



Metreleptin in lipodystrophy: a profile of its use

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Abstract

Metreleptin [Myalepta[®] (EU); Myalept[®] (USA)] is a recombinant analogue of human leptin and currently the only drug available for the specific treatment of lipodystrophy (LD). In the EU, metreleptin (administered once daily via subcutaneous injection) is indicated as replacement therapy to treat the complications of leptin deficiency in patients aged ≥ 2 years with generalized LD and in patients aged ≥ 12 years with partial LD who have failed to achieve adequate metabolic control with standard treatments. Its use in these rare settings is supported by data from open-label clinical studies and clinical practice, with the totality of evidence indicating that metreleptin improves metabolic abnormalities associated with generalized or partial LD, including in paediatric patients. Other potential benefits include improved hepatic parameters/disease, nephropathy and survival, although the impact of the drug on these outcomes would benefit from further analysis. Metreleptin is generally well tolerated.

Adis evaluation of metreleptin in the treatment of lipodystrophy

Recombinant analogue of human leptin
Administered once daily via subcutaneous injection
Improves metabolic abnormalities of generalized or partial lipodystrophy, including in paediatric patients
May potentially improve hepatic parameters/disease, nephropathy and survival
Hypoglycaemia and decreased bodyweight are the most common adverse effects

What is the rationale for using metreleptin in lipodystrophy?

Lipodystrophies (LDs) are a group of rare, acquired or genetic, medical conditions characterized by adipose (fat) tissue deficiency in the absence of a catabolic state or nutritional deprivation [1, 2]. The deficiency of fat may be

throughout the entire body (i.e. generalized LD) or only in specific areas (i.e. partial LD) [1], with abnormal accumulation of fat in unaffected regions often evident [3]. Fat tissue plays a key role in lipid metabolism and glucose homeostasis [4], and its loss in LD interferes with hunger/satiety signals (commonly leading to hyperphagia), resulting in inappropriate lipid storage in muscle, the liver and other organs [1, 2]. Consequently, patients with LD often have extreme insulin resistance, leading to hypertriglyceridaemia, diabetes, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), pancreatitis and other metabolic/endocrine abnormalities [1, 5].

Given the lack of curative therapies for LD, the standard-of-care is to manage the metabolic complications of the disorder, with options including lifestyle modification (i.e. diet and exercise) and pharmacotherapy for each specific complication (e.g. statins for hyperlipidaemia; glucose-lowering agents for diabetes) [2, 6]. However, these conventional therapies do not address the underlying causes of LD and often provide insufficient metabolic control [6]. These limitations and the knowledge that serum levels of leptin (an adipose tissue-secreted hormone with effects such as appetite suppression, promotion of hepatic lipolysis and glucose usage in skeletal muscle, and inhibition of insulin secretion [5, 7]) tend to be low in patients with LD [2], prompted investigation of leptin replacement therapy as a potential treatment option [6]. Metreleptin [Myalepta[®] (EU); Myalept[®] (USA)] is a recombinant analogue of human leptin [3, 5]

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and is currently the only drug available for the specific treatment of LD.

For whom is metreleptin indicated?

In the EU, metreleptin is indicated as a replacement therapy to treat the complications of leptin deficiency in patients aged ≥ 2 years with generalized LD, and in patients aged ≥ 12 years with partial LD who have failed to achieve adequate metabolic control with standard treatment [8]. A summary of how metreleptin should be administered in these patient populations is shown in Table 1.

How does metreleptin work?

