

CLADRIBINE REGIMEN FOR TREATING MYASTHENIA GRAVIS**FIELD OF THE INVENTION**

The present invention relates to compounds or compositions for the treatment of Myasthenia Gravis and related methods and dosing regimens. Specifically, the invention pertains to dosing regimens comprising the oral administration of cladribine or pharmaceutically acceptable salts thereof and is of relevance for the treatment of Myasthenia Gravis, in particular generalized Myasthenia Gravis.

BACKGROUND

Myasthenia gravis (MG) is a rare autoimmune disease characterized by the production of autoantibodies targeting proteins that are critical for the normal transmission of electrical signals from nerves to muscles, more precisely of components of the neuromuscular junction (NMJ) on the post synaptic membrane of the striated skeletal muscles. The disease is characterized by fluctuating fatigable muscle weakness, which typically begins in the ocular muscles before progressing to other muscles (limb, axial, bulbar and respiratory muscles) resulting in generalized Myasthenia Gravis (gMG, see Gilhus 2015, Lazaridis 2020). The severity of symptoms varies, both between patients and from day to day in the same patient, and adversely affects quality of life by impacting the physical capacities and psychological wellbeing of patients (Boldingh 2015).

The prevalence of MG in the United States is estimated at approximately 90,000 cases. The symptoms of MG result from impaired signaling at the NMJ, which is caused by autoantibodies that target components of the postsynaptic membrane (Phillips 2016). MG comes in 2 main types, (1) the ocular form, where symptoms are confined to the ocular muscles; and (2) the generalized form, where not only ocular muscles but multiple muscle groups are affected. Approximately 15% of patients with MG present with the ocular form, the remaining patients with gMG. Patients with gMG present with muscle weakness that typically becomes more severe with repeated muscle use and recovers with rest. Generalized MG symptoms can become life-threatening when muscle weakness involves the diaphragm and intercostal muscles in the chest wall that are responsible for breathing. The most dangerous complication of gMG, known as myasthenic crisis, requires hospitalization, intubation, and mechanical ventilation. Approximately 15% to 20% of patients with gMG will experience a myasthenic crisis within 2 years of diagnosis.

In 8 out of 10 people with MG, the autoimmune response is mediated by antibodies against the acetylcholine receptor (AChR), while less common MG antibodies are muscle-specific kinase (MUSK) and lipoprotein-related protein 4 (LRP4). Only 5 out of every 100 people with MG will be seronegative. Different types of MG antibodies cause weakness in different areas of the body (Gilhus 2015).

The MG population can be classified according to the age of onset. Before the age of 50, studies on large series of patients showed that early-onset MG (EOMG) is characterized by female predominance (60-70%), whereas between the age of 50 and 60, there is no gender difference (Carr 2010). A very late onset MG, appearing after the age of 60, has been described for 20 years. This form is characterized by a clear male predominance (Alkhawajah 2013).

Because the clinical manifestations of MG vary not only according to the age of onset, but also according to the antibody implicated and the presence of thymic pathology, the disease forms are generally divided in several subgroups according to the presence of autoantibodies, i.e. anti-AChR, anti-MUSK, anti-LRP4 and seronegative.

The diagnosis of MG remains mostly clinical and rests on the medical history and physical findings of fatigable, fluctuating muscle weakness in a specific distribution. However, ancillary bedside tests and laboratory methods are now available and have been increasingly used to help confirm the NMJ dysfunction, classify MG according to the causative antibodies, define its type and severity, and assess the effect of treatment objectively (Rousseff 2021). In particular, serological methods, useful in identifying the presence of a specific antibody, have become the first-line investigation in suspected MG.

Currently, the most commonly used treatments comprise AChE inhibitors, of which pyridostigmine is the most commonly used, steroids, such as prednisolone, or immunosuppressant, such as azathioprine or mycophenolate mofetil. Surgery to remove the thymus gland, known as a thymectomy, is recommended in patients with an unusually large thymus.

In the recent years, several molecules have been approved for the treatment of gMG: eculizumab ravulizumab and zilucoplan, which are complement inhibitors, and efgartigimod and rozanolixizumab, both neonatal fragment crystallizable receptor (FcRn) inhibitors. All act via a downstream immune effector targeting mechanism, and all are administered parenterally. To date, no disease modifying treatment acting on the upstream pathway of the disease,

namely on immune mechanisms involving B cells and their interaction with T cells in autoantibody production, have been approved for the treatment of MG.

Cladribine, a chlorinated purine analogue 2-chloro-2'-deoxyadenosine analogue (2-CdA), has been suggested to be useful in the treatment of MG based on subcutaneous injection of a liquid formulation comprising cladribine (US20200163986 and Rejdak 2020). Several oral dosage forms comprising cladribine as an active ingredient have been described (EP 2428201 and US7888328, or WO2004/087101 for instance).

There remains a need for compounds or compositions and methods for treating MG with disease modifying drugs. Despite the existence of available treatments, including the introduction of recently approved targeted treatments for gMG that have been tested together with immunosuppressants in patients that had to continue on such treatment, several unmet needs remain. These include improving efficacy, treatment adherence, and compliance, as well as reducing the need for invasive or burdensome procedures, which can lead to "treatment fatigue" experienced by patients with gMG under continuous long-term dosing and/or parenteral administration. An infrequently administered oral treatment, with retreatment based on an individual patient's clinical need, would be less burdensome for patients and may improve treatment adherence and compliance.

The present disclosure provides compositions and methods related to the use of cladribine in the treatment of MG, and more specifically a dosing regimen comprising the oral administration of cladribine, resulting in a safe and effective treatment of MG.

SUMMARY OF THE INVENTION

The invention pertains to a method of treating Myasthenia Gravis, in a patient in need thereof, comprising orally administering cladribine or a pharmaceutically acceptable salt thereof to the patient according to an initial dosing regimen comprising or consisting of two treatment courses, separated by about 4 weeks or about a month, wherein the total administered dose of cladribine or a pharmaceutically acceptable salt thereof, administered under said initial dosing regimen is from about 35 mg to about 210 mg. The total dose of the initial dosing regimen is also referred to as the "full dose" herein.

Preferably, the total dose of cladribine or pharmaceutically acceptable salt thereof, administered under said initial dosing regimen is of about 35 mg, of about 52.5 mg, of about

70 mg, of about 87.5 mg, of about 105 mg, of about 122.5 mg, of about 140 mg, of about 157.5 mg, of about 175 mg, of about 192.5 mg or of about 210 mg.

Preferably, in one embodiment the total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 52.5 mg, wherein about 35 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the second treatment course. Preferably, in that embodiment, the about 35 mg of cladribine or a pharmaceutically acceptable salt thereof administered during the first treatment course is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one and on day two of the first treatment course, and the about 17.5 mg of cladribine or pharmaceutically acceptable salt thereof administered during the second treatment course is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered on day one of the second treatment course.

Preferably, in another embodiment the total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 105 mg, and wherein about 52.5 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 52.5 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the second treatment course. Preferably, in that embodiment, 52.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered during the first treatment course is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one, day two and day three of the first treatment course, and the about 52.5 mg of cladribine or pharmaceutically acceptable salt thereof administered during the second treatment course is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one, day two and day three of the second treatment course.

Alternatively, the following (e.g. one or more of the following) initial dosing regimens are possible:

- a) The total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 35 mg, and wherein about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 17.5 mg of cladribine or a pharmaceutically acceptable

salt thereof is administered during the second treatment course; e.g., a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is orally administered to the patient in need thereof on day one of the first treatment course and a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is orally administered to the patient in need thereof on day one of the second treatment course;

- b) The total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 52.5 mg, and wherein about 35 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the second treatment course; e.g., a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is orally administered to the patient in need thereof on day one and day two of the first treatment course and a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is orally administered to the patient in need thereof on day one of the second treatment course;
- c) The total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 70 mg, and wherein about 35 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 35 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the second treatment course; e.g., a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is orally administered to the patient in need thereof on day one and day two of the first treatment course and a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is orally administered to the patient in need thereof on day one and day two of the second treatment course;
- d) The total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 87.5 mg, and wherein about 52.5 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 35 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the second treatment course; e.g., a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is orally administered to the patient in need thereof on day one, day two and day three of the first treatment course and a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is orally administered to the patient in need thereof on day one and day two of the second treatment course;

- e) The total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 122.5 mg, and wherein about 70 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 52.5 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the second treatment course; e.g., a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is orally administered to the patient in need thereof on day one, day two, day three and day four of the first treatment course and a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is orally administered to the patient in need thereof on day one, day two and day three of the second treatment course;
- f) The total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 140 mg, and wherein about 70 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 70 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the second treatment course; e.g., a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is orally administered to the patient in need thereof on day one, day two, day three and day four of the first treatment course and a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is orally administered to the patient in need thereof on day one, day two, day three and day four of the second treatment course;
- g) The total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 157.5 mg, and wherein about 87.5 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 70 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the second treatment course; e.g., a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is orally administered to the patient in need thereof on day one, day two, day three, day four and day five of the first treatment course and a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is orally administered to the patient in need thereof on day one, day two, day three and day four of the second treatment course;
- h) The total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 175 mg, and wherein about 87.5 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 87.5 mg of cladribine or a pharmaceutically acceptable

salt thereof is administered during the second treatment course; e.g., a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is orally administered to the patient in need thereof on day one, day two, day three, day four and day five of the first treatment course and a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is orally administered to the patient in need thereof on day one, day two, day three, day four and day five of the second treatment course;

