 12 in liver volume (measured by magnetic resonance imaging), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were also evaluated.

Safety endpoints included metreleptin exposure, incidence of treatment-emergent adverse events (TEAEs), and changes from baseline in laboratory parameters. TEAEs

were coded by preferred term using the Medical Dictionary for Regulatory Activities, version 19.0. Events possibly associated with hypersensitivity (to study medication or other substance) were evaluated and defined using a standardized Medical Dictionary for Regulatory Activities query for angioedema, anaphylactic reaction, anaphylactic/anaphylactoid shock conditions, and severe cutaneous reactions.

## Statistical analyses

All efficacy endpoints were evaluated in the full analysis set, and safety endpoints were measured in the safety analysis set. Primary endpoints and key secondary endpoints were also analyzed in the controlled concomitant medication full analysis set. All analyses were conducted in the overall PL population and PL subgroup 1. The co-primary endpoints were also evaluated in PL subgroup 2 (full analysis set). Baseline demographics and disease characteristics, metreleptin exposure, changes from baseline in efficacy endpoints, and incidence of TEAEs were reported with descriptive statistics.

*P*-values for changes from baseline to month 12 were computed using paired *t* tests (after visual inspection of data to check normal distribution) with a one-sided  $\alpha$  level of 0.025. The analysis visit interval from baseline to month 12 was 365 ( $\pm 65$ ) days. Missing month-12 values were imputed using the last observation carried forward (LOCF) method with results only from  $\geq 6$  months post baseline.

To evaluate changes over time, a mixed-effects model for repeated measures (MMRM) analysis assessed average levels of HbA1c, fasting TGs, and FPG across all assessment time points from baseline to months 12, 24, and 36; the overall MMRM analysis assessed the average levels across all visits. The number and percentage of patients achieving target decreases in HbA1c and fasting TGs were evaluated with two-sided exact binomial 95% confidence intervals.

## Results

### Patient disposition and baseline demographics

A total of 41 patients with a PL diagnosis were enrolled, including 31 patients with HbA1c  $\geq 6.5\%$  or TGs  $\geq 5.65$  mmol/L at baseline who comprised PL subgroup 1 (Table 2) and 22 patients with HbA1c  $\geq 8.0\%$  or TGs  $\geq 5.65$  mmol/L at baseline who comprised PL subgroup 2. Overall, 85.4% of patients were initially classified as having FPLD and 14.6% as having APL (none with Barraquer–Simons syndrome). During the study period, disease categorization became more precise (Table 3). Over

**Table 3** Baseline demographics and patient characteristics in the safety analysis set for PL subgroups and overall population

	Overall PL population (N = 41)	PL subgroup 1 <sup>a</sup> (n = 31)	PL subgroup 2 <sup>b</sup> (n = 22)
Sex, n (%)			
Female	40 (97.6)	30 (96.8)	21 (95.5)
Male	1 (2.4)	1 (3.2)	1 (4.5)
Race, n (%)			
White	36 (87.8)	26 (83.9)	18 (81.8)
Black	0	0	0
Asian	1 (2.4)	1 (3.2)	0
Native American	0	0	0
Hispanic	2 (4.9)	2 (6.5)	2 (9.1)
Other	2 (4.9)	2 (6.5)	2 (9.1)
Age, years, median (min, max)	34.0 (10.0, 64.0)	38.0 (15.0, 64.0)	35.5 (15.0, 64.0)
Lipodystrophy subtype, n (%)			
Acquired <sup>c</sup>	6 (14.6)	4 (12.9)	4 (18.2)
Familial	35 (85.4)	27 (87.1)	18 (81.8)
Medical history, n (%)			
Hypertriglyceridemia	38 (92.7)	29 (93.5)	21 (95.5)
Diabetes mellitus <sup>d</sup>	32 (78.1)	26 (83.9)	18 (81.8)
Hypertension	21 (51.2)	17 (54.8)	12 (54.5)
Hepatic steatosis <sup>e</sup>	14 (34.1)	12 (38.7)	9 (40.9)
Pancreatitis	15 (36.5)	12 (38.7)	10 (45.5)
NASH or steatohepatitis	13 (31.7)	8 (25.8)	6 (27.3)
Polycystic ovary	11 (26.8)	7 (22.6)	5 (22.7)
Fasting leptin, ng/mL, mean (SD)	6.4 (3.5)	6.7 (3.7)	6.5 (3.9)
HbA1c, %, mean (SD)	8.0 (2.2)	8.8 (1.9)	9.4 (1.9)
Fasting TGs, mmol/L, mean (SD)	12.0 (22.9)	14.8 (25.7)	19.6 (29.4)
mg/dL, mean (SD)	1063.2 (2024.3)	1314.5 (2278.1)	1735.0 (2602.1)
FPG, mmol/L, mean (SD)	8.7 (4.4)	9.9 (4.3)	10.8 (4.4)
mg/dL, mean (SD)	157.0 (78.3)	178.5 (78.1)	194.2 (79.6)
Liver volume, mL, mean (SD) <sup>f,g</sup>	2624.6 (936.2) (n = 9)	2411.7 (731.9) (n = 8)	NA
ALT, U/L, mean (SD)	54.0 (57.5)	38.6 (27.8)	39.3 (31.9)
ALT above ULN, n (%)	14 (34.1)	9 (29.0)	6 (27.3)
AST, U/L, mean (SD)	37.7 (33.3)	31.3 (19.6)	32.3 (22.0)
AST above ULN, n (%)	10 (24.4)	7 (22.6)	6 (27.3)
On glucose-lowering medications, n (%)	37 (90.2)	30 (96.8)	21 (95.5)
Insulin alone	6 (14.6)	6 (19.4)	6 (27.3)
Insulin plus oral agent	13 (31.7)	10 (32.3)	7 (31.8)
Oral agent only	15 (36.6)	12 (38.7)	8 (36.4)
On lipid-lowering medications, n (%)	34 (82.9)	26 (83.9)	19 (86.4)