Metreleptin is a protein of ≈ 16 kDa that differs from endogenous human leptin by having an amino-terminal methionine residue [5]. Being an analogue of human leptin [3, 5], metreleptin binds to and activates the leptin receptor, thus mimicking the physiological effects of endogenous leptin [8]. Metreleptin improves metabolic abnormalities associated with LD, including glycaemic control, hypertriglyceridaemia and insulin sensitivity [5, 9]. How metreleptin ameliorates these metabolic abnormalities is not entirely clear, but is likely to involve a variety of factors [9]. One such factor is regulation of appetite/eating behaviour, with metreleptin reducing hunger [10, 11], eating importance/frequency [10], caloric intake [12] and time to satiety [12], as well as increasing satiety [11, 12]; however, some effects of metreleptin (including insulin sensitivity improvements) may be independent of food intake [13]. Changes in appetite/eating with metreleptin can lead to weight loss [5], although, even in lean hypoleptinaemic women, the drug reduced body fat without impacting lean body mass [14]. Reductions in facial soft tissue volume (in areas with adipose tissue compartments) have occurred with metreleptin in patients with LD, with the changes being of varying magnitude and generally not visible to the naked eye [15]. However, metreleptin did not increase patient energy expenditure in a recent non-randomized crossover study [13].

Metreleptin may disrupt events that lead to lipotoxicity, as improvements in hepatic and intramyocellular lipid content, liver volume and steatohepatitis have occurred with the drug in LD patients [5, 9]. Elevated levels of apolipoprotein CII and ANGPTL3 (proteins that inhibit lipoprotein lipase) in patients with LD may contribute to hypertriglyceridaemia, with levels of ANGPTL3 (but not apolipoprotein CII) being reduced by metreleptin [16, 17]. Reductions in plasma levels of PCSK9 (a protein that promotes hypercholesterolaemia) have also been seen with metreleptin in LD patients, with

this change correlating with a reduction in low-density lipoprotein cholesterol [18].

What is the efficacy of metreleptin?

Generalized lipodystrophy

Metreleptin improved glycaemic control and hypertriglyceridaemia in patients aged ≥ 6 months (median age 15 years) with generalized LD in an integrated analysis of an open-label pilot study + its long-term extension [19], representing the largest available data set. In this analysis, metreleptin significantly reduced levels of glycosylated haemoglobin (HbA_{1C}) and triglycerides from baseline over 12 months of treatment (co-primary endpoints; Table 2) and sustained these benefits through to month 48. Most metreleptin recipients (79.7%) achieved a metabolic response (i.e. a $\geq 1\%$ reduction in HbA_{1C} or a $\geq 30\%$ reduction in triglycerides) by month 12. After starting metreleptin, some patients were able to discontinue treatment with insulin (16 of 39; 41%), oral anti-diabetic agents (7 of 32; 22%) and lipid-lowering medications (8 of 34; 24%) [19].

Having worse metabolic characteristics at baseline appeared to enhance these benefits of metreleptin, as indicated by co-primary endpoint analyses in patients with HbA_{1C} $\geq 7\%$ or triglycerides ≥ 5.65 mmol/L at baseline (Table 2) [8] and the proportion of patients who achieved a metabolic response at 12 months despite a baseline HbA_{1C} level ≥ 6.5 or $\geq 8.0\%$ (89 and 79 vs 11% of patients with baseline level $< 6.5\%$) or a baseline triglyceride level ≥ 2.26 or ≥ 5.65 mmol/L (83 and 49 vs 15% of patients with baseline level < 2.26 mmol/L) [19].

At 12 months, metreleptin also improved some hepatic and renal outcomes from baseline. Metreleptin was associated with significant reductions from baseline in mean liver volume in 12 evaluable patients (33.8% reduction; $p < 0.001$), as well as ALT levels (44%; $p = 0.01$), but not AST levels (32%; $p = 0.29$), in the full analysis set [19]. The mean rate of protein excretion (a renal impairment measure) decreased from baseline by 54% (decrease of 906 mg/24 h from a baseline of 1676 mg/24 h) in 12 patients with renal data [8].