- i) The total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 192.5 mg, and wherein about 105 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 87.5 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the second treatment course; e.g., a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is orally administered to the patient in need thereof on day one, day two, day three, day four, day five and day six of the first treatment course and a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is orally administered to the patient in need thereof on day one, day two, day three, day four and day five of the second treatment course;
- j) The total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 210 mg, and wherein about 105 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 105 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the second treatment course; e.g., a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is orally administered to the patient in need thereof on day one, day two, day three, day four, day five and day six of the first treatment course and a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is orally administered to the patient in need thereof on day one, day two, day three, day four, day five and day six of the second treatment course;
- k) The total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 35 mg, and wherein about 35 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first treatment course, and no cladribine or a pharmaceutically acceptable salt thereof is administered during the second treatment course; e.g., a two dosage forms comprising each about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof are orally administered to the patient in need thereof on day one of the first treatment

course, no cladribine or a pharmaceutically acceptable salt thereof is orally administered to the patient during the second treatment course;

- l) The total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 52.5 mg, and wherein about 35 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the second treatment course; e.g., a two dosage forms comprising each about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof are orally administered to the patient in need thereof on day one of the first treatment course and one dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is orally administered to the patient in need thereof on day one of the second treatment course;
- m) The total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 70 mg, and wherein about 35 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 35 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the second treatment course; e.g., a two dosage forms comprising each about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof are orally administered to the patient in need thereof on day one of the first treatment course and two dosage forms comprising each about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof are orally administered to the patient in need thereof on day one of the second treatment course;
- n) The total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 87.5 mg, and wherein about 52.5 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 35 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the second treatment course; e.g., a two dosage forms comprising each about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof are orally administered to the patient in need thereof on day one of the first treatment course, and one dosage form of about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is administered to patient in need thereof on day two of the first treatment course and two dosage forms comprising each about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof are orally administered to the patient in need thereof on day one of the second treatment course;
- o) The total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 105 mg, and wherein about 70 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first

treatment course, and about 35 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the second treatment course; e.g., a two dosage forms comprising each about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof are orally administered to the patient in need thereof on day one and on day two of the first treatment course and two dosage forms comprising each about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof are orally administered to the patient in need thereof on day one of the second treatment course;

- p) The total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 122.5 mg, and wherein about 70 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 52.5 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the second treatment course; e.g., a two dosage forms comprising each about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof are orally administered to the patient in need thereof on day one and on day two of the first treatment course and two dosage forms comprising each about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof are orally administered to the patient in need thereof on day one and one dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is administered to the patient in need thereof on day two of the second treatment course;
- q) The total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 140 mg, and wherein about 70 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 70 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the second treatment course; e.g., a two dosage forms comprising each about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof are orally administered to the patient in need thereof on day one and on day two of the first treatment course and two dosage forms comprising each about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof are orally administered to the patient in need thereof on day one and day two of the second treatment course;
- r) The total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 157.5 mg, and wherein about 87.5 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 70 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the second treatment course; e.g., a two dosage forms comprising each about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof are orally administered to the patient in need thereof on day one and on day two of the first treatment course, one dosage form comprising about 17.5 mg of

cladribine or a pharmaceutically acceptable salt thereof is orally administered to the patient in need thereof on day three of the first treatment course and two dosage forms comprising each about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof are orally administered to the patient in need thereof on day one and day two of the second treatment course;

- s) The total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 175 mg, and wherein about 105 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 70 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the second treatment course; e.g., a two dosage forms comprising each about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof are orally administered to the patient in need thereof on day one, day two and day three of the first treatment course and two dosage forms comprising each about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof are orally administered to the patient in need thereof on day one and day two of the second treatment course;
- t) The total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 192.5 mg, and wherein about 105 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 87.5 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the second treatment course; e.g., a two dosage forms comprising each about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof are orally administered to the patient in need thereof on day one, day two and day three of the first treatment course, two dosage forms comprising each about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof are orally administered to the patient in need thereof on day one and day two of the second treatment course and one dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is administered to the patient in need thereof on day 3 of the second treatment course;
- u) The total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 210 mg, and wherein about 105 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 105 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the second treatment course; e.g., a two dosage forms comprising each about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof are orally administered to the patient in need thereof on day one, day two and day three of the first treatment course and two dosage forms comprising each about

17.5 mg of cladribine or a pharmaceutically acceptable salt thereof are orally administered to the patient in need thereof on day one, day two and day three of the second treatment course.

Preferably, the method of the invention comprises a period of time after the initial dosing regimen without any administration of cladribine or a pharmaceutically acceptable salt thereof.

In some embodiments, the method according to the invention comprises a period of at least about 24 weeks, at least about 26 weeks, at least about 6 months, preferably of at least about 48 weeks, at least about 12 months, at least about one year, more preferably of at least about 24 months or about 2 years, after the last administration of cladribine or a pharmaceutically acceptable salt thereof under the initial dosing regimen, where no cladribine or a pharmaceutically acceptable salt thereof is administered.

In some embodiments, the method according to the invention comprises a period of at least about 24 weeks, at least about 26 weeks, at least about 6 months, preferably of at least about 48 weeks, at least about 12 months, at least about one year, more preferably of at least about 24 months or about 2 years, after the first administration of cladribine or a pharmaceutically acceptable salt thereof under the initial dosing regimen, where no cladribine or a pharmaceutically acceptable salt thereof is administered.

In some embodiments, the dosing regimen comprises besides the initial dosing regimen, i.e. the initial treatment period, one or more later treatment periods, each also referred to as a "retreatment" herein, with cladribine or a pharmaceutically acceptable salt thereof. Such retreatment may be done, e.g., if clinically justified. A physician or clinician of ordinary skill can readily determine whether a retreatment should be done, for instance, in case of worsening of symptoms or in case of disease progression. Possible triggering events include loss of MG-ADL (Myasthenia Gravis Activities of Daily Living) improvement previously obtained, an observed increase of MG-ADL, or a total MG-ADL score of ≥ 6 . Each retreatment may consist of one or multiple treatment courses.

In some embodiments, the method according to the invention comprises a step of retreatment using a low dose of cladribine or a pharmaceutically acceptable salt thereof, also referred to as a supplemental dose. In some embodiments, the total dose of the supplemental dose is lower than the full dose. In some embodiments, the supplemental dose corresponds to a total dose of cladribine or a pharmaceutically acceptable salt thereof from about 17.5 mg to about 35 mg.

In some embodiments, such supplemental dose is administered no earlier than about 24 weeks, about 26 weeks, about 6 months or about half a year and no later than about 48 weeks, about 52 weeks, about 12 months or about one year after the last administration of cladribine or a pharmaceutically acceptable salt thereof under the last treatment period, which preferably is a treatment period in which a full dose was administered. In some embodiments, such supplemental dose is only administered if clinically justified.

Preferably, such supplemental dose is administered no earlier than about 24 weeks and no later than about 48 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof under the last treatment period, which preferably is a treatment period in which a full dose was administered. In some embodiments, such supplemental dose is only administered if clinically justified.

In other embodiments, in the method according to the invention the supplemental dose is administered no earlier than about 24 weeks, about 26 weeks, about 6 months or about half a year and no later than about 48 weeks, about 52 weeks, about 12 months or about one year after the first administration of cladribine or a pharmaceutically acceptable salt thereof under the last treatment period, preferably, the first administration under the last treatment period where a full dose was administered. In some embodiments, such supplemental dose is only administered if clinically justified.

Preferably, in the method according to the invention the supplemental dose is administered no earlier than about 24 weeks and no later than about 48 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof under the last treatment period, preferably, the first administration under the last treatment period where a full dose was administered. In some embodiments, such supplemental dose is only administered if clinically justified.

In some embodiments, the method according to the invention comprises a step of retreatment wherein the total administered dose of cladribine or a pharmaceutically acceptable salt thereof administered during said retreatment step equals the full dose. The retreatment with the full dose may be done identically to the initial dosing regimen. The retreatment with the full dose may consist of two treatment courses, said treatment courses being separated by about a month or about 4 weeks. Moreover, the retreatment with the full dose may take place at least about 52 weeks, at least about 12 months, at least about one year, preferably at least about 48 weeks after the last administration of cladribine or a pharmaceutically acceptable salt

thereof of the last treatment period where a full dose was administered or at least about 6 months, at least about half a year, preferably at least about 24 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof of the last treatment period where a supplemental dose was administered. In some embodiments, such retreatment is only done if clinically justified.

Moreover, the retreatment with the full dose may take place at least about 52 weeks, at least about 12 months, at least about one year, preferably at least about 48 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof of the last treatment period where a full dose was administered or at least about 6 months, at least about half a year, preferably at least about 24 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof of the last treatment period where a supplemental dose was administered. In some embodiments, such retreatment is only done if clinically justified.

As for the initial dosing regimen, after each retreatment there may be a period where no cladribine or a pharmaceutically acceptable salt thereof is administered. The duration of such periods may be as defined above for the initial dosing regimen.

Preferably cladribine or the pharmaceutically acceptable salt thereof is formulated as a solid dosage form.