**Table 3** (continued)

	Overall PL population ( <i>N</i> = 41)	PL subgroup 1 <sup>a</sup> ( <i>n</i> = 31)	PL subgroup 2 <sup>b</sup> ( <i>n</i> = 22)
Fibrates	21 (51.2)	17 (54.8)	12 (54.5)
Statins	13 (31.7)	12 (38.7)	8 (36.4)
Other lipid-lowering agents	19 (46.3)	15 (48.4)	10 (45.5)

*ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *BL* baseline, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *NA* not applicable, *NASH* nonalcoholic steatohepatitis, *PL* partial lipodystrophy, *SD* standard deviation, *TG* triglycerides, *ULN* upper limit of normal

<sup>a</sup>HbA1c  $\geq$  6.5% or TGs  $\geq$  5.65 mmol/L at BL

<sup>b</sup>HbA1c  $\geq$  8.0% or TGs  $\geq$  5.65 mmol/L at BL

<sup>c</sup>Subsequently, two patients classified as having acquired PL were reclassified as having acquired generalized lipodystrophy on the basis of progressive fat loss. Another patient classified as having acquired PL was later found to have a recessive mutation and therefore had familial PL, and two additional patients were likely to have familial PL with an unknown genetic mutation. These reclassifications are unlikely to have meaningfully affected the analyses. No patient classified as having acquired PL had Barraquer–Simons syndrome

<sup>d</sup>Based on medical history documentation

<sup>e</sup>By clinical assessment

<sup>f</sup>Full analysis set

<sup>g</sup>Measured by magnetic resonance imaging

the 14-year study period, 15 patients (36.6%) in the overall PL population and 11 (35.5%) in PL subgroup 1 discontinued the study. Reasons for discontinuation among the overall PL population and PL subgroup 1, respectively, included nonadherence ( $n = 6$  [14.6%] and  $n = 6$  [19.4%]), lack of efficacy ( $n = 5$  [12.2%] and  $n = 3$  [9.7%]), transfer to another metreleptin treatment program ( $n = 2$  [4.9%] and  $n = 1$  [3.2%]), and death ( $n = 1$  [2.4%] and  $n = 1$  [3.2%]).

Table 3 shows baseline demographics for the overall PL population and PL subgroups 1 and 2. Almost all patients were female, most were white, and the median age in the overall PL population was 34 years. Most patients had hypertriglyceridemia or diabetes. Mean (standard deviation [SD]) baseline fasting leptin levels in the overall PL population, PL subgroup 1, and PL subgroup 2 were 6.4 (3.5), 6.7 (3.7), and 6.5 (3.9) ng/mL, respectively. Individual patient listings of HbA1c, TGs, and FPG at baseline and month 12 for the overall PL population are included in the Online Resource.

The mean (SD) overall duration of metreleptin exposure was 48.1 (44.1) months in the overall PL population and 47.5 (47.1) months in PL subgroup 1. The mean (SD) weighted average daily dose of metreleptin in the overall PL population and PL subgroup 1 was 0.123 (0.030) mg/kg/day

(equivalent to 8.4 [2.5] mg/day) and 0.124 (0.030) mg/kg/day (equivalent to 8.4 [2.4] mg/day), respectively.