The findings of this analysis generally support those of earlier analyses of the pilot/extension study [20–22], as well as a trial in seven Japanese patients with generalized LD [23], the latter of which also reported improvements from baseline in insulin secretion and insulin resistance with metreleptin [23]. Moreover, a significant ($p < 0.001$) reduction from baseline in proteinuria was observed after 4 months of leptin therapy in some patients with generalized LD in an open-label study (11 of 15; 73%), with this benefit maintained for up to 36 months and being associated with

Table 1 Summary of metreleptin administration in lipodystrophy in the EU [8]

What is the approved indication for the drug?	
Adjunct to diet as a replacement therapy to treat complications of leptin deficiency	In adult and paediatric patients (aged ≥ 2 years) with congenital (Berardinelli-Seip syndrome) or acquired (Lawrence syndrome) generalized LD In adult and paediatric patients (aged ≥ 12 years) with familial or acquired (Barraquer-Simons syndrome) partial LD for whom standard treatments have failed to achieve adequate metabolic control
How is metreleptin available?	
Powder containing 3, 5.8 or 11.3 mg of metreleptin for reconstitution (to concentration of 5 mg/mL) for once-daily injection	
How is metreleptin reconstituted?	
Reconstitute in water using a syringe with a 40 mm, 21 gauge needle	
Select syringe size based on the volume of water needed for reconstitution	0.6 mL water (3 mg metreleptin): 1.0 mL syringe 1.1 mL water (5.8 mg metreleptin): 3.0 mL syringe 2.2 mL water (11.3 mg metreleptin): 3.0 mL syringe
How should the dosage of metreleptin be calculated?	
Calculate daily dosages based on patient weight; prescribe in mL as well as mg, to ensure patient/carer understands correct dose for injection	
Initial daily dosage	Males/females weighing 9–25 kg: 0.06 mg/kg (0.012 mL/kg) rounded down to the nearest 0.01 mL (total dose 0.10–0.30 mL) Males/females weighing > 25 to ≤ 40 kg: 0.06 mg/kg (0.012 mL/kg) Males weighing > 40 kg: 2.5 mg (0.5 mL) Females weighing > 40 kg: 5 mg (1 mL)
Dose titration	Males/females weighing 9 to ≤ 40 kg : adjust by 0.02 mg/kg (0.004 mL/kg) as necessary Males/females weighing > 40 kg: adjust by 1.25–2.5 mg (0.25–0.5 mL) as necessary
Maximum daily dosage	Males/females weighing 9 to ≤ 40 kg: 0.13 mg /kg (0.026 mL/kg) Males/females weighing > 40 kg: 10 mg (2 mL)
How should metreleptin be administered?	
Subcutaneous injection into the abdomen, thigh or upper arm at the same time each day, without regard to meals	
To minimize potential discomfort at the injection site, doses > 1 mL can be divided equally into two injections for sequential administration	
Select syringe size and needle gauge/length based on dose	Dose ≤ 1.5 mg (≤ 0.3 mL): 0.3 mL U100 insulin syringe (8 mm, 31 gauge needle) Dose > 1.5 to 5 mg (> 0.3 to 1.0 mL): 1.0 mL syringe (13 mm, 30 gauge needle) Dose > 5 to 10 mg (> 1.0 to 2 mL): 2.5 mL syringe (13 mm, 30 gauge needle)
When should the metreleptin dose be adjusted?	
Adjust dosage based on clinical response ^a or factors such as excessive weight loss or other tolerability issues	
Adults and children: incomplete or no response after ≥ 6 months	Ensure patient is administering metreleptin correctly at an appropriate dose and is adhering to diet Consider dose increase before stopping metreleptin
Children	Dosage increases are likely necessary with increasing age (particularly at puberty), as abnormalities in HbA _{1C} and triglycerides increase If metabolic abnormalities are absent, base dose adjustments primarily on weight changes

HbA_{1C} glycosylated haemoglobin, LD lipodystrophy

^aMinimum clinical response: $\geq 0.5\%$ reduction in HbA_{1C} $\pm \geq 25\%$ reduction in insulin requirements $\pm \geq 15\%$ reduction in triglycerides

a decline in creatinine clearance (likely indicating reduced glomerular hyperfiltration) [24].