BRIEF DESCRIPTION OF THE FIGURE

Figure 1. Brief description of the dosing regimens as applied in example 1. After randomization (1:1:1), gMG patients are administered either placebo or cladribine ("low dose" or "high dose" refer to different treatment regimen) as described in example 1. BEA: end of blinded extension period follow-up analysis; D: day; DBPC: double-blind placebo-controlled; IA: interim analysis; PA: primary analysis; PK: pharmacokinetic; RTA: end of retreatment period follow-up analysis; Supp. Dose: supplemental dose; Tc: treatment course; W: week. Rich PK: Review of PK and safety data from the rich PK sampling group (i.e. the first ~24 participants of the study), either continue with initial doses or switch to an alternative dose regimen based on a predefined framework. IA: An IA is scheduled when the first approximately 60 (~ 25%) participants have completed their Week 24 assessments to evaluate futility. PA: PA for all the efficacy and safety endpoints will be performed at the end of the DBPC period, after the primary completion date when all participants complete the Week 24 assessments, if not having withdrawn from the study prematurely during this period. BEA: follow-up analysis will be performed at the end of

the BE period, i.e. when the Week 48 (from baseline) assessments are complete for all participants who have not withdrawn from the study. RTA: follow-up analysis (final) will be performed at the end of the RT period when all participants have completed the period if not having withdrawn. Note: in the rare case a participant who was on placebo during the DBPC period has an ALC Grade > 1 ($< 800/\text{mm}^3$) at Week 24, placebo will be given at Week 25. These participants will be eligible to receive a full dose in case of need for retreatment.

Figure 2. Schematic process flow chart

Figure 3. Tabletability plot of Blend-3. Mpa: Megapascal; kN: Kilonewton.

Figure 4. Dissolution Profile for low (8 count, 4.375 mg) dose capsules, manufactured from Blend-3, according to Pharm. Eur. 2.9.3 using Apparatus II (paddle); 75 rpm over 60 minutes; $37.0 \pm 0.5^\circ\text{C}$; 500 mL phosphate buffer pH 6.8; six replicates whiskers referring to standard deviation in percent

Figure 5. Dissolution Profile for high (32 count, 17.5 mg) dose capsules, manufactured from Blend-3, according to Pharm. Eur. 2.9.3 using Apparatus II (paddle); 75 rpm over 60 minutes; $37.0 \pm 0.5^\circ\text{C}$; 500 mL phosphate buffer pH 6.8; six replicates whiskers referring to standard deviation in percent.

Figure 6. Tabletability plot for Blend-4

Figure 7. Dissolution profile for low (8 count, 4.375 mg) dose capsules, manufactured from Blend-4, according to Pharm. Eur. 2.9.3 using Apparatus I (basket); 100 rpm (200 rpm after 60 minutes); $37.0 \pm 0.5^\circ\text{C}$; 500 mL phosphate buffer pH 6.8; six replicates whiskers referring to standard deviation in percent.

Figure 8. Dissolution profile for high (32 count, 17.5 mg) dose capsules, manufactured from Blend-4, according to Pharm. Eur. 2.9.3 using Apparatus I (basket); 100 rpm (200 rpm after 60 minutes); $37.0 \pm 0.5^\circ\text{C}$; 500 mL phosphate buffer pH 6.8; six replicates whiskers referring to standard deviation in percent.

DEFINITIONS

The terms “treating”, “treatment”, or the like as used herein should be construed as generally understood in the art, that is to say as meaning reducing, hindering the development of, controlling, delaying, alleviating and/or reversing symptoms of a condition or disease in a subject or relieving or attenuating the disorder or disease, i.e.,

causing regression of the disorder or disease. In one embodiment, the term "treat" "treating" "treatment" or "therapy", as used herein, means obtaining beneficial or desired results, for example, clinical results. One aspect of the treatment is, for example, that said treatment should have a minimal adverse effect on the patient. In one embodiment, the term "method for the treatment", as used herein, refers to "method to treat".

Within the context of this invention, the therapeutic effect of the treatment, including but not limited to reducing, hindering the development of, controlling, alleviating and/or reversing symptoms of the disorder or disease or relieving or attenuating the disorder or disease, may be seen after one or more treatment courses.

In the context of the invention, the term "treatment course" should be construed as generally understood in the art, that is to say as a period of time where a medicament is administered on at least one day or for several consecutive days. In the context of the invention the term treatment course refers to periods of 1 to 6, preferably 1 to 3 consecutive days of daily administration of the medicament or active principle, herein cladribine or a pharmaceutically acceptable salt thereof. In other embodiments, a treatment course consists of a period of 1 to 6, preferably 1 to 3 consecutive days of daily administration of the composition comprising cladribine or a pharmaceutically acceptable salt thereof. One treatment period, such as the initial dosing regimen or a retreatment, may comprise multiple treatment courses. Preferably, the retreatment with a supplemental dose only comprises a single treatment course.

The term "supplemental dose, as used herein, refers, in one embodiment, to one capsule of about 17.5mg of cladribine, or pharmaceutically acceptable salt thereof, given as a retreatment as per clinical need, after 6 months but within 1 year post cladribine treatment initiation.

The term "about" when used to modify a numerically defined parameter refers to any minimal alteration in such parameter that does not change the overall effect, e.g., the efficacy of the agent in treatment of a disease or disorder. In some embodiments, the term "about" means that the parameter may vary by as much as 10% below or above the stated numerical value for that parameter (e.g. a numerical value X means, for example, $X \pm 10\%$, including all the values within this range). In some embodiments, when "about" is used to define a temporal parameter, such as weeks, months or years, it refers to such period of time plus or minus 2 days. In some embodiments, when "about" is used to define a temporal parameter, such as days or weeks, it refers to this exact period of time, e.g., "about one week" refers to 7 days.

The term “week” means 7 days. The term “month” means 28, 29, 30 or 31 days. The term “year” means 356 or 366 days.

As used herein, the term "patient" refers to a subject who is diseased and would benefit from the treatment.

As used herein, the term "subject" refers to a mammalian organism, preferably a human being.

As used herein, a subject is "in need of" a treatment, if such a subject (patient) would benefit biologically, medically or in quality of life from such a treatment.

The term “MG patient”, as used herein, refers to a patient with MG, preferably a patient with gMG, as defined herein.

The term "a therapeutically effective amount" or "an effective amount" of a compound of the present invention refers to an amount of a compound of the present invention that elicits the biological or medical response of a subject. In another embodiment, the term refers to the amount of the compound of the present invention that, when administered to a subject, is effective to at least partially ameliorate a condition, or a disorder or a disease.

The term "compound of the present invention", as used herein, refers to cladribine (i.e. free form) or a pharmaceutically acceptable salt thereof.

As used herein, the terms "salt", "salts" or "salt form" refers to an acid addition or base addition salt of a compound. "Salts" include in particular "pharmaceutically acceptable salts". The term "pharmaceutically acceptable salts" refers to salts that retain the biological effectiveness and properties of the compounds and, which typically are not biologically or otherwise undesirable.

The term “composition” or “pharmaceutical composition” is defined herein to refer, for example, to a mixture or solution containing at least one active ingredient or therapeutic agent to be administered to a subject, in order to treat a subject, for example as herein defined.

The term “concomitant”, as used herein, for example in relation to “concomitant with corticosteroid or AChEI treatment”, refers to both simultaneous and sequential administration.

The term "one or more" refers to either one or a number above one (e.g. 2, 3, 4, 5, etc.).

The term “steroid-sparing drug”, as used herein, means a drug that allows for decreasing, for example gradually decreasing, the daily dose of corticosteroids. The terms “drug”, “active substance”, “active ingredient”, “pharmaceutically active ingredient”, “active agent”, “therapeutic agent” or “agent” are to be understood as meaning a compound in free form or in the form of a pharmaceutically acceptable salt.

The term “MG-ADL” or “MGADL” or “Myasthenia Gravis Activities of Daily Living”, as used herein, refers, for example, to the clinical rating scale, which is an 8-item patient reported scale that assesses MG symptoms and their impact on daily activities (e.g. *in* Wolfe 1999). The scale evaluates the capacity to perform different activities of daily living such as talking, chewing, swallowing, breathing, brushing teeth, combing hair, or ability to arise from a chair. The scale also assesses double vision and eyelid drooping. Each item is measured on a 4-point Likert Scale from 0 (=normal) to 3 (=most severe). The total score can range from 0 to 24, with higher total scores indicating greater symptom severity and impairment.

The term “QMG” or “Quantitative Myasthenia Gravis”, as used herein, refers, for example, to the clinical rating scale, which quantifies disease severity based on impairments of body functions and structures (for example, as defined by the International Classification of Functioning, Disability and Health – WHO 2001; or, e.g. *in* Barohn 1998). The QMG consists of 13 items that assess ocular, bulbar, and limb function. 6 out of the 13 items are timed tests of endurance measured in seconds. Each item has a possible score from 0 to 3, with a total possible score of 39, where higher total scores indicate more severe impairments.

The term “MGC” or “Myasthenia Gravis Composite”, as used herein, refers, for example, to the clinical rating scale, which has 10 items and combines a clinician’s examination and patient reported outcome items (e.g. *in* Burns 2010). Each item is scored on an ordinal scale with 4 possible categories. The impairments that need to be examined by the clinician (or a qualified evaluating designee) include ptosis (upward gaze), double vision, eye closure, neck flexion, shoulder abduction, and hip flexion. The patient reported outcome items within MGC cover talking, chewing, swallowing, and breathing. The maximum total possible score is 50, with higher total scores reflecting more severe impairments.