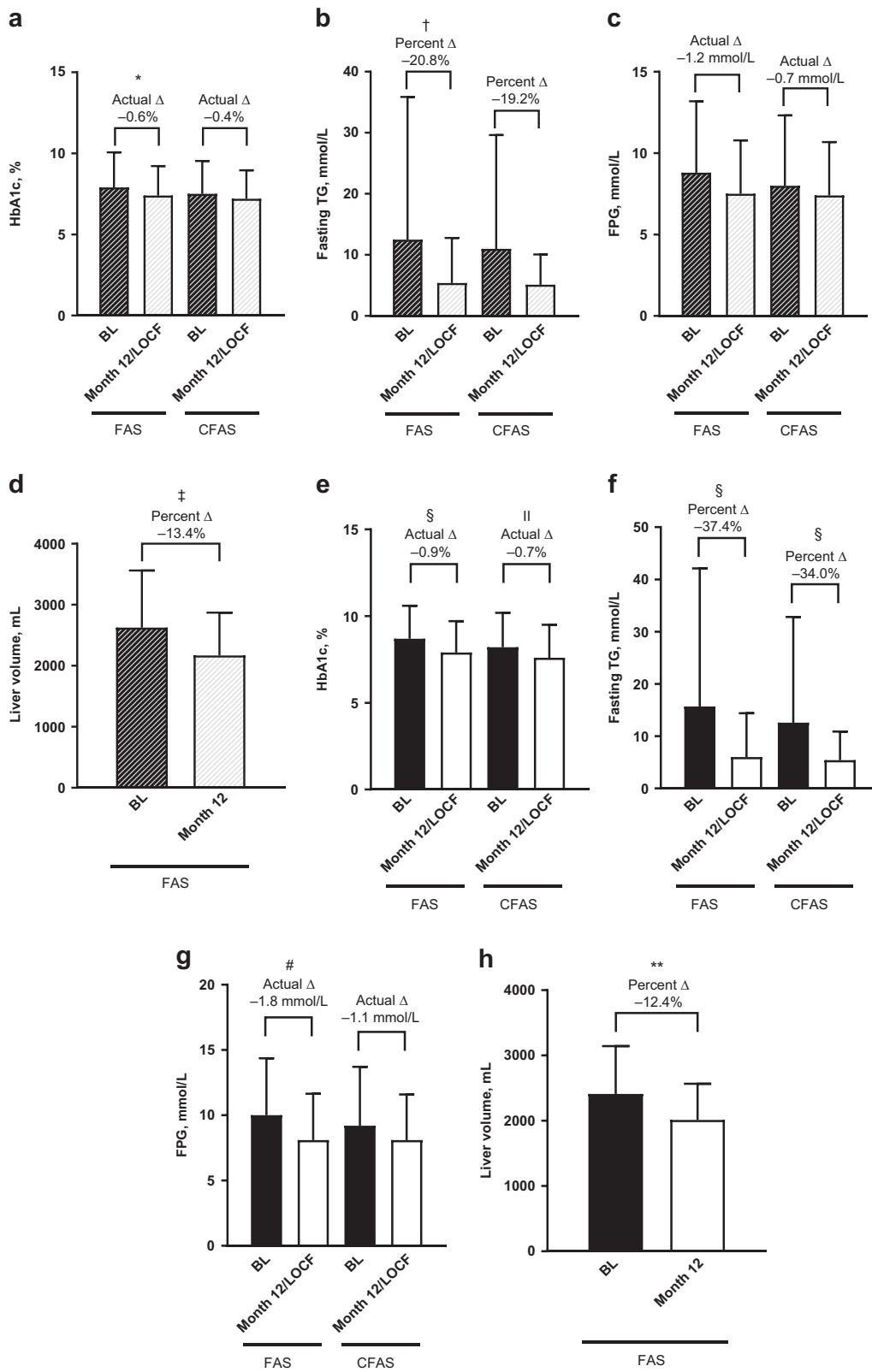
## Efficacy

In the overall PL population full analysis set, metreleptin treatment led to a 0.6% mean actual reduction in HbA1c from 7.9% at baseline to 7.4% at month 12/LOCF ( $p = 0.005$ ; Fig. 1a). Because of an extreme outlying result for one patient (later withdrawn from the study due to non-adherence), fasting TG results showed a small mean percent increase between baseline and month 12/LOCF. When calculated without the outlier, fasting TGs decreased by 20.8%, from a mean (median) of 12.5 (4.6) mmol/L at baseline to 5.4 (3.5) mmol/L at month 12/LOCF ( $p = 0.013$ ; Fig. 1b). Mean FPG decreased by 6.1%, from 8.8 mmol/L at baseline to 7.5 mmol/L at month 12/LOCF ( $p = 0.219$ ; Fig. 1c). Although reductions from baseline were observed for HbA1c, fasting TGs, and FPG in the controlled concomitant medication full analysis set, these were not statistically significant (Fig. 1a–c).

In PL subgroup 1, treatment with metreleptin led to clinically meaningful and statistically significant reductions in HbA1c in the full analysis set, from 8.7% at baseline to 7.9% at month 12/LOCF (mean actual reduction, 0.9%;  $p < 0.001$ ; Fig. 1e). Fasting TGs decreased by 37.4% ( $p < 0.001$ ) in the full analysis set, from a mean (median) of 15.7 (5.7) mmol/L at baseline to 6.0 (3.4) mmol/L at month 12/LOCF (Fig. 1f). Mean FPG decreased by 13.2%, from 10.0 mmol/L at baseline to 8.1 mmol/L at month 12/LOCF ( $p = 0.023$ ; Fig. 1g). Results in the controlled concomitant medication full analysis set were very similar to those in the full analysis set, with an actual decrease in HbA1c of 0.7%, from 8.2% at baseline to 7.6% at month 12/LOCF ( $p = 0.008$ ; Fig. 1e). Mean (median) TG concentrations in the controlled concomitant medication full analysis set were reduced by 34%, from 12.6 (5.7) mmol/L at baseline to 5.4 (3.9) mmol/L at month 12/LOCF ( $p < 0.001$ ; Fig. 1f). FPG did not significantly change ( $p = 0.6$ ; Fig. 1g).

Analysis of the co-primary endpoints in patients with HbA1c  $\geq$  8.0% or TGs  $\geq$  5.65 mmol/L (PL subgroup 2) found significant reductions in HbA1c and fasting TGs after 12 months of metreleptin therapy. The mean actual decrease in HbA1c in this subgroup was 1.0%, from 9.4% at baseline to 8.4% at month 12/LOCF ( $p = 0.003$ ). The mean percent decrease in fasting TGs was 42.8% ( $p < 0.001$ ), from 20.4 mmol/L at baseline to 7.1 mmol/L at month 12/LOCF.

