Proposal for assessment of new health technologies

Important information – read this first!

- Submitted proposals for national health technologies (HTAs) will be published in full. If the proposer thinks there is information necessary for filling out the form, that should not be made public, please contact the secretariat (Nye Metoder) before submission.

  The proposer is aware that the form will be published in its entirety (tick): ☒

- Proposer has filled out point 19 below «Interests and, if any, conflicts of interest» (tick): ☒
- This form serves the purpose to submit proposals for health technology assessment (HTA) at the national level in Nye Metoder - the national system for managed introduction of new health technologies within the specialist health service in Norway. The form does not apply to proposals for research projects. A health technology assessment is a type of evidence review, and for this to be possible, documentation is required, e.g. from completed clinical trials. Lack of documentation may be one of the reasons why the Commissioning Forum (Bestillerforum RHF) does not assign a health technology assessment.
- If the proposal concerns a medical device, the proposer is familiar with the document «Guidance criteria for management of medical devices in the National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway» (link) (tick): ☐

Contact information:

Name of the proposer (organization / institution / company / manufacturer)**:**

AMRYT PHARMACEUTICALS DAC

Name of proposal contact:

Fleur Taylor

Representative in Norway – Karolina Fetingyte

Telephone number:

Fleur Taylor +44791534703

Karolina Fetingyte +4550176214

E-mail address:

Fleur Taylor fleur.taylor@amrytpharma.com

Karolina Fetingyte k.fetingyte@grynumberhealth.com (direct contact)

Date and locality:

4th June, 2020, Dublin

1. Proposer's title on the proposal: *
   *This may be changed during the course of the process"

Metreleptin (Myalepta) for patients with lipodystrophy (LD)

2. Brief description of the health technology proposed to be considered:

Myalepta is a recombinant human leptin analogue in the form of a powder for solution for self-administered subcutaneous injection. Myalepta is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients: • with confirmed congenital generalized LD (*Berardinelli-Seip syndrome*) or acquired generalized LD (*Lawrence syndrome*) in adults and children 2 years of age and above • with confirmed familial partial LD or acquired partial LD (*Barraquer-Simons syndrome*), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control.

3. Brief description of current standard of care (SOC) (Which health technology (ies) are currently used. What is the status of the technology (ies)? Whether it provides curative treatment, life extension, etc.)
   Will the proposed technology replace or be a supplement to today's SOC?

There is no curative therapy for lipodystrophy (LD), the current best supportive care is to manage the metabolic complications of LD with lifestyle modification (i.e. diet and exercise) and conventional pharmacotherapy for specific symptomatic treatment (e.g. anti-hyperglycemic and lipid-lowering medications). Conventional pharmacotherapy is unlicensed in LD. Myalepta is licensed as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy patients. Lipodystrophy patients are generally refractory to conventional treatments, especially anti-hyperglycaemic agents, resulting in the use of very high insulin doses. This leaves patients at higher risk of disease complications across multiple organs and premature mortality. In NIH studies 991265/20010769, GL patients treated with Myalepta were able to stop background therapy for diabetes (41% insulin, 22% OAD) and hypertriglyceridemia (24%).

4. This proposal concerns:

	Yes	No
A brand new and innovative health technology	☒	☐
Anew application, or a new indication for an established method	☐	☒
A comparison between several methods	☐	☒
A technology that is already in use	☒	☐
If yes – technology used in clinical practice	☒	☐
If yes – technology used in research/clinical trials	☐	☒
A re-evaluation of technology used in clinical practice	☐	☒

The technology is relevant for disinvestment	☐	☒

"Please include further details about any use of the technology"

5. This health technology involves (Multiple ticks are possible)

Pharmaceutical	☒
Medical device/IVD medical device that is CE-marked*	☐

"*If the technology is CE-marked: What is it CE- marked as and for which indication? Please describe"

Medical device/IVD medical device that is not CE-marked	☐
Procedure	☐
Screening	☐
Highly specialized services / national offers	☐
Organization of the health services	☐
Other (describe)	☐

"If relevant, please include who should be responsible for developing the technology."

6. Application of the technology:

Prevention	☐
Assessment and diagnostics	☐
Treatment	☒
Rehabilitation	☒
Specialist health care	☐
Primary health care	☐

Myalepta is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients:

• with confirmed congenital generalized LD (Berardinelli-Seip syndrome) or acquired generalized LD (Lawrence syndrome) in adults and children 2 years of age and above

• with confirmed familial partial LD or acquired partial LD (Barraquer-Simons syndrome), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control.