The term “MG-QoL15r” or “Myasthenia Gravis 15-Item Quality of Life Scale – Revised”, as used herein, refers, for example, to a health-related quality of life measure for patients with MG (e.g. *in* Burns 2016). It addresses MG-specific psychological, wellbeing and social functioning. The questionnaire is completed by the participant and each item is measured on a 3-point Likert scale from 0 (=Not at all) to 2 (=very much). A total score can range from 0 to 30, with a lower score indicating a better quality of life.

The term “EQ-5D-5L” or “EuroQoL 5 Dimension 5 Levels”, as used herein, refers, for example, to a standardized instrument (EuroQoL Research Foundation) developed as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments (e.g. *in* Herdman 2011). For example, it addresses mobility, self-care, usual activities (e.g. work, study, housework, family or leisure activities), pain or discomfort, anxiety and depression. The EQ-5D-5L essentially consists of 2 pages: the EQ-5D descriptive system and the EQ-VAS, which are completed by the patient. Higher scores on both EQ-5D-5L health utility values and EQ-VAS represent a better health-related quality of life.

The term “reduction of the impact of the severity of symptoms of MG on activities of daily living”, as used herein, refers, for example, to the reduction (e.g. as compared to baseline or placebo) of the severity of the impairment, associated with MG, to perform activities of daily living, for example, talking, chewing, swallowing, breathing, brushing teeth, combing hair, or ability to arise from a chair; for example as assessed by using standard scales, such as a patient reported scale, for example the MG-ADL scale.

The term “reduction of the impact of muscle weakness to effort associated with MG”, as used herein, refers, for example, to the reduction (e.g. as compared to baseline or placebo) of muscle weakness to effort associated with MG related to movement of body parts [e.g. facial muscles, ocular muscles (e.g. ptosis, double vision), bulbar muscles (e.g. swallowing 4 oz water, speech after counting aloud from 1 to 50) or limb movement (e.g. right arm outstretched, left arm outstretched, right hand grip, left hand grip, right leg outstretched, left leg outstretched)]; for example as assessed by using standard scales, such as a clinical scale, for example the QMG scale. In another embodiment, “muscle weakness to effort associated with MG” comprises, for example, one or more selected from the group consisting of ptosis, double vision, neck flexion or extension, shoulder abduction and hip flexion; for example as assessed by using standard scales, for example the MGC scale.

The term “treatment for the improvement of the quality of life of a MG patient”, as used herein, refers, for example, to a treatment for the reduction (e.g. as compared to baseline or placebo) of psychological impact associated with MG. In another embodiment, the term “treatment for the improvement of the quality of life of a MG patient”, as used herein, refers, for example, to a treatment for the improvement (e.g. as compared to baseline or placebo) of wellbeing impaired by MG. In yet another embodiment, the term “treatment for the improvement of the quality of life of a MG patient”, as used herein, refers, for example, to a treatment for the reduction (e.g. as compared to baseline or placebo) of social life impact associated with MG. In a further embodiment, the term “treatment for the improvement of the quality of life of a MG patient”, as used herein, refers, for example, to a treatment for the reduction (e.g. as compared to baseline

or placebo) of one or more selected from the group consisting of psychological impact associated with MG and of social life impact associated with MG. In another embodiment, the term "treatment for the improvement of the quality of life of a MG patient", as used herein, refers, for example, to a treatment for the improvement (e.g. as compared to baseline or placebo) of one or more selected from the group consisting of psychological function associated with MG, wellbeing associated with MG and social life function associated with MG. The "reduction" or "improvement", for example, as compared to baseline or placebo, is assessed by using standard scales, such as a patient reported scale, for example the MG-QoL15r scale. In a further embodiment, the term "treatment for the improvement of health related quality of life of an MG patient", as used herein, refers, for example, to a treatment for the improvement (e.g. as compared to baseline or placebo) of one or more selected from the group consisting of mobility, self-care, usual activities (e.g. work, study, housework, family or leisure activities), pain, discomfort, anxiety and depression (e.g. as assessed by using standard scales, such as a patient reported scale, for example the EQ-5D-5L scale).

The term "baseline" as used herein, for example, refers to the level or amount of the measure of interest (e.g. MG-ADL total score) in the subject prior to administering drug (e.g. cladribine) (i.e. prior to commencing dosing or prior to drug administration).

The term "minitablet", "mini-tablet", "microtablet" or "micro-tablet", as used herein, refers, for example, to small tablets with a diameter equal to or less than 4 mm that are, for example, filled into a capsule, sachet or dispenser. In one embodiment, the thickness of this minitablets is equal to or less than 3 mm. The minitablets have, for example, round shape or cylindrical shape (e.g. cylindrical shape having a convex upper side and underside). In one embodiment, as used herein, it refers, for example, to small tablets. In one embodiment, it refers to a compressed pharmaceutical formulation that has dimensions of length and breadth (or, depending on its shape, a diameter) each less than about 4 mm, for example, (each) equal to or less than about 2 mm. The minitablets are, for example, filled into a capsule, sachet or dispensers. The minitablets are coated or uncoated.

As used herein, reference to an amount (e.g. mg, mg/ml, percentage) of cladribine, or a pharmaceutical acceptable salt thereof, is to be understood to refer the amount of cladribine in the free form, which will be adapted accordingly for a pharmaceutically acceptable salt thereof.

As used herein, the terms "free form" or "free forms" or "in free form" or "in the free form" refers to the compound in non-salt form, such as the base free form.

The term "refractory MG" or "refractory gMG", as used herein, refers, for example, to "MG" or "gMG", respectively, in which patients do not achieve an adequate response to treatment (e.g. inadequate response to immunosuppressive therapy), or are intolerant to conventional treatment (e.g. intolerant to immunosuppressive therapy), or require chronic treatment with rescue treatment (e.g. as described in Schneider-Gold 2019).

The term "inadequate response to immunosuppressive therapy", as used herein, refers, for example, to presence of remaining disease activity for example (e.g. as described in Wiendl 2023). In one embodiment, "inadequate response to immunosuppressive therapy", as used herein, refers, for example, to failure to respond adequately to conventionally used immunosuppressive drugs, for example persistence of moderate to severe weakness while on maximal safe doses of steroids and/or at least one non-steroidal immunosuppressive drug at an adequate dose and duration (e.g. as described in Mantegazza 2018).

The term "intolerant to immunosuppressive therapy", as used herein, refers, for example, to inability to tolerate immunosuppressive drugs, for example presence of severe or intolerable adverse effects or comorbid conditions that restrict the use of immunosuppressive drugs (e.g. as described in Mantegazza 2018)

The term "rescue treatment", as used herein, refers, for example, to the use of IVIg and/or plasma exchange methods (e.g. as described in Wiendl 2023).

As used herein, in one embodiment, the term "disease-modifying therapy" or "disease-modifying treatment" refers, for example, to a drug that can modify the immune pathology of myasthenia gravis at the level of immune cells that contribute in T/B cell interaction to drive plasmacell development. In other embodiment, "disease-modifying therapy" or "disease-modifying treatment" refers, for example, to a drug that can modify the immune pathology of myasthenia gravis at the level of immune cells that are directly involved in the production of autoantibodies. In yet another embodiment, the term "disease-modifying therapy" or "disease-modifying treatment" refers, for example, to a drug that can reconstitute the immune system to restore immune homeostasis by the repopulation of immune cells that are anti-inflammatory.

As used herein, the term "immune cells" comprises one or more selected from the group consisting of T lymphocytes and B lymphocytes.

In one embodiment, as used herein, the term "T lymphocytes" comprises one or more selected from the group consisting of CD4+Tcells and CD8+T cells.

In another embodiment, as used herein, the term T lymphocytes comprises one or more selected from the group consisting of central memory T cells, effector memory T cells, TH1 cells, TH2 cells, T follicular helper cells, regulatory T cells and naïve T cells; preferably effector memory T cells.

As used herein, the term “TH1 cells” comprises one or more selected from the group consisting of IFN γ + T cells and GMCSF+ T cells.

As used herein, the term “B lymphocytes” comprises one or more selected from the group consisting of CD19+ B cells, CD20+ B cells, IL6+ B cells, naïve B cells, memory B cells, activated B cells (e.g. CD69+), short-lived plasma cells, CD38+ plasma cells, long lived plasma cells and regulatory B cells; preferably memory B cells.

The term “corticosteroids” or “corticosteroid”, as used herein, refers, for example, to oral corticosteroid preparations used in MG treatment, for example prednisolone (e.g. as described in Wiendl 2023)

The term “AChE inhibitors” or “AChE inhibitor”, as used herein, refers, for example, to oral acetylcholinesterase inhibitors used as symptomatic MG treatment, for example pyridostigmine (e.g. as described in Wiendl 2023).

The term “hydroxypropyl cellulose” is a nonionic polymer derived from cellulose by partial etherification of hydroxyl groups of its constitutional glucose ($C_6H_{10}O_5$) units with hydroxypropyl groups, generally having a hydroxypropoxyl content of 50 to 80% by weight, and when having a hydroxypropoxyl content of 5.0 to 16.0% by weight is called “low-substituted hydroxypropyl cellulose”, and its properties are different from those of ordinary hydroxypropyl cellulose (https://doi.usp.org/USPNF/USPNF_M39150_06_01.html).