MMRM analysis of metreleptin effects across all time points in the overall PL population showed a mean actual decrease in HbA1c of 0.4% overall ( $p = 0.007$ ; Fig. 2a); reductions were statistically significant at month 12 (0.5%;  $p = 0.024$ ), but not at months 24 (0.7%) and 36 (0.6%). Percent changes in fasting TGs at months 12, 24, and 36



◀ **Fig. 1** Mean values at baseline and month 12/LOCF in **a** HbA1c, **b** fasting TGs, **c** FPG, and **d** liver volume in the overall PL population, and mean changes in **e** HbA1c, **f** fasting TGs, **g** FPG, and **h** liver volume among patients in PL subgroup 1. **a** Mean values for HbA1c were 7.9% at baseline and 7.4% at month 12 in the FAS and 7.5% at baseline and 7.2% at month 12 in the CFAS. **b** Mean (median) values for fasting TGs were 12.5 (4.6) mmol/L at baseline and 5.4 (3.5) mmol/L at month 12 in the FAS and 11.0 (4.7) mmol/L at baseline and 5.1 (3.9) mmol/L at month 12 in the CFAS. **c** Mean FPG was 8.8 mmol/L at baseline and 7.5 mmol/L at month 12 in the FAS and 8.0 mmol/L at baseline and 7.4 mmol/L at month 12 in the CFAS. **d** Mean liver volume was 2624.6 mL at baseline and 2169.9 mL at month 12. **e** Mean values for HbA1c were 8.7% at baseline and 7.9% at month 12 in the FAS and 8.2% at baseline and 7.6% at month 12 in the CFAS. **f** Mean (median) values for fasting TGs were 15.7 (5.7) mmol/L at baseline and 6.0 (3.4) mmol/L at month 12 in the FAS and 12.6 (5.7) mmol/L at baseline and 5.4 (3.9) mmol/L at month 12 in the CFAS. **g** Mean FPG was 10.0 mmol/L at baseline and 8.1 mmol/L at month 12 in the FAS and 9.2 mmol/L at baseline and 8.1 mmol/L at month 12 in the CFAS. **h** Mean liver volume was 2411.7 mL at baseline and 2013.3 mL at month 12. Error bars show the standard deviation. One patient was withdrawn from the study for nonadherence to study drug administration and had a > 1000% increase from baseline to month 12 in fasting TG level and was thus excluded from the fasting TG analysis. \* $p = 0.005$ ; <sup>†</sup> $p = 0.013$ ; <sup>‡</sup> $p = 0.004$ ; <sup>§</sup> $p < 0.001$ ; <sup>||</sup> $p = 0.008$ ; <sup>#</sup> $p = 0.023$ ; <sup>\*\*</sup> $p = 0.011$ .  $\Delta$  change from BL, BL baseline, CFAS controlled concomitant medication full analysis set, FAS full analysis set, FPG fasting plasma glucose, HbA1c glycated hemoglobin, LOCF last observation carried forward, PL partial lipodystrophy, TG triglycerides

were also not statistically significant (−16.7%, −9.4%, and 4.4%, respectively), with an overall decrease of 8.3% ( $p = 0.131$ ; Fig. 2b). Least-squares mean changes in FPG were statistically significant at months 12, 24, and 36 (−1.2, −1.9, and −3.0 mmol/L, respectively;  $p < 0.05$  for all), with an overall decrease of 0.8 mmol/L ( $p = 0.002$ ; Fig. 2c).

In PL subgroup 1, MMRM analysis showed that long-term treatment with metreleptin led to clinically meaningful and statistically significant reductions in all metabolic parameters over time. The mean actual decrease in HbA1c was 0.9%, 1.3%, and 1.0% at months 12, 24, and 36, respectively, with an overall reduction of 0.6% ( $p < 0.001$ ; Fig. 2d). Fasting TG reductions were 36.2%, 31.7%, and 13.7% at months 12, 24, and 36, respectively, with an overall decrease of 18.6% ( $p = 0.004$ ; Fig. 2e). FPG decreased by 1.9, 2.4, and 3.0 mmol/L at months 12, 24, and 36, respectively, with an overall reduction of 1.2 mmol/L ( $p < 0.001$ ; Fig. 2f).

In the overall PL population full analysis set, 51.4% of patients achieved a  $\geq 1\%$  actual decrease in HbA1c or  $\geq 30\%$  decrease in TGs at month 12/LOCF, and 32.4% achieved a target decrease of  $\geq 2\%$  in HbA1c or  $\geq 40\%$  in TGs (Fig. 3a); corresponding values in the controlled concomitant medication full analysis set were 41.4% and 20.7%, respectively. Higher proportions of patients in the PL subgroup 1 full analysis set achieved target decreases in HbA1c or fasting TGs (Fig. 3b), with 67.9% of patients achieving a  $\geq 1\%$  actual decrease in HbA1c or  $\geq 30\%$  decrease in TGs at

month 12/LOCF and 42.9% achieving the highest target decreases of  $\geq 2\%$  in HbA1c or  $\geq 40\%$  in TGs; corresponding values in the controlled concomitant medication full analysis set were 54.5% and 27.3%, respectively.