7. Responsibility for funding

	Yes	No
Is the specialized health service responsible for financing the technology today?	☐	☒
May the specialized health service become responsible for funding the health technology?	☒	☐

In Norway, there are currently 3 patients diagnosed with GL. No patients have been diagnosed with PL.

8. Is the technology mentioned in the national guidelines or action programs prepared by the Norwegian Directorate of Health?

Yes	No
☐	☒

There are no specific guidelines in Norway for the treatment of lipodystrophy.

However, there are multi national and multi-society guidelines „The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline“ by R.Brown 2016

9. Does the technology involve the use of radiation (ionizing/ non- ionizing)? Yes ☐ No ☒

"Give a short description of type of radiation source, device and degree of radiation exposure"

10. Which discipline(s) does the health technology apply to, and which patients are affected? (Could the health technology also affect other groups (e.g. health personnel or relatives)?)

Key medical specialists involved in diagnosis and management of lipodystrophy include endocrinologists and pediatric endocrinologists. Diabetologists, cardiologists, lipidologists, hepatologists, dieticians etc. may also be involved. There are 3 diagnosed generalized lipodystrophy (GL) patients in Norway

11. Which aspects are relevant to the assessment? (Multiple ticks are possible)

Clinical efficacy	☒
Safety/adverse effects	☒
Costs/resource use	☒
Cost-effectiveness	☒
Organizational consequences	☐
Ethical	☒
Legal	☐

12. Please suggest the main scope/objective for the health technology assessment, as well as secondary scopes/objectives (in compliance with question 10). For those familiar with "PICO" (Patient, Intervention, Comparator, Outcome) – please include tentative suggestions for PICO.

Patients: 3 patients with generalised lipodystrophy. Intervention: Metreleptin (Myalepta) powder for solution for subcutaneous injection. Comparison: Myalepta is the first leptin replacement therapy and the only authorised treatment which addresses the multiple complications of leptin deficiency in lipodystrophy. Outcome: Improvements in hypertriglyceridemia, glycaemic control and liver volume.

13. Please give a brief explanation of why it is important that the health technology assessment proposed should be conducted.

Metreleptin (recombinant human methionyl leptin) is an analogue of the human hormone leptin with the addition of a methionine residue at its amino terminus leading to a prolonged half-life. Lipodystrophy is an ultra-rare but potentially life-threatening disease characterised by complete or partial loss or absence of subcutaneous adipose tissue which causes two major issues: a reduction of the fat storage capacity as well as leptin deficiency. As a consequence, lipodystrophy patients suffer from ectopical fat accumulation in non-adipose tissues such as the liver and the musculature. The storage of free fatty acids in organs and the musculature is lipotoxic and leads to severe organ damage and insulin resistance. Adipose tissue, the primary source for leptin, plays a key role in energy metabolism and insulin sensitivity through the control of lipid and glucose metabolism, which is regulated via the secretion of leptin (1).

Metreleptin binds to and activates the human leptin receptor, belonging to the Class I cytokine family of receptors, these signals through the JAK/STAT transduction pathway. It acts via multiple mechanisms to decrease glucose, triglyceride and other lipid intermediates, thus reducing their accumulation in tissues such as liver and muscle and ameliorating severe insulin resistance. As such, this improves hyperglycaemia and hypertriglyceridaemia (2), and thus reducing the risk and slowing the progression of associated diseases and complications such as heart disease, liver disease, renal failure, pancreatitis and insulin resistance.

The current management paradigm for patients with lipodystrophy has been focused upon symptom management via standard of care including diet and exercise, conventional therapies for hyperglycaemia and hypertriglyceridaemia. Lipodystrophy patients are usually refractory to conventional treatments, especially anti-hyperglycaemic agents, resulting in the use of very high insulin doses. This leaves patients at higher risk of disease complications across multiple organs and premature mortality.

Metreleptin has the potential to provide significant benefit to patients with lipodystrophy compared with existing symptomatic treatments because it is the first and only licenced treatment that addresses the cause of the underlying disease (i.e. leptin deficiency). Metreleptin is a leptin analogue, replacing leptin in the body, restoring metabolic pathways, and thus increasing fat breakdown in the blood, muscles and liver, thereby correcting some abnormalities in patients with lipodystrophy including insulin resistance and organ damage (2). As such, metreleptin holds the potential to halt and slow disease progression, reducing the risk of complications such as pancreatitis and premature mortality.