The term “at least two”, as used herein, refers to a minimum of two, for example 2, 3, 4 or 5, such as 2 or 3, for example 2.

The term “at least one”, as used herein, refers to a minimum of one, for example 1, 2, 3, 4 or 5, such as 1 or 2, for example 1.

The term “at least two different fillers”, as used herein, is construed to mean “more than one filler, namely, two or more fillers (e.g. 2, 3, 4 or 5 fillers, such as 2 or 3, for example 2), wherein a minimum of two fillers are chemically different (e.g. a sugar alcohol and a cellulose derivative).

The term “about”, as used herein, encompasses the explicitly recited amounts as well as deviations therefrom of $\pm 15\%$, such as a deviation of $\pm 10\%$, e.g. a deviation of $\pm 5\%$.

The term "solid pharmaceutical composition", as used herein, refers to one or more of tablet, capsule, powder, disc, caplet, granules, pellets, granules in capsule, minitabets, minitabets in capsule, pellets in capsule, Sachet and the like. The solid pharmaceutical composition also includes multilayer tablets. The solid pharmaceutical compositions are meant for oral administration.

As used herein, the terms "free form" or "free forms" or "in free form" or "in the free form" refers to the compound in non-salt form.

The term "film-coated" as used herein relates to a mixture of pharmaceutically acceptable excipients which is typically applied to a compressed tablet, minitabets, beads, granules, or particles of active ingredient that are compressed into tablets or minitabets. Alternatively, it may also be combined with, mixed with or otherwise added to the active agent.

The term "enteric film-coated" as used herein relates to a mixture of pharmaceutically acceptable excipients which is typically applied to a compressed tablet, minitabets, beads, granules, or particles of active ingredient that are compressed into tablets or minitabets and that provides a barrier to prevent the gastric acids in the stomach from disintegrating and dissolving it or degrading it. Alternatively, it may also be combined with, mixed with or otherwise added to the active agent and it still provides a barrier to prevent the gastric acids in the stomach from dissolving it or degrading it.

The term "enteric" as used herein relates, for example, to the characteristics that satisfy at least the following condition (i). (i) It conforms to the harmonized dissolution test regarding delayed-release dosage form as described in the Japanese Pharmacopoeia chapter 6.10, 17th Edition (hereinafter sometimes simply referred to as "JP"), or the European Pharmacopoeia version 11.5 chapter 2.9.3 (hereinafter sometimes simply referred to as "Pharm. Eur."), or the United States Pharmacopoeia chapter <711> official as of 01-May-2023 (hereinafter sometimes simply referred to as "USP").

The terms "capsule" and "capsule shell" are often used interchangeably, also in this invention, sometimes, for example in prior art publications, a distinction is made, and then usually the term "capsule shell" means the empty capsule and the term "capsule" means the capsule filled with a pharmaceutical or some other substance.

The term "hard capsule" refers to an empty capsule shell in which a content is filled, and usually, the hard capsule includes a cap portion and a body portion, and it is also called a hard capsule or a two-piece capsule. The "hard capsule" in the present disclosure can have imparted thereto a shape that is the same as or similar to that of a related-art hard capsule that is commercially available, which is intended to be orally administered to a target such as

a human. The “hard capsule” according to the present disclosure does not encompass a soft capsule manufactured by filling a content between two films and causing the films to adhere to each other, a seamless capsule manufactured by dropping a content together with a film solution onto a solidification liquid, or a microcapsule prepared by incorporating an active ingredient inside through base precipitation or emulsification. In the present disclosure, the term “enteric hard capsule” refers to a hard capsule in which a film of a capsule itself has “enteric” characteristics or in which an enteric film-coating is applied to the capsule.

The term “w/w” as used herein means, for example, weight of component by total weight of composition (e.g. uncoated minitab, coated minitab, uncoated capsule comprising minitab, or coated capsule comprising minitab). In one embodiment, the term “w/w” as used herein means weight of a component by total weight of an uncoated minitab, and it is thus adapted accordingly for a coated minitab or adapted accordingly for a capsule (i.e. coated capsule or uncoated capsule) comprising minitab.

The term “% w/w” as used herein means, for example, to the percentage weight of component by total weight of composition (e.g. uncoated minitab, coated minitab, uncoated capsule comprising minitab, or coated capsule comprising minitab). In one embodiment, the term “% w/w” as used herein means the percentage weight of a component by total weight of an uncoated minitab, and it is thus adapted accordingly for a coated minitab or adapted accordingly for a capsule (i.e. coated capsule or uncoated capsule) comprising minitab. In one embodiment, the term “% w/w” as used herein means weight of component by total weight of the uncoated minitab.

The term “total weight of the pharmaceutical composition”, refers for example to the total weight of a pharmaceutical composition, for example in the form of an uncoated minitab, coated minitab, uncoated capsule comprising one or more minitab, or coated capsule comprising one or more minitab; for example a minitab, such as an uncoated minitab.

The term “titanium-dioxide free” as used herein refers to a pharmaceutical composition with no added titanium dioxide. In one embodiment, it means that no titanium dioxide is intentionally added to or is present in the pharmaceutical composition.

The term “cyclodextrin free” as used herein refers to a pharmaceutical composition, for example as described herein, with no added cyclodextrin. In one embodiment, it means that no cyclodextrin is intentionally added to (or present) in the pharmaceutical composition.

The term "sugar free", as used herein, refers to a pharmaceutical composition, for example as described herein, with no added sugar added to (or present) in the pharmaceutical composition.

The term "mean particle", as used here means the particle size fraction below which 50% of the material is contained, i.e. the Dv50 value, for example as measured by laser diffraction.

The term "Dv50", as used herein, means the cumulative particle size distribution at the particle size point below which 50% of the material is contained using the volume distribution as used for the majority of light scattering techniques including laser diffraction, for example a Dv50 of 100 μm means that 50% of the measured particles have a size of 100 μm or less. In one embodiment, the term Dv50, as used herein, refers to the value of the particle diameter at 50% of the cumulative volume distribution, for example as measured by laser diffraction.

The term "primary particle", as used herein means the smallest unit of a powder that cannot be readily subdivided, for example, several primary particles can aggregate to form agglomerates or lumps, which may be separated by means of various techniques.

The term "primary particle size", as used herein refers to the average size of non-agglomerated primary particles, for example, as measured by laser diffraction, for example by utilizing ultrasound treatment during sample preparation.

The term "Dv90", as used herein means the cumulative particle size distribution at the particle size point below which 90% of the material is contained using the volume distribution as used for the majority of light scattering techniques including laser diffraction, for example a Dv90 of 900 μm means that 90% of the measured particles have a size of 900 μm or less. *In one embodiment, the term Dv90*, as used herein, refers to the value of the particle diameter at 90% of the cumulative volume distribution, for example as measured by laser diffraction.

The term "D90", as used herein, refers to the particle size at which, up to and including, about 90 % of the total mass of materials in the sample is contained (e.g. as analyzed by means of analytical sieving according to Pharm. Eur. 2.9.3). It thus represents the 90 % quantile in the particle size distribution.

The term "D50" as used herein, refers to the particle size at which, up to and including, 50 % of the total mass of materials in the sample is contained (e.g. as analyzed by means of analytical sieving according to Pharm. Eur. 2.9.3). It thus represents the 50 % quantile in the particle size distribution.

The term "D10" as used herein, refers to the particle size at which, up to and including, 10 % of the total mass of materials in the sample is contained (e.g. as analyzed by means of analytical sieving according to Pharm. Eur. 2.9.3). It thus represents the 10 % quantile in the particle size distribution.

The term "micronized", as used herein, refers to particles which have been significantly reduced in particle size, for example, by means of milling or grinding (e.g. jet mill), for example having an average particle diameter of less than about 400 microns, for example of from about 2 to 400 microns; such as of from about 2 to about 200 microns (e.g. of from about 2 to about 100 microns). In one embodiment, it refers to particles having an average particle diameter as of from about 2 to about 200 microns (e.g. of from about 2 to about 100 microns).

The term "oral administration", as used herein, refers, for example, to any form of delivery of a therapeutic agent (i.e. active ingredient) or a composition thereof to a subject wherein the agent or composition is placed in the mouth of the subject, whether or not the agent or composition is swallowed. Thus "oral administration" comprises, for example, buccal, sublingual and esophageal administration, such as esophageal administration.

The term "excipient" or "pharmaceutical excipient" or "pharmaceutically acceptable excipient" means a pharmacologically inactive compound such as a diluent, a lubricant, a glidant or a binder comprised in a pharmaceutical product (e.g. dosage form).