Among patients with HbA1c  $\geq 7\%$  at baseline ( $n = 23$ ), 21.7% had a reduction in HbA1c to  $< 7\%$  (not shown) and 43.5% had a reduction in HbA1c to  $< 7\%$  or a decrease of  $\geq 1\%$  at month 12/LOCF (Fig. 3c, d). Among patients with TGs  $\geq 5.65$  mmol/L at baseline ( $n = 31$ ), 6.7% achieved TGs  $< 5.65$  mmol/L (not shown), but 86.7% achieved TGs  $< 5.65$  mmol/L or  $\geq 30\%$  decrease from baseline at month 12/LOCF (Fig. 3c, d). Among patients with baseline TGs  $\geq 2.26$  mmol/L in the overall PL population ( $n = 15$ ) and PL subgroup 1 ( $n = 15$ ), 54.8% and 68.0%, respectively, achieved TGs  $< 2.26$  mmol/L or  $\geq 30\%$  decrease from baseline at month 12/LOCF (Fig. 3c, d).

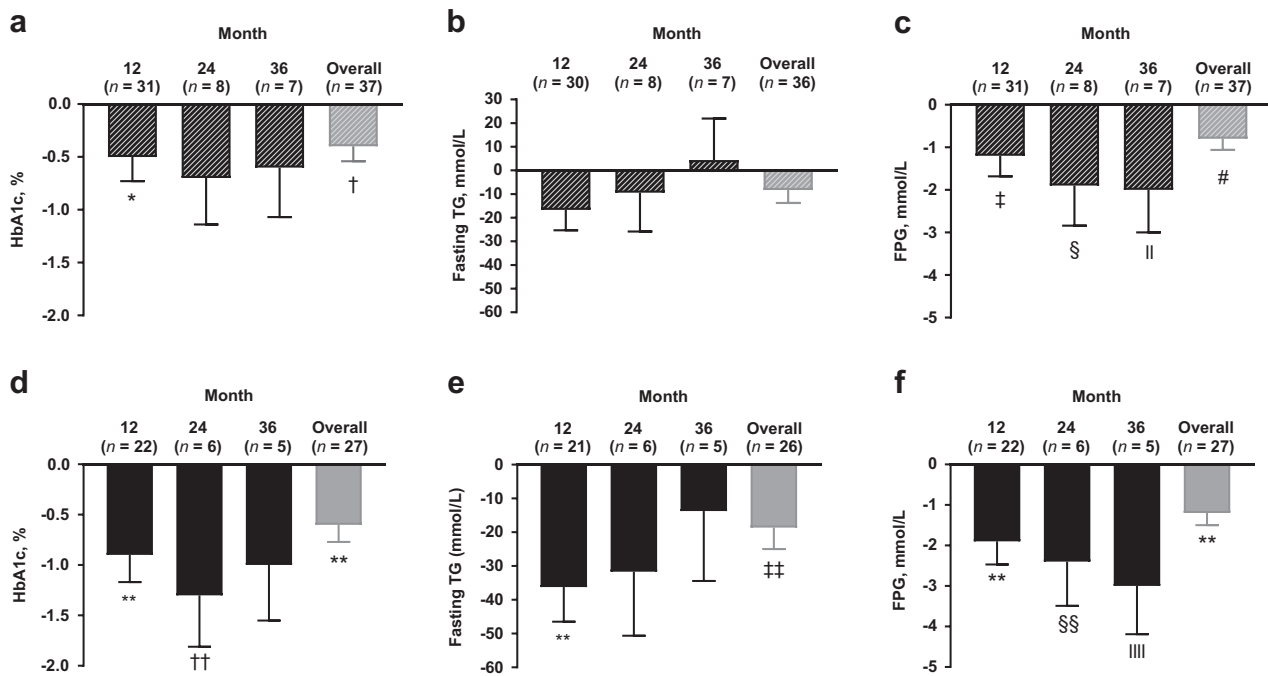
Liver volume was significantly reduced at month 12 in the overall PL population and PL subgroup 1 (Fig. 1d, h). Among nine patients in the overall PL population with liver volume assessments, mean percent change was  $-13.4\%$  ( $p = 0.004$ ), from a mean baseline liver volume of 2624.6 mL to 2169.0 mL at month 12 (Fig. 1d). In PL subgroup 1 ( $n = 8$ ), mean reduction in liver volume was 12.4% ( $p = 0.011$ ), from 2411.7 mL at baseline to 2013.3 mL at month 12 (Fig. 1h).

Changes in liver function tests were not statistically significant. In the overall PL population and PL subgroup 1, mean changes in ALT from baseline to month 12 were  $-0.4$  U/L ( $p = 0.941$ ) and  $-5.0$  U/L ( $p = 0.070$ ), respectively, from mean baseline values of 54.8 U/L and 39.2 U/L, respectively, to 59.9 U/L and 34.5 U/L at month 12. Mean changes in AST in the overall PL population and PL subgroup 1 were  $-5.1$  U/L ( $p = 0.198$ ) and  $-6.0$  U/L ( $p = 0.077$ ), respectively, from mean baseline levels of 38.4 U/L and 31.9 U/L, respectively, to 35.8 U/L and 25.8 U/L at month 12.