14. Please comment on the technology that is proposed to be assessed with regard to the following points:

The severity of the disease/condition the health technology targets

Lipodystrophy is an ultra-rare, complex, and clinically heterogenous disorder associated with severe metabolic comorbidities including hard to treat diabetes, hypertriglyceridaemia, and organ damage which can lead to premature mortality, and other co-morbidities such as insatiable hunger, pain, fatigue and reduced quality of life (1,4). It is characterised by complete or partial loss or absence of subcutaneous adipose tissue (1,3,4) resulting in reduced fat storage capacity and leptin deficiency. As a consequence, patients experience a complex range of conditions, including ectopic fat accumulation in non-adipose tissues, such as organs (e.g. liver, heart, pancreas) and muscles, insulin resistance and severe hypertriglyceridaemia (1,4,5). Patients are, as a result, at high risk of developing life-threatening complications across multiple organs such as pancreatitis and organ failure and premature mortality (4,5). In a systematic review, the mean age of death is 12.5 years for patients with Congenital Generalised Lipodystrophy (CGL), 32.2 years for Acquired Generalised Lipodystrophy (AGL), 27.8 years for Familial Partial Lipodystrophy (FPL) and 22.7 years for Acquired Partial Lipodystrophy (APL) (5).

Leptin is produced by adipose tissue and plays an essential role in energy homeostasis, neuro-endocrinology, and metabolism (4). Leptin deficiency manifests as a multitude of metabolic defects such as insulin resistance and hyperglycaemia leading to hard-to-treat diabetes and hypertriglyceridaemia (6). These metabolic defects are distressing, severely affecting patients' quality of life, and can lead to further, potentially life-threatening, complications such as cardiovascular disease, nephropathy, kidney disease, pancreatitis and liver conditions such as non-alcoholic fatty liver disease (NAFLD), steatohepatitis and cirrhosis (3,7).

As well as facing the multiple complications associated with the disease, people affected by lipodystrophy suffer from uncontrollable hunger, an altered physical appearance which many patients suggest can be even more distressing for patients than metabolic complications such as insulin resistance and diabetes.

Lipodystrophy poses a severe impact on quality of life and reduces life expectancy, with some patients not living past childhood.

Expected effect

Sustained improvements in hypertriglyceridaemia, glycaemic control and liver volume.

A minimum clinical response was defined by the European Medicines Agency (EMA) and is addressed in the SmPC as at least:

• 0.5% HbA1c reduction and/or 25% reduction in insulin requirements and / or

• 15% reduction in triglycerides (TGs)

Metreleptin has been shown to improve metabolic status such as high triglyceride and HbA1c levels unresponsive to other treatments. In the NIH studies 991265/20010769, clinically meaningful and statistically significant improvements in HbA1c were demonstrated in addition to baseline therapy: mean actual change in HbA1c from Baseline to Month 12 was -2.2% ($p<0.001$) for Generalised Lipodystrophy (GL) patients and -0.9% ($p<0.001$) for patients in the Partial Lipodystrophy (PL) subgroup, corresponding to indicated PL population for metreleptin. HbA1c reductions of this magnitude are associated with significant reductions in clinical complications associated with hyperglycaemia; results of the UK Prospective Diabetes Study (UKPDS) conducted in over 4,500 patients showed that each 1% reduction in HbA1c was associated with a statistically significant 21% reduction in risk of death due to diabetes, 14% reduction in risk for myocardial infarction, and 37% reduction in risk for microvascular complications. By extension, the HbA1c reductions achieved by metreleptin treatment reduces the risk of the micro and macrovascular complications associated with diabetes, thereby improving the QoL of patients.

Elevated triglyceride levels are a known risk factor for cardiovascular disease and pancreatitis. Metreleptin was associated with clinically meaningful and statistically significant improvements in hypertriglyceridaemia: the mean percent change in triglycerides from Baseline to Month 12 was -32.1% ($p=0.001$) for the GL group and -37.4% ($p<0.001$) in the PL subgroup (excluding one outlying noncompliant patient). These improvements in triglyceride levels are likely to reduce the risk of developing cardiovascular disease and have been shown to dramatically reduce the risk of pancreatitis.