The terms "filler", "glidant", "lubricant" or "disintegrant", as used herein, have the ordinary meaning to the person skilled in the art in the formulation field. A "filler", refers, for example, to an agent increasing the bulk of a pharmaceutical composition. A "lubricant", refers, for example, to an inactive ingredient used to reduce adhesive forces of between the newly formed tablet and machine parts like die and punches when, for example, dry granulated, filled in capsules or compressed to tablets. A suitable lubricant is, for example, stearic acid, magnesium stearate, calcium stearate, zinc stearate, glyceryl palmitostearate, sodium stearyl fumarate, canola oil, hydrogenated vegetable oil such as hydrogenated castor oil (e.g. Cutina® or Lubriwax® 101), mineral oil, sodium lauryl sulfate, polyethylene glycol, talc, or a mixture of any of the above. In one embodiment, the lubricant is, for example, magnesium stearate, stearic acid or sodium stearyl fumarate. A "disintegrant", refers, for example, to a compound that expands when wet, to cause disintegration of tablets or granulates to break apart and release the active pharmaceutical agent. A "glidant", refers, for example, to an inactive ingredient used as a flow aid that improves the flow characteristics of, for example, particulates such as powders or granules. A suitable glidant is, for example, magnesium

oxide or colloidal silicon dioxide (also known as pyrogenic silica or fumed silica or colloidal silica).

The term "direct compression", as used herein, has the ordinary meaning to the person skilled in the art in the formulation field. It refers, for example, to the process by which tablets or minitables are compressed directly from powder blends of the active ingredient (i.e., a physiologically active substance) and suitable excipients (e.g. filler, disintegrant, lubricant, or lubricant) and no pretreatment of the powder blends by wet or dry granulation procedures is necessary.

The term "solid pharmaceutical composition" encompasses, but is not restricted to, pharmaceutical compositions being in the solid state, for example, at room temperature (e.g. about 23°C ±0.5°C), including, for example, a powder, for example a powder that can be combined with an aqueous medium, for example, for oral administration."

The term "pharmaceutical preparation" or "solid dosage form" or "pharmaceutical dosage form" or "dosage form" refers, for example, to one or more of tablet, capsule, powder, disc, caplet, granules, pellets, granules in capsule, minitables, minitables in capsule, pellets in capsule, Sachet and the like.

The term "crystalline form", as used herein, refers to a crystal form or modification that can be characterized by analytical methods such as, e.g., X-ray powder diffraction or Raman spectroscopy.

The term "crystalline anhydrous form", as used herein, refers to a crystalline form substantially or completely free from water, for example particularly water of crystallization.

The term "tablet", as used herein, refer to compressed pharmaceutical dosage forms of all shape and size, whether coated or uncoated.

The term "immediate release", as used herein, refers to a pharmaceutical preparation that does not contain a dissolution rate controlling material (e.g. a material that delays or prolongs the dissolution rate). Typically, it is used to describe a release profile effecting the delivery of an active ingredient as soon as possible. For example, a *pharmaceutical preparation* that releases at least *about* 85 % w/w/ of the active of the active ingredient within 60 minutes in vitro (e.g. according to Pharm. Eur. 2.9.3 using Apparatus II (paddle) or Apparatus I (basket); for example under the conditions described in the Examples herein).

The term "different", as used herein, for example in the expression "two different fillers" or "two different sugars", means, for example, chemically different.

The term “optionally”, as used herein, means that the referenced “element” (e.g. excipient, such as “sugar”) may be present or not.

The term “sugar”, as used herein, refers, for example, to monosaccharides, disaccharides or oligosaccharides, for example sucrose (saccharose), glucose, fructose, maltose, lactose or galactose.

The term "sugar alcohol" as used herein, refers, for example, to sugar derivatives having a hydroxyl group attached to each carbon atom, for example, mannitol (e.g. D-mannitol), xylitol and sorbitol. In one embodiment, the sugar alcohol is prepared from a spray-dried composition, e.g. mannitol composition, e.g. having a high specific surface area. The use of this type of mannitol composition may assist adhesion of micronized cladribine particles to the filler, For example, in one embodiment, the surface area of the sugar alcohol, e.g. mannitol (e.g. D-mannitol), is of from about 1 to about 7 m²/g, e.g. of from about 1 to about 5 m²/g, for example as measured according to well-established methods [e.g. by gas adsorption according to Brunauer, Emmett, Teller (e.g. ISO 9277:1995)]. The mannitol preparation may suitably have a mean particle size (D50) of from about 100 to about 200 µm, e.g. of from about 100 to about 150 µm and a bulk density of from about 0.4 to about 0.5 g/mL, e.g. of from about 0.45 to about 0.50 g/mL, such as of from about 0.47 to about 0.48 g/mL, such as. A suitable high surface area mannitol is, for example, Parreck M200, Pearlitol 200SD or Pearlitol 100SD.

DETAILED DESCRIPTION]

Compounds and Compositions

A first aspect of the invention is a method of treating Myasthenia Gravis (MG), in a patient in need thereof, comprising administering a composition comprising cladribine or a pharmaceutically acceptable salt thereof, wherein said composition is to be administered orally.

The invention thus pertains to methods and uses of cladribine or a pharmaceutically acceptable salt thereof, as well as formulations thereof appropriate for oral administration, for the treatment of MG, in particular gMG.

Cladribine, also named 2-Chloro-2'-deoxyadenosine, is a known active substance, which is monographed both in European pharmacopoeia and US pharmacopoeia. Cladribine may be prepared by processes well known in the art, such as those described in US 7,572,909, US 5,208,327, WO2000064918 and Kazimierczuk, 1984.

In the context of the invention, the term pharmaceutically acceptable salts should be construed as generally understood in the art, that is to say as non-toxic acid addition salts that are generally prepared by reacting a compound with a suitable organic or inorganic acid. In the context of the invention, examples of pharmaceutically acceptable cladribine salts include the hydrochloride, hydrobromide sulphate, phosphate, citrate, acetate and maleate salts.

Cladribine or a pharmaceutically acceptable salt thereof may be formulated into compositions for enteric administration, preferably into compositions for oral administration, i.e. formulated for oral administration. Examples of compositions appropriate for oral administration comprise capsules, tablets, suspensions, or syrup form.

Compositions of this invention may further comprise one or more pharmaceutically acceptable additional ingredient(s) such as alum, stabilizers, antimicrobial agents, buffers, coloring agents, flavoring agents, adjuvants, and the like.

Compositions according to the invention may be liquid formulations including, but not limited to, aqueous or oily suspensions, solutions, emulsions, syrups, and elixirs. The compositions may also be formulated as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain additives including, but not limited to, suspending agents, emulsifying agents, nonaqueous vehicles and preservatives. Suspending agents include, but are not limited to, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel, and hydrogenated edible fats. Emulsifying agents include, but are not limited to, lecithin, sorbitan monooleate, and acacia. Nonaqueous vehicles include, but are not limited to, edible oils, almond oil, fractionated coconut oil, oily esters, propylene glycol, and ethyl alcohol. Preservatives include, but are not limited to, methyl or propyl p-hydroxybenzoate and sorbic acid.

Compositions according to the invention may also be solid formulations, such as tablets or lozenges formulated in a conventional manner. For example, tablets and capsules for oral administration may contain conventional excipients including, but not limited to, binding agents, fillers, lubricants, disintegrants and wetting agents. Binding agents include, but are not limited to, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch and polyvinylpyrrolidone.

Fillers include, but are not limited to, lactose, sugar, microcrystalline cellulose, maize starch, calcium phosphate, mannitol and sorbitol. Lubricants include, but are not limited to, silica, also called fumed silica or pyrogenic silica, magnesium stearate, stearic acid, talc, polyethylene glycol, and silica. Disintegrants include, but are not limited to, croscarmellose sodium, potato starch and sodium starch glycolate. Wetting agents include, but are not limited to, sodium lauryl sulfate. Tablets may be coated according to methods well known in the art.

Preferably, the composition appropriate for oral administration is a solid formulation. In another preferred embodiment, the composition according to the invention presents as a solid dosage form. In another preferred embodiment, cladribine or a pharmaceutically acceptable salt thereof is formulated as a solid dosage form.

Examples of solid formulations of cladribine appropriate for oral administration which may be used in the context of the invention have been described for instance in WO 2004/087100 and in EP 2 428 201. The present invention provides a composition comprising or consisting of cladribine or a pharmaceutically acceptable salt thereof, a filler which is preferably mannitol, microcrystalline cellulose, or a combination of both, a disintegrant which is preferably croscarmellose sodium, a lubricant which is preferably silica, also called fumed silica or pyrogenic silica, magnesium stearate or a combination of both. In one embodiment, the composition consists of 7.8%w/w cladribine or a pharmaceutically acceptable salt thereof, 27.2%w/w mannitol, 56.0%w/w microcrystalline cellulose, 5.0%w/w croscarmellose sodium, 1.0%w/w pyrogenic silica and 3.0%w/w magnesium stearate.

In a preferred embodiment, the composition comprising cladribine or the pharmaceutically acceptable salt thereof presents as a solid dosage form comprising a fixed dose of cladribine or a pharmaceutically acceptable salt thereof of about 17.5 mg or about 4.375 mg. In a preferred embodiment, the composition comprising cladribine or the pharmaceutically acceptable salt thereof presents as a solid dosage form chosen in the list consisting of granules and tablets, preferably mini-tablets, and more preferably coated minitables presented in a capsule, preferably a hard capsule. The minitables preferably have the composition mentioned above. In this preferred embodiment, the total dose of cladribine or a pharmaceutically acceptable salt thereof comprised in the minitables comprised in one hard capsule is of about 17.5 mg or about 4.375 mg. The hard capsule is preferably made of HPMC (hydroxypropylmethylcellulose).