None of the 19 patients in the overall PL population who received insulin at baseline were able to discontinue it after starting metreleptin. One patient who received oral glucose-lowering medications at baseline ( $n = 1/28$  [3.6%]) and another who received lipid-lowering medications at baseline ( $n = 1/34$  [2.9%]) were able to discontinue these medications with metreleptin treatment.

## Safety

Metreleptin was generally well tolerated. A total of 35 patients (85.4%) in the overall PL population and 27 (87.1%) in PL subgroup 1 experienced  $\geq 1$  TEAE (Table 4). There was no difference in safety signals between PL subgroup 1 and the overall PL population. In the overall PL population, drug-related TEAEs were reported in eight patients. Serious AEs (SAEs) were reported in 10 patients;



**Fig. 2** MMRM analysis of the least-squares mean change from baseline at months 12, 24, and 36 and the overall MMRM analysis in **a** HbA1c, **b** fasting TGs, and **c** FPG in the FAS of the overall PL population, and **d** HbA1c, **e** fasting TGs, and **f** FPG in the FAS of PL subgroup 1. Error bars show the standard error of the mean. One patient was withdrawn from the study for nonadherence to study drug administration and had a > 1000% increase from baseline to month 12

in TG levels and was thus excluded from the fasting TG analysis. \* $p = 0.024$ ; † $p = 0.007$ ; ‡ $p = 0.014$ ; § $p = 0.044$ ; || $p = 0.049$ ; # $p = 0.002$ ; \*\* $p < 0.001$ ; †† $p = 0.009$ ; ‡‡ $p = 0.004$ ; §§ $p = 0.027$ ; ||| $p = 0.011$ . FAS full analysis set, FPG fasting plasma glucose, HbA1c glycated hemoglobin, MMRM mixed-effects model for repeated measures, PL partial lipodystrophy, TG triglycerides

no SAEs were drug related. There was one death due to hypoxic ischemic encephalopathy that was unrelated to study treatment.

Six patients (14.6%) experienced a possible hypersensitivity event. Potential hypersensitivity events were edema and erythema ( $n = 2$  each) and cough, anaphylactic reaction, rash, and urticaria ( $n = 1$  each). All possible hypersensitivity events were mild-to-moderate intensity and unrelated to study treatment; none of them were SAEs or led to treatment discontinuation. Seven patients experienced hypoglycemia events, which were treatment related in three patients; all patients who experienced events were taking glucose-lowering medications (insulin with or without oral treatment). All hypoglycemia events were mild to moderate in severity, and none of them led to treatment discontinuation.

Five patients developed a neoplasm while on study; none of them were related to study treatment. Adrenal adenoma, anogenital warts, benign neoplasm of the thyroid, and benign ovarian germ cell teratoma occurred in one patient each, and one patient with a history of schwannoma before leptin therapy developed both a schwannoma and a nervous system neoplasm (sciatic tumor). The schwannoma and benign ovarian germ cell teratoma were reported as SAEs.

Two patients (4.9%) experienced a newly diagnosed hepatic disorder. Both were steatohepatitis, assessed as mild