The improvements in HbA1c and triglycerides occurred in some patients despite reductions in or even discontinuation of the use of antidiabetic medications (insulin, orally administered agents, or both) and/or lipid lowering medications. This suggests metreleptin offers the potential to reduce the burden of diabetes and/or hypertriglyceridaemia management itself, on both the patient (e.g. reducing pill burden) and the health service.

Metreleptin is also associated with improvements in lipodystrophy associated liver disease. Significant improvements in steatosis, ballooning injury and non-alcoholic steatohepatitis (NASH) scores have been reported as a result of metreleptin (6). NASH, a frequent condition in lipodystrophy patients, is commonly associated with elevated measurements of liver function, such as ALT, AST and liver volume. Thus, these markers are useful surrogates for NASH. Accordingly, metreleptin is associated with reductions in ALT, AST and liver volume.

Safety

The EMA EPAR reports the overall safety profile of metreleptin is considered acceptable (2)

The most frequently occurring adverse reactions from the clinical studies were hypoglycaemia (14%) and weight decreased (17%).

Key risks associated with Myalepta include:

● Hypoglycaemia with concomitant use of insulin and other anti-diabetics.

Metreleptin may decrease insulin resistance in diabetic patients, resulting in hypoglycaemia in patients with lipodystrophy and co-existing diabetes. Hypoglycaemia, deemed as related to metreleptin treatment, occurred in 14.2% of patients studied. All reports of hypoglycaemia in patients with GL and in the PL subgroup, have been mild in nature with no pattern of onset or clinical sequelae. Generally the majority of events could be managed by food intake with only relatively few modifications of anti-diabetic medicine dosage occurring (2).

● Acute pancreatitis associated with abrupt discontinuation of Myalepta.

One of the primary metabolic abnormalities in patients with lipodystrophy is severe hypertriglyceridaemia, which can result in life-threatening bouts of acute pancreatitis. In study NIH 991265/20010769, where medical history was more consistently recorded than in study FHA101, 31% of patients (33 of 107) reported a history of pancreatitis .

Across the 148 patients included in both lipodystrophy studies, 6 (4%) patients (4 with GL and 2 with PL), experienced treatment-emergent pancreatitis. All patients had a history of pancreatitis and hypertriglyceridaemia so were predisposed to recurrent episodes of recurrent pancreatitis. One of the patients who developed septic shock concurrent with pancreatitis died; the other 5 patients recovered and continued treatment (2). Abrupt interruption and/or non-compliance with metreleptin dosing was suspected to have contributed to the occurrence of pancreatitis in several of these patients. The mechanism for pancreatitis in these patients was presumed to be return of hypertriglyceridaemia and therefore increased risk of pancreatitis in the setting of discontinuation of effective therapy for hypertriglyceridaemia (2).

● Unplanned pregnancy due to improvement of hormonal dysfunction with Myalepta.

● Medication errors as a result of reconstitution or administration.

● Potentially Serious Adverse Drug Reactions, including T cell lymphomas, serious and severe infections secondary to neutralising antibodies and hypersensitivity reactions (2,9).

Total number of patients in Norway the health technology is applicable to

3 GL patients diagnosed in Norway

Consequences for resource use in the public health service

“Click in the field and type”

Need for revision of existing national guidelines or preparation of new guidelines

"Click in the field and type"

15. Please provide references to documentation of the health technology's effect and safety (i.e. previous technology assessments). (Up to 10 key references can be provided, please do not send attachments in this step of the process):

1. Rodriguez A.J., Mastronardi C.A., Paz-Filho G.J. New advances in the treatment of generalized lipodystrophy: Role of metreleptin. Ther Clin Risk Manage. 2015;11((Rodriguez A.J.) Department of Medicine, Monash Medical Centre, Clayton, VIC, Australia):1391–400.

2. Myalepta : EPAR - Product Information [Internet]. European Medicines Agency Europe; 2018 [cited 2020 Jan 15]. Available from: https://www.ema.europa.eu/en/documents/product-information/myalepta-epar-product-information_en.pdf

3. Rodríguez AJ, Neeman T, Giles AG, Mastronardi CA, Paz Filho G. Leptin replacement therapy for the treatment of non-HAART associated lipodystrophy syndromes: a meta-analysis into the effects of leptin on metabolic and hepatic endpoints. Arq Bras Endocrinol Metabol. 2014 Nov;58(8):783–97.