In the context of the invention, the term mini-tablets, sometimes also referred to as microtablets, should be construed as generally understood in the art, that is to say as referring to tablets with typical diameters of one to four millimeters. In the context of the invention, the

term granules should be construed as generally understood in the art, that is to say as dosage forms with typical diameter smaller than 2.5 mm.

Patients

In the context of the invention, the patients to be administered the composition according to the method of the invention are patients in need thereof. In the context of the invention, the term “patient in need thereof”, unless otherwise specified, should be construed as encompassing any subject who has developed or is developing MG, preferably who has developed or is developing gMG. Preferably, the term “patient in need thereof” pertains to any subject who has been diagnosed with MG, preferably who has been diagnosed with gMG.

The criteria for diagnosing MG, preferably gMG, in a patient are well known in the art and have been described by many including recently by Rousseff (Rousseff 2021). Most gMG patients present autoantibodies, in particular one or more selected from anti-AChR antibodies, anti-MuSK antibodies, and anti-LRP4 antibodies. Subjects who are autoantibody negative, in particular to the autoantibodies referred to in the previous sentence, may still have gMG. Although the diagnosis of gMG remains mostly clinical and rests on the history and physical findings of fatigable, fluctuating muscle weakness in a specific distribution, bedside tests and laboratory methods identifying the type of auto-antibodies present in a specific patient are also recognized in the field.

Preferably, the term “patient in need thereof”, comprises any subject who has been diagnosed with MG, preferably gMG, and is autoantibody positive or autoantibody negative. In the context of the invention, the term “autoantibody positive” should be construed as generally understood in the field of MG, that is to say as pertaining to a human subject who is anti-AChR antibody positive, anti-MuSK antibody positive, or anti-LRP4 antibody positive.

The terms “anti-AChR antibody positive” should be construed as generally understood in the field, that is to say meaning that the subject produces anti-AChR antibodies, preferably circulating anti-AChR antibodies. The skilled person understands that in practice, anti-AChR antibodies can be detected in a biological sample from the subject, preferably a biological sample derived from blood, such as blood, plasma or serum. In a preferred embodiment, the patient in need thereof is anti-AChR antibody positive. In a preferred embodiment, the patient in need thereof is a subject who has developed or is developing gMG and is anti-AChR antibody positive. In one embodiment, the term “Anti-AChR antibody positive”, as used herein, refers to anti-acetylcholine receptor antibody-positive, for example, as

measured in serum by ELISA (Enzyme-Linked Immunosorbent Assay) for the determination of the titers of autoantibodies against AChR.

The terms “anti-MuSK antibody positive” should be construed as generally understood in the field, that is to say meaning that the subject produces anti-MuSK antibodies, preferably circulating anti-MuSK antibodies. The skilled person understands that in practice, anti-MuSK antibodies can be detected in a biological sample from the subject, preferably a biological sample derived from blood, such as blood, plasma or serum. In a preferred embodiment, the patient in need thereof is anti-MuSK antibody positive. In a preferred embodiment, the patient in need thereof is a subject who has developed or is developing gMG and is anti-MuSK antibody positive. In one embodiment, the term “Anti-MuSK antibody positive”, as used herein, refers to anti-muscle-specific tyrosine kinase antibody-positive, for example, as measured in serum by ELISA (Enzyme-Linked Immunosorbent Assay) for the determination of the titers of autoantibodies against Anti-MuSK.

The terms “anti-LRP4 antibody positive” should be construed as generally understood in the field, that is to say meaning that the subject produces expresses anti-LRP4 antibodies, preferably circulating anti-LRP4 antibodies. The skilled person understands that in practice, anti-LRP4 antibodies can be detected in a biological sample from the subject, preferably a biological sample derived from blood, such as blood, plasma or serum. In a preferred embodiment, the patient in need thereof is anti-LRP4 antibody positive. In a preferred embodiment, the patient in need thereof is a subject who has developed or is developing gMG and is anti-LRP4 antibody positive. In one embodiment, the term “Anti-LRP4 antibody positive”, as used herein, refers to anti-low density lipoprotein receptor-related protein 4 antibody-positive, for example, as measured in serum by ELISA (Enzyme-Linked Immunosorbent Assay) for the determination of the titers of autoantibodies against Anti-LRP4.

The term “seronegative for Anti-AChR antibody”, as used herein, refers to anti-acetylcholine receptor antibody-negative, for example, as measured in serum by ELISA (Enzyme-Linked Immunosorbent Assay) for the determination of the titers of autoantibodies against Anti-AChR.

The term “seronegative for Anti-MuSK antibody”, as used herein, refers to anti-muscle-specific tyrosine kinase antibody-negative, for example, as measured in serum by ELISA (Enzyme-Linked Immunosorbent Assay) for the determination of the titers of autoantibodies against Anti-MuSK.

The term “seronegative for Anti-LRP4 antibody”, as used herein, refers anti-low density lipoprotein receptor-related protein 4 antibody-negative, for example, as measured in serum

by ELISA (Enzyme-Linked Immunosorbent Assay) for the determination of the titers of autoantibodies against Anti-LRP4.

Dosing and administration regimen

The present invention is directed towards cladribine or a pharmaceutically acceptable salt thereof, for its use in treating Myasthenia Gravis, wherein cladribine or said pharmaceutically acceptable salt thereof, is to be administered orally. In other embodiments, the invention pertains to a method of treating Myasthenia Gravis, in a patient in need thereof, comprising the administration of cladribine or a pharmaceutically acceptable salt thereof, wherein said cladribine or a pharmaceutically acceptable salt thereof is to be administered orally.

The present invention is directed towards a composition comprising cladribine or a pharmaceutically acceptable salt thereof, for its use in treating Myasthenia Gravis, wherein the composition is to be administered orally. In other embodiments, the invention is directed towards a use of cladribine or a pharmaceutically acceptable salt thereof, for the manufacture of a composition for the treatment of Myasthenia Gravis, wherein the composition is to be administered orally. In other embodiments, the invention is directed towards a use of cladribine or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment of Myasthenia Gravis, wherein the pharmaceutical composition is to be administered orally. In other embodiments, the invention is directed towards a use of cladribine or a pharmaceutically acceptable salt thereof, for the manufacture of a composition for the treatment of Myasthenia Gravis, wherein the composition is appropriate for oral administration. In other embodiments, the invention is directed towards a use of cladribine or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment of Myasthenia Gravis, wherein the pharmaceutical composition is appropriate for oral administration.

The dosing regimen of the invention comprises an initial dosing regimen that may be followed by one or more retreatments, each such initial dosing regimen and retreatment also referred to herein as a "treatment period".

One of the many advantages of the invention lies in that the composition according to the invention can be administered to patients in need thereof according to an initial dosing regimen comprising or consisting of two courses of administration of the medicine, the two courses being separated by about a month, about 4 weeks or about 28 days, with no need for

continuous treatment or regular predefined retreatments thereafter, for at least about 6 months, at least about half a year, preferably at least about 24 weeks after the last day or the first day when cladribine is administered in the initial dosing regimen. Further, a total dose of cladribine of between 35 mg and 210 mg of cladribine administered according to such an initial dosing regimen is considered safe and effective in treating Myasthenia Gravis patients.

Preferably, the invention pertains to a method of treating Myasthenia Gravis, in a patient in need thereof, comprising orally administering cladribine or a pharmaceutically acceptable salt thereof to the patient according to an initial dosing regimen comprising or consisting of two treatment courses, separated by about a month, about 4 weeks or about 28 days. In other embodiments, the invention pertains preferably to cladribine or a pharmaceutically acceptable salt thereof, for its use in treating Myasthenia Gravis, wherein cladribine or said pharmaceutically acceptable salt thereof is to be administered orally according to an initial dosing regimen comprising or consisting of two treatment courses, said treatment courses being separated by about a month, about 4 weeks or about 28 days. In other embodiments, the invention pertains preferably to a composition comprising cladribine or a pharmaceutically acceptable salt thereof, for its use in treating Myasthenia Gravis, wherein said composition is to be administered orally according to an initial dosing regimen comprising or consisting of two treatment courses, said treatment courses being separated by about a month, about 4 weeks or about 28 days. In other embodiments, the invention preferably pertains to the use of cladribine or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment of Myasthenia Gravis, wherein the pharmaceutical composition is to be administered orally according to an initial dosing regimen comprising or consisting of two treatment courses, said treatment courses being separated by about a month, about 4 weeks or about 28 days.

Preferably, in the invention, each treatment course of the initial dosing regimen consists of a period of 1 to 6 consecutive days, 1 to 5 consecutive days, 1 to 4 consecutive days, 1 to 3 consecutive days, 1 to 2 consecutive days or 1 day of daily administration of cladribine or a pharmaceutically acceptable salt thereof. Preferably, in the invention, each treatment course of the initial dosing regimen consists of a period of 1 to 6 consecutive days, 1 to 5 consecutive days, 1 to 4 consecutive days, 1 to 3 consecutive days, 1 to 2 consecutive days or 1 day of daily administration of a composition comprising cladribine or a pharmaceutically acceptable salt thereof.

Preferably, in the invention, the two treatment courses of the initial dosing regimen are separated by about 3 to 5 weeks, preferably about 4 weeks. Preferably, in the invention, the

two treatment courses of the dosing regimen are separated by about 20 to 40 days, preferably about 21 to 35 days, more preferably about 28 days.