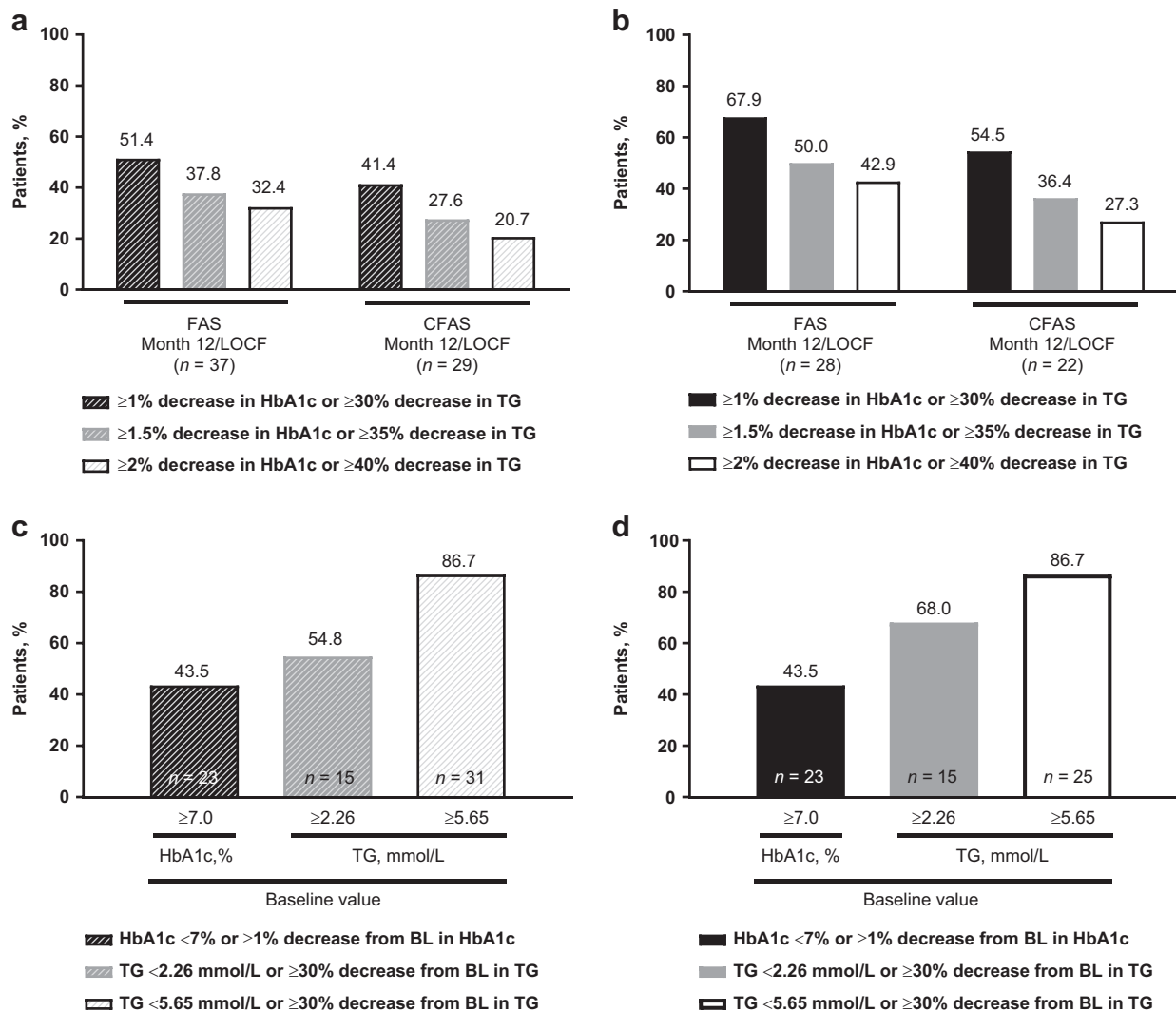
and unrelated to study treatment, and did not lead to treatment withdrawal. One of these patients had hepatomegaly at baseline, and ALT and AST were in the normal range at baseline for both patients. Two patients (4.9%) experienced pancreatitis. In one of these patients who had a history of pancreatitis and hypertriglyceridemia, pancreatitis was related to suspected nonadherence to metreleptin treatment. In the other patient, pancreatitis was due to abrupt interruption of metreleptin treatment. Both pancreatitis events were of severe intensity and unrelated to the study drug, per investigator assessment.

No autoimmune disorders were reported. Serious infections, including cellulitis, streptococcal infection, pharyngitis, and osteomyelitis, were reported in three patients (7.3%) and were unrelated to study treatment. Three patients (7.3%) experienced injection-site reactions of moderate intensity that were nonserious and did not lead to treatment withdrawal.

## Discussion

In this study, patients with PL, serum leptin < 12.0 ng/mL (or lower depending on age and sex), and  $\geq 1$  metabolic abnormality showed statistically significant reductions in





**Fig. 3** Proportions of patients achieving target decreases in HbA1c or fasting TGs in **a** the overall PL population and **b** PL subgroup 1 in the FAS and CFAS at month 12/LOCF, and by high baseline HbA1c or fasting TG levels achieving target decreases in HbA1c or fasting TGs

in **c** the overall PL population and **d** PL subgroup 1. BL baseline, CFAS controlled concomitant medication full analysis set, FAS full analysis set, HbA1c glycated hemoglobin, LOCF last observation carried forward, PL partial lipodystrophy, TG triglycerides

HbA1c and fasting TGs from baseline to month 12 with metreleptin treatment in the full analysis set. Because these improvements were not statistically significant when analyzed in the controlled concomitant medication full analysis set, it is unclear whether these improvements in the overall PL population could be attributed to metreleptin therapy. However, in a subgroup of patients with HbA1c  $\geq 6.5\%$  or TGs  $\geq 5.65$  mmol/L at baseline (PL subgroup 1), significant improvements in HbA1c, fasting TGs, and FPG were seen in the full analysis set, and improvements in HbA1c and fasting TGs were also statistically significant and clinically meaningful in the controlled concomitant medication full analysis set. Thus, it can be concluded that metreleptin treatment led to meaningful improvements in this subgroup. Furthermore, statistically significant reductions in HbA1c and fasting TGs—the co-primary endpoints of the study—were observed in

the subgroup of patients with more severe metabolic abnormalities (HbA1c  $\geq 8.0\%$  or TGs  $\geq 5.65$  mmol/L at baseline; PL subgroup 2) in the full analysis set.

MMRM analysis showed significant improvements from baseline in HbA1c, fasting TGs, and FPG across visits over the 14-year study period in PL subgroup 1. However, in the overall PL population, only improvements in FPG and the overall and month-12 reductions in HbA1c were statistically significant. High proportions of patients in the overall PL population and PL subgroup 1 achieved target decreases in HbA1c or fasting TGs at month 12/LOCF, and significant decreases in liver volume were observed in the subsets of patients who were assessed in the overall PL population and PL subgroup 1.