Metreleptin also generally reversed metabolic complications in paediatric patients with generalized LD [8, 25]. At 12 months in the integrated analysis of the pilot/extension study, 5 patients aged < 6 years, 12 aged ≥ 6 to < 12 years and 28 aged ≥ 12 to < 18 years had mean changes from baseline in triglycerides of -10.5 , -14.1 and -42.9% , respectively, and mean changes from baseline in HbA_{1C} of $+0.2$, -1.1 and -2.6% , with the between-age-group differences in the latter parameter likely being due to their mean HbA_{1C} levels

at baseline (5.7, 6.4 and 9.7%) [8]. Similarly, among seven children aged 2.4–13.6 years with Berardinelli-Seip congenital lipodystrophy who received metreleptin for 4 months in an open-label trial, fasting triglyceride levels significantly ($p=0.017$) declined from baseline and, although fasting plasma glucose levels did not change significantly, there was a significant ($p=0.04$) improvement in the fasting glucose to insulin ratio and a significant ($p=0.002$) reduction in liver volume [25].

The findings of clinical trials are generally supported by real-world experience in European countries [26, 27] and

Table 2 Efficacy of metreleptin after 12 months of treatment in patients with lipodystrophy in an integrated analysis of a pilot study and its long-term extension

Pt population	No. of evaluable pts	Mean change from BL in HbA _{1C} (%) [BL]	Mean pt-level change from BL in fasting TG (%) [BL]
Generalized lipodystrophy			
Overall pt population ^a [19]	59 ^b	-2.2*** [8.6]	-32*** [14.7 mmol/L]
Pts with BL HbA _{1C} ≥ 7% [8]	45	-2.8*** ^c [9.6]	
Pts with BL triglycerides ≥ 5.65 mmol/L [8]	24		-72*** ^c [31.7 mmol/L]
Partial lipodystrophy			
Overall pt population ^d [29]	37 ^b	-0.6** [7.9]	-20.8* [12.5 mmol/L]
Pts with BL HbA _{1C} ≥ 6.5% or TG ≥ 5.65 mmol/L ^d [29]	27 ^b	-0.9*** [8.7]	-37*** [15.7 mmol/L]
Pts with BL HbA _{1C} ≥ 8% [8]	18	-1.3*** ^c [9.9]	
Pts with BL TG ≥ 5.65 mmol/L [8]	15		-54*** ^c [27.6 mmol/L]
Pts with BL HbA _{1C} ≥ 8.0% or TG ≥ 5.65 mmol/L ^d [29]	22	-1.0** [9.4]	-43*** [20.4 mmol/L]

Weighted average daily metreleptin dose in first 12 months differed between the generalized lipodystrophy (2.6 or 5.3 mg in males and females weighing > 40 kg; 2.0 or 2.3 mg in males and females weighing ≤ 40 kg) and partial lipodystrophy (7.0 mg in males and females weighing > 40 kg) groups

BL baseline, HbA_{1C} glycosylated haemoglobin, pt(s) patients(s)

* $p < 0.05$, ** $p \leq 0.005$, *** $p \leq 0.001$ vs BL

^aAt BL, the median fasting leptin levels was 1 ng/mL [8]

^bPts evaluated for HbA_{1C}; number of pts evaluated for fasting TG was generally similar

^c p value obtained from an additional source [39]

^dThe mean fasting leptin level at BL was 6–7 ng/mL [8]

Brazil [28] ($n = 9-28$). For instance, in the largest analysis (a retrospective collection of data from 28 patients in the metreleptin early access programme in Italy, Spain, France and the UK; treatment duration ≤ 14.7 years) [26], metreleptin significantly ($p \leq 0.001$ vs baseline) reduced levels of triglyceride by a median of 61% and HbA_{1C} by a mean of 1.9% after 12 months of therapy. Moreover, at this time-point versus baseline, an increased proportion of metreleptin recipients had a triglyceride level of < 2.3 mmol/L (50 vs 5%) or a HbA_{1C} level of < 8% (70 vs 26%) [26].