In the context of the invention, the indication that the first and second treatment courses are separated by about a month, about 4 weeks or about 28 days, should be understood as meaning that day 1 of treatment course 2 occurs about a month, about 4 weeks or about 28 days after day 1 of treatment course 1, respectively.

Preferably, the total administered dose of cladribine or a pharmaceutically acceptable salt thereof, administered under said initial dosing regimen is from about 35 mg to about 210 mg. In other embodiments, the invention preferably pertains to a method of treating Myasthenia Gravis, in a patient in need thereof, comprising orally administering cladribine or a pharmaceutically acceptable salt thereof to the patient, according to an initial dosing regimen comprising two treatment courses, said treatment courses being separated by about a month or about 28 days, wherein the total dose of cladribine or a pharmaceutically acceptable salt thereof, administered under said initial dosing regimen is from about 35 mg to about 210 mg.

Preferably, the total dose of cladribine or pharmaceutically acceptable salt thereof, administered during said initial dosing regimen is of about 35 mg, of about 52.5 mg, of about 70 mg, of about 87.5 mg, of about 105 mg, of about 122.5 mg, of about 140 mg, of about 157.5 mg, of about 175 mg, of about 192.5 mg or of about 210 mg. More preferably, the total dose of cladribine or a pharmaceutically acceptable salt thereof administered during said initial dosing regimen is of about 52.5 mg. More preferably, the total administered dose of cladribine or a pharmaceutically acceptable salt thereof administered during said initial dosing regimen is of about 105 mg.

In the context of the invention, the total dose corresponds to the dose of the active principle, herein cladribine or a pharmaceutically acceptable salt thereof, administered during the period referred to, such as the particular treatment period. When used in reference to, e.g., the initial dosing regimen consisting of two treatment courses, the total administered dose corresponds to the sum of the active principle cladribine or a pharmaceutically acceptable salt thereof administered during the first and the second treatment course.

Moreover, it is understood that when reference is made to a total dose of cladribine or a pharmaceutically acceptable salt thereof, e.g., the total dose of cladribine or a pharmaceutically acceptable salt thereof is from about 35 mg to about 210 mg, such total dose refers to the total amount of any cladribine and pharmaceutically acceptable salt(s) thereof. In some embodiments, only cladribine is administered and then the total dose only refers to the

amount of cladribine administered. In other embodiment, cladribine is administered with one or more pharmaceutically acceptable salts thereof in combination, in which case the total dose refers to the total amount of cladribine and its pharmaceutically acceptable salts thereof that is administered. In yet other embodiments, only one or more pharmaceutically acceptable salts of cladribine are administered, in which case the total dose refers to the total amount of the one or more pharmaceutically acceptable salts thereof that are administered.

It is also understood that the dose amounts referred to herein in respect of the pharmaceutically acceptable salt of cladribine refer to the amount of the active ingredient, i.e. cladribine, in such salt. For instance, cladribine 5'-monophosphate ammonium salt has a molecular weight of 382.7 g/mol as compared to a molecular weight of 285.69 g/mol of cladribine. A total dose of 52.5 mg of the cladribine 5'-monophosphate ammonium salt thus refers to a total dose of 52.5 mg cladribine corresponding to a dose of 70.3 mg of the salt form.

It should be understood that the total administered dose of cladribine to be administered during the initial dosing regimen can be split evenly between the two treatment courses, such that half of the total administered dose of cladribine is administered during each treatment course. Alternatively, the total administered dose of cladribine may be divided into different doses for each treatment course, e.g., so as to take into account the specificities of the dosage form. For instance, in embodiments where the composition comprising cladribine according to the invention is in the form of a solid dosage form comprising 17.5 mg of cladribine, administering 52.5 mg of cladribine in a dosing regimen will imply administering 3 dosage forms during the two treatment courses, which could be achieved according to a regimen where 2 dosage forms are administered as part of the first treatment course and 1 dosage form is administered as part of the second treatment course.

In one embodiment, in the use or the method of the invention, cladribine or a pharmaceutically acceptable salt thereof or the composition according to the invention is to be administered according to an initial dosing regimen comprising or consisting of two treatment courses, separated by about a month, about 28 days, or, preferably, about 4 weeks, wherein the total administered dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 52.5 mg, and wherein about 17.5 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the first treatment course of the initial dosing regimen, and about 35 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the second treatment course of the initial dosing regimen. Preferably, in this embodiment, the about 17.5 mg of cladribine or pharmaceutically acceptable salt thereof administered during the first treatment course of the initial dosing regimen is

administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one of the first treatment course of the initial dosing regimen, and the about 35 mg of cladribine or pharmaceutically acceptable salt thereof administered during the second treatment course of the initial dosing regimen is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one and on day two of the second treatment course of the initial dosing regimen. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-AChR antibody positive. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-MuSK antibody positive. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-LRP4 antibody positive or seronegative.

In a preferred embodiment, in the use or the method of the invention, cladribine or a pharmaceutically acceptable salt thereof is to be administered according to an initial dosing regimen comprising or consisting of two treatment courses, separated by about a month, about 28 days, or, preferably, about 4 weeks, wherein the total administered dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 52.5 mg, and wherein about 35 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the first treatment course of the initial dosing regimen, and about 17.5 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the second treatment course of the initial dosing regimen. Preferably, in this embodiment, the about 35 mg of cladribine or pharmaceutically acceptable salt thereof administered during the second treatment course of the initial dosing regimen is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one and on day two of the first treatment course of the initial dosing regimen, and the about 17.5 mg of cladribine or pharmaceutically acceptable salt thereof administered during the first treatment course of the initial dosing regimen is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one of the second treatment course of the initial dosing regimen. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-AChR antibody positive. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-MuSK antibody positive. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-LRP4 antibody positive or seronegative.

In a preferred embodiment, in the use or the method of the invention, cladribine or a pharmaceutically acceptable salt thereof or the composition according to the invention is to be administered according to an initial dosing regimen comprising or consisting of two treatment courses separated by about a month, about 28 days, or, preferably, about 4 weeks, wherein the total administered dose of cladribine or a pharmaceutically acceptable salt thereof administered during said initial dosing regimen is of about 87.5 mg, and wherein about 52.5 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the first treatment course of the initial dosing regimen, and about 35 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the second treatment course of the initial dosing regimen. Preferably, in this embodiment, the about 52.5 mg of cladribine or pharmaceutically acceptable salt thereof administered during the first treatment course of the initial dosing regimen is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one, day two and day three of the first treatment course of the initial dosing regimen, and the about 35 mg of cladribine or pharmaceutically acceptable salt thereof administered during the second treatment course of the initial dosing regimen is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one and on day two of the second treatment course of the initial dosing regimen. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-AChR antibody positive. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-MuSK antibody positive. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-LRP4 antibody positive or seronegative.

In another preferred embodiment, in the use or the method of the invention, cladribine or a pharmaceutically acceptable salt thereof or the composition according to the invention is to be administered according to an initial dosing regimen comprising or consisting of two treatment courses, said treatment courses being separated by about a month, about 28 days, or, preferably, about 4 weeks, wherein the total administered dose of cladribine or a pharmaceutically acceptable salt thereof administered during said initial dosing regimen is of about 87.5 mg, and wherein about 35 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the first treatment course of the initial dosing regimen, and about 52.5 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the second treatment course of the initial dosing regimen. Preferably, in this embodiment, the about 35 mg of cladribine or pharmaceutically acceptable salt thereof administered during the first treatment course of the initial dosing regimen is administered in the form of a dosage form

comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof on day one and on day two of the first treatment course of the initial dosing regimen, and the about 52.5 mg of cladribine or pharmaceutically acceptable salt thereof administered during the second treatment course of the initial dosing regimen is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one, day two and day three of the second treatment course of the initial dosing regimen. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-AChR antibody positive. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-MuSK antibody positive. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-LRP4 antibody positive or seronegative.

In a preferred embodiment, in the use or the method of the invention, cladribine or a pharmaceutically acceptable salt thereof or the composition according to the invention is to be administered according to an initial dosing regimen comprising or consisting of two treatment courses, said treatment courses being separated by about a month, about 28 days, or, preferably, about 4 weeks, wherein the total administered dose of cladribine or a pharmaceutically acceptable salt thereof administered during said initial dosing regimen is of about 105 mg, and wherein about 52.5 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the first treatment course of the initial dosing regimen, and about 52.5 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the second treatment course of the initial dosing regimen. Preferably, in this embodiment, the about 52.5 mg of cladribine or pharmaceutically acceptable salt thereof administered during the first treatment course of the initial dosing regimen is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one, day two and day three of the first treatment course of the initial dosing regimen, and the about 52.5 mg of cladribine or pharmaceutically acceptable salt thereof administered during the second treatment course of the initial dosing regimen is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one, day two and day three of the second treatment course of the initial dosing regimen. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-AChR antibody positive. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-MuSK antibody positive. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-LRP4 antibody positive or seronegative.

In an embodiment, in the use or the method of the invention, cladribine or a pharmaceutically acceptable salt thereof or the composition according to the invention is to be administered according to an initial dosing regimen comprising or consisting of two treatment courses, said treatment courses being separated by about a month, about 28 days, or, preferably, about 4 weeks, wherein the total administered dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 105 mg, and wherein about 70 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the first treatment course of the initial dosing regimen, and about 35 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the second treatment course of the initial dosing regimen. Preferably, in