4. Rebecca J. Brown, David Araujo-Vilar, Pik To Cheung, David Dunger, Abhimanyu Garg, Michelle Jack, Lucy Mungai, Elif A. Oral, Nivedita Patni, Kristina I. Rother, Julia von Schnurbein, Ekaterina Sorkina, Takara Stanley, Corinne Vigouroux, Martin Wabitsch, Rachel Williams, Tohru Yorifuji. The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline. The Journal of Clinical Endocrinology & Metabolism. 2016; 101 (12): 4500–4511.

5. Gupta N., Asi N., Farah W., Almasri J., Barrionuevo P., Alsawas M., et al. Clinical features and management of non-HIV-related lipodystrophy in children: A systematic review. J Clin Endocrinol Metab. 2017;102(2):363–74.

6. Kassai A, Muniyappa R, Levenson A, Walter M, Abel B, Ring M, et al. Effect of leptin administration on circulating apolipoprotein CIII levels in patients with lipodystrophy. Journal of clinical endocrinology and metabolism. 2016;101(4):1790-1797.

7. Safar Zadeh E., Lungu A.O., Cochran E.K., Brown R.J., Ghany M.G., Heller T., et al. The liver diseases of lipodystrophy: The long-term effect of leptin treatment. J Hepatol. 2013;59(1):131–7.

8. Brown R.J., Oral E.A., Cochran E., Araújo-Vilar D., Savage D.B., Long A., et al. Long-term effectiveness and safety of metreleptin in the treatment of patients with generalized lipodystrophy. Endocrine. 2018;60(3):479–89.

9. Deeks E. Metreleptin in lipodystrophy: a profile of its use. Drugs & Therapy Perspectives. 2019;35:201–208.

10. Oral EA, Gorden P, Cochran E, Araújo-Vilar D, Savage DB, Long A, Fine G, Salinardi T, Brown RJ. Long-term effectiveness and safety of metreleptin in the treatment of patients with partial lipodystrophy. Endocrine. 2019;64(3):500-511.

16. Please provide the name of the marketing authorization holder/manufacturer/supplier of the health technology (if applicable/available):

AMRYT PHARMACEUTICAL DAC

17. Marketing Authorization Status (MA) or CE-marking: When is MA or CE- marking expected? If possible, provide the time of planned marketing:

Myalepta was granted a marketing authorization under exceptional circumstances by the European Medicines Agency (EMA) on the 29 July 2018

18. Additional relevant information (up to 300 words.)

Metreleptin (recombinant human methionyl leptin) is an analogue of the human hormone leptin with the addition of a methionine residue at its amino terminus leading to a prolonged half-life. Lipodystrophy is an ultra-rare but potentially life-threatening disease characterised by complete or partial loss or absence of subcutaneous adipose tissue which causes two major issues: a reduction of the fat storage capacity as well as leptin deficiency. As a consequence, lipodystrophy patients suffer from ectopical fat accumulation in non-adipose tissues such as the liver and the musculature. The storage of free fatty acids in organs and the musculature is lipotoxic and leads to severe organ damage and insulin resistance. Adipose tissue, the primary source for leptin, plays a key role in energy metabolism and insulin sensitivity through the control of lipid and glucose metabolism, which is regulated via the secretion of leptin. (1) Metreleptin binds to and activates the human leptin receptorand signals through the JAK/STAT transduction pathway. It acts via multiple mechanisms to decrease glucose, triglyceride and other lipid intermediates, thus reducing their accumulation in tissues such as liver and muscle and ameliorating severe insulin resistance. As such, this improves hyperglycaemia and hypertriglyceridaemia (2), and thus reducing the risk of pancreatitis and slowing the progression of associated diseases and complications such as heart disease, liver disease, renal failure and insulin resistance.

19. Interests and potential conflicts of interests

Please describe the proposer's relationships or activities that may affect, be influenced by, or be perceived by others to be important for further management of the health technology that is proposed assessed. (E.g. proposer has financial interests in the matter. Proposer has or has had assignments in connection with the technology or to other actors with interest in the technology)

Proposer (Amryt) has financial interest in the matter and interest to provide the treatment for ultra-orphan disease patients. No potential conflicts of interests.