Partial lipodystrophy

Metreleptin improved glycaemic control and hypertriglyceridaemia in patients aged ≥ 6 months (overall median age 34 years) with partial LD in the integrated analysis of the pilot/extension study, significantly reducing levels of HbA_{1C} and triglycerides over 12 months of treatment (co-primary endpoints) in the overall patient population and each of the patient subgroups assessed (Table 2) [8, 29]. Similar to patients with generalized LD, these benefits were more notable in the partial LD patients with higher baseline HbA_{1C} or triglyceride levels (Table 2) [8, 29]. Consistent with these findings, some partial LD metreleptin recipients achieved a metabolic response, including 51.4% of the overall population and 67.9% of the patient subgroup with baseline HbA_{1C} ≥ 6.5% or triglyceride ≥ 5.65 mmol/L [29].

None of the 19 patients receiving insulin at baseline were able to discontinue it once receiving metreleptin, although 1 of 28 patients receiving oral glucose-lowering medications at baseline, and 1 of 34 patients receiving lipid-lowering medications at baseline, discontinued these therapies once receiving metreleptin [29].

Whether the improvements in metabolic complications seen with metreleptin in this setting could be impacted by the degree of hypoleptinaemia was evaluated in an open-label observational study in 24 patients with familial partial LD of the Dunnigan variety (mean age ≈ 40 years) [30]. In this study, median fasting serum triglyceride levels significantly ($p < 0.05$) decreased from baseline to a similar degree after 6 months of treatment regardless of whether patients were moderately hypoleptinaemic (serum leptin 4–7 ng/mL; $n = 10$) [from 4.8 to 3.8 mmol/L] or severely hypoleptinaemic (serum leptin < 4 ng/mL; $n = 14$) [from 2.6 to 2.1 mmol/L]. Neither patient group experienced significant improvements in glycaemic control (i.e. HbA_{1C} levels, fasting plasma glucose levels, fasting serum insulin levels or glucose tolerance), although each population had a significant ($p < 0.005$) decrease from baseline in median intrahepatic lipid content (23.7 to 9.2% in moderately hypoleptinaemic group; 8.8 to 4.9% in severely hypoleptinaemic group) [30].

Metreleptin therapy for 12 months was associated with significant reductions in liver volume in the integrated

analysis [–13.4% in overall population ($n=9$); –12.4% in subgroup with baseline $\text{HbA}_{1\text{C}} \geq 6.5\%$ or triglyceride ≥ 5.65 mmol/L ($n=8$)], although liver enzyme levels were not significantly altered [29]. Notably, in an analysis of data from two clinical trials in patients with partial LD and NAFLD, 9 of the 18 patients who completed 12 months' treatment with metreleptin achieved a clinical hepatic response (i.e. a 2-point reduction in total NASH score without an increase in fibrosis) [31]. Among pre-selected parameters, baseline carbohydrate consumption was the best predictor of response, with others including the baseline level of free fatty acid, leptin or insulin [31].

Data for metreleptin in paediatric patients with partial LD are more limited, with only four patients aged ≥ 12 to < 18 years available in the subgroup of partial LD patients evaluated in the integrated analysis [8]. The mean change from baseline to month 12 in this paediatric subgroup was –0.7% for $\text{HbA}_{1\text{C}}$ and –55.1% for triglycerides [8].

Real-world data from a long-term open-label expanded-access study of metreleptin in 23 patients with partial LD [32] generally support the findings of clinical trial analyses, although the observed mean improvements from baseline in $\text{HbA}_{1\text{C}}$ (–0.88% from a mean baseline of 7.9%) and triglyceride (–1.35 mmol/L from a mean baseline of 4.54 mmol/L) levels after 12 months' treatment with metreleptin, did not reach statistical significance.

Mixed lipodystrophy populations

Clinical study [33–35] and real-world [36] data from mixed populations of patients with generalized or partial LD, including paediatric patients (aged 6 months to < 18 years) [35], support the efficacy of metreleptin in improving metabolic parameters associated with LD. In addition to these benefits, one of the clinical trials (of open-label, prospective design) assessed the long-term effect of metreleptin on LD-associated liver disease and found that the drug reversed NASH in some patients [significantly ($p=0.0002$) fewer patients had NASH after 25.8 months' metreleptin therapy than at baseline; 33 vs 86% of 27 patients] and stabilized liver fibrosis [34]. The potential clinical benefit of metreleptin on liver disease and other LD-related complications (including hyperphagia and heart/kidney damage) in patients with generalized or partial LD was also observed in a combined analysis of 290 retrospective chart reviews [37]. Leptin replacement therapy may also improve survival in patients with LD, according to a matched analysis of 114 treated and 178 untreated patients, with the risk of death being significantly ($p < 0.05$) reduced by 66% (79% when adjusted for covariates) [38].

What is the tolerability profile of metreleptin?

Metreleptin is generally well tolerated in patients with LD, with an overall tolerability profile that is similar in adults and children [8]. Among patients with generalized LD and a subgroup of patients with partial LD (aged ≥ 12 years, with $\text{HbA}_{1\text{C}} \geq 8\%$, triglyceride ≥ 5.65 mmol/L and/or leptin < 12 ng/mL) who received metreleptin in clinical studies, the most common adverse reactions were decreased body weight (17%) and hypoglycaemia (14%), with the latter possibly requiring insulin recipients to reduce anti-diabetic agent dosages and monitor blood glucose levels (Table 3) [8]. Other commonly occurring (incidence ≥ 1 to $< 10\%$) adverse reactions with metreleptin in this analysis included nausea, abdominal pain, decreased appetite, headache, alopecia, menorrhagia, fatigue, injection-site reactions, including bruising and erythema (all mild/moderate and none resulting in metreleptin discontinuation) and neutralizing antibodies [8]. There are various warnings and precautions pertaining to metreleptin use (Table 3), including the potential for immunogenicity, pancreatitis and T-cell lymphoma [8].

Antibodies against metreleptin have been detected in most patients with LD treated with the drug [8, 40] (e.g. 65 of 74 patients across the pilot/extension and expanded-access studies; 88% [8]), with titres usually peaking in 4–6 months and declining thereafter [40]. In an extended data set, 98 of 102 recipients (96%) had blood that blocked metreleptin reacting with a recombinant leptin receptor in vitro [8]. Whether such activity may impact metreleptin efficacy is not clear [8], although all four patients with generalized LD in the extension study who developed in vitro neutralizing activity on metreleptin therapy had concurrent poor or worsening metabolic control [40]. The development of neutralizing activity has also been temporally associated with serious and/or severe infections in some patients (five generalized LD patients with $> 80\%$ neutralizing activity and one partial LD patient; all responded to standard treatment) [8].

Six patients (four with generalized LD and two with partial LD, all of whom had had pancreatitis and hypertriglyceridaemia previously) experienced pancreatitis in clinical trials of metreleptin; potential contributing factors included not complying with, or abruptly interrupting, metreleptin treatment [8].

T-cell lymphoma occurred in three patients with generalized LD receiving metreleptin in clinical trials. Two of these patients developed peripheral T-cell lymphoma and had immunodeficiency and significant haematological abnormalities before receiving metreleptin, whereas the third was a paediatric patient without pre-treatment haematological abnormalities who developed anaplastic large cell lymphoma [8]. However, a causal relationship between metreleptin and lymphoma development/progression has not been established [8].

Table 3 Summary of the warnings/precautions and drug interactions associated with metreleptin use in lipodystrophy in the EU [8]

How should metreleptin be used in special populations?	
Pregnant women	Use is not recommended
Breast-feeding women	Consider benefits of treatment in the mother and the risks in the breast-fed infant
Elderly patients	Select and adjust the daily dose with caution
Patients with renal or hepatic impairment	No dosage adjustments can be recommended at present
What other special warnings/precautions pertain to the use of metreleptin?	
Immunogenicity	Neutralizing antibodies may develop against metreleptin that could potentially reduce the drug's efficacy and/or inhibit endogenous leptin activity Continuing metreleptin after severe/serious infections have developed is at the prescriber's discretion
Acute pancreatitis	Abruptly discontinuing or being non-compliant to metreleptin may worsen hypertriglyceridaemia and pancreatitis, especially in patients with pancreatitis risk factors If pancreatitis develops, evaluate promptly and, if necessary, taper the dose over 2 weeks in combination with a low-fat diet, triglyceride monitoring and lipid-lowering therapy initiation/dosage adjustment
T-cell lymphoma	Consider risk/benefits of metreleptin in patients with significant haematological abnormalities and/or acquired generalized lipodystrophy, as T-cell lymphoma has occurred in some metreleptin recipients
Hypersensitivity reactions	Permanently discontinue metreleptin if a serious allergic reaction occurs
What clinically relevant drug interactions may potentially occur with metreleptin?	
Anti-diabetic drugs	Due to increased hypoglycaemia risk (metreleptin may reduce insulin resistance), may need to reduce dosages of anti-diabetic agents and monitor blood glucose levels in insulin recipients Alternatively, for non-severe hypoglycaemia, consider managing food intake
Hormonal contraception	Consider additional non-hormonal contraception during metreleptin therapy (as reduction of CYP3A substrate exposure via CYP3A induction cannot be excluded with metreleptin)
Other CYP450 substrates	When initiating or discontinuing metreleptin in recipients of narrow therapeutic index drugs that are CYP450 substrates, monitor the effects or concentrations of these agents and adjust the dosage as required

In paediatric patients

Among 48 paediatric patients with generalized LD who received metreleptin in two clinical trials (pilot/extension and expanded-access studies), adverse reactions occurred with similar incidence irrespective of patient age and were serious in two patients (anaplastic large cell lymphoma and worsening hypertension) [8]. No adverse reactions were reported in the four paediatric patients in the partial LD subgroup assessed in the integrated analysis of the pilot/extension study [8].

What is the current clinical role of metreleptin in lipodystrophy?

Treating lipodystrophy-related metabolic abnormalities is a challenge, with many patients (particularly those with severe insulin resistance and hypertriglyceridaemia) unable to achieve adequate metabolic control with standard therapies [3, 6]. Metreleptin is the first drug available for the specific treatment of lipodystrophy and has been a welcome addition to the conventional treatment options available. Although the rarity of the disease limits the number of patients in whom treatment can be evaluated, overall, the totality of evidence

from clinical trials and real-world experience indicate that metreleptin improves glycaemic control and triglyceride levels in patients with generalized or partial LD, with data from the largest clinical trial set indicating that these benefits are generally more notable in patients with worse metabolic parameters at baseline in each of these populations. There is also evidence (albeit more limited) that metreleptin has metabolic benefit in paediatric patients with generalized or partial LD. Patients with partial LD can have leptin levels ranging from low to normal with varying degrees of fat loss [3], although data from one study suggest that metreleptin may lower triglyceride levels regardless of whether a partial LD patient is moderately or severely hypoleptinaemic; however, no glycaemic control improvements were evident in either group. Whether metreleptin may be of benefit in partial LD patients without hypoleptinaemia is of interest.

Various other benefits have occurred with leptin therapy in patients with generalized or partial LD, including improvements in hepatic parameters/disease, such as liver volume, intrahepatic lipid content and NASH (a major complication of LD that can progress despite adequate metabolic control [3]), nephropathy and survival. However, the impact of metreleptin on these outcomes, particularly life expectancy, would benefit from further analysis.

Metreleptin is generally well tolerated in patients with LD, with a similar tolerability profile in adults and children. As with other therapeutic proteins, antibodies against leptin may develop in metreleptin recipients, and whether such antibodies may impact the efficacy of the drug long-term remains to be determined.

Although formal guidance for the treatment of lipodystrophy is limited, a 2016 multi-society practice guideline recommends metreleptin (in conjunction with diet) as a first-line option for the treatment of metabolic and endocrine abnormalities in patients with generalized LD and as an option to consider for preventing these abnormalities in children with generalized LD [1]. The guideline also recommends considering metreleptin for the treatment of hypoleptinaemic patients with partial LD who have severe metabolic abnormalities ($\text{HbA}_{1\text{C}} > 8\%$ and/or triglycerides $> 5.6 \text{ mmol/L}$) [1].

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Compliance with ethical standards

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