These results are generally consistent with metreleptin studies in other small cohorts of patients with PL, but results

**Table 4** Summary of adverse events in the safety analysis set

Adverse event, <i>n</i> (%)	Overall PL population ( <i>N</i> = 41)	PL subgroup 1 ( <i>n</i> = 31)
≥ 1 TEAE	35 (85.4)	27 (87.1)
Drug-related TEAE	8 (19.5)	7 (22.6)
Severe TEAE	16 (39.0)	13 (41.9)
Drug-related severe TEAE	0	0
Treatment-emergent SAE	10 (24.4)	7 (22.6)
Drug-related treatment-emergent SAE	0	0
TEAE leading to discontinuation	1 (2.4)	1 (3.2)
On-study deaths	1 (2.4)	1 (3.2)
TEAE by preferred term (≥ 5% incidence) <sup>a</sup>		
Abdominal pain	6 (14.6)	6 (19.4)
Hypoglycemia	7 (17.1)	6 (19.4)
Nausea	6 (14.6)	5 (16.1)
Fatigue	3 (7.3)	3 (9.7)
Alopecia	3 (7.3)	3 (9.7)
Constipation	3 (7.3)	3 (9.7)
Arthralgia	3 (7.3)	2 (6.5)
Back pain	2 (4.9)	2 (6.5)
Pain in extremity	3 (7.3)	2 (6.5)
Weight decrease	2 (4.9)	2 (6.5)

PL partial lipodystrophy, SAE serious adverse event, TEAE treatment-emergent adverse event

<sup>a</sup>Medical Dictionary for Regulatory Activities, version 19.0

cannot be directly compared because of differences in inclusion criteria. The earliest description of the efficacy of metreleptin in patients with lipodystrophy included one patient with FPLD and reported benefit in this patient [24]. Another study showed that HbA1c, TGs, and liver enzymes significantly decreased after 1 year of metreleptin therapy in nine patients with FPLD, diabetes, and fasting leptin ≤ 6 ng/mL [25]. A study in patients with the Dunnigan variety of FPLD showed that median fasting TGs significantly decreased in patients with moderate or severe hypoleptinemia (all had serum leptin < 7 ng/mL) after 6 months of metreleptin treatment, but HbA1c and FPG did not significantly improve [26]. However, baseline HbA1c, fasting TGs, and FPG were lower than those in the present study, and greater decreases in HbA1c, TGs, and FPG have been observed in previous studies of patients with PL who had more severe baseline metabolic abnormalities than those in the present study [27].

While improvements in metabolic parameters in response to metreleptin treatment in patients with PL were observed, reductions in HbA1c and FPG appeared to be of a lower magnitude than in patients with GL. When data from the NIH study of patients with GL are compared with those from PL subgroup 1 in the full analysis set of the present

study, the actual change in HbA1c from baseline to month 12/LOCF was −2.2% in patients with GL and −0.9% in PL subgroup 1 [23]. Mean change in FPG was −3.0 mmol/L in patients with GL and −1.8 mmol/L in PL subgroup 1. In comparison, the improvement in TGs was greater in patients with PL versus those with GL, with a mean decrease of 37.4% versus 32.1%. In patients with PL and GL, higher baseline elevations in HbA1c and fasting TGs were associated with greater response to metreleptin treatment.

Metreleptin was generally well tolerated in patients with PL, with no unexpected safety signals over the 14-year study period. Most events were mild-to-moderate severity, and the most common TEAEs were abdominal pain, hypoglycemia, and nausea. TEAEs were generally consistent with those observed in the NIH study of patients with GL [23], although the incidence among patients with PL tended to be lower. There were no reports of lymphoma in patients with PL in the present study, which is noteworthy considering that the US label for metreleptin has a boxed warning that T-cell lymphoma has been reported in patients with AGL, even in those not treated with metreleptin [15]. The one death in the PL population in the present study due to hypoxic ischemic encephalopathy was not related to study treatment.

A limitation of this study is the relatively small sample size. This was expected because of the rarity of PL; most forms of FPLD have an estimated prevalence of 1 in 1,000,000 people [28, 29]. Despite the small study population and the number of study withdrawals, the MMRM analysis allowed the use of all available information for each patient to estimate treatment effects in cases of missing data, which complemented the single imputation method of LOCF. Another potential limitation is that almost all patients with PL were female, which likely reflects underdiagnosis or mild metabolic abnormalities that did not meet the inclusion criteria in males.

In conclusion, this study shows that metreleptin appears to be beneficial in the treatment of PL, especially for patients with more severe metabolic disease, and is tolerable in long-term use.

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## Compliance with ethical standards

**Conflict of interest** E.A.O. has served as a consultant to Aegerion Pharmaceuticals, Akcea Therapeutics, AstraZeneca, Regeneron Therapeutics, and Thera Therapeutics; has received grant support from Aegerion Pharmaceuticals, Akcea Therapeutics, AstraZeneca, Gemphire Therapeutics, GIDynamics, and Ionis Pharmaceuticals; and has received nonmaterial support from Aegerion Pharmaceuticals and Boehringer Ingelheim. D.A.V. and D.B.S. have served as consultants to Aegerion Pharmaceuticals. A.L. and T.S. are former employees and G.F. is a current employee of Aegerion Pharmaceuticals. E.C., P.G., and R.B. report no conflicts of interest.

**Ethical approval** The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice and was approved by the National Institute of Diabetes and Digestive and Kidney Diseases and the National Institute of Arthritis and Musculoskeletal and Skin Diseases institutional review boards.

**Informed consent** Informed consent was obtained from all patients or their legal guardians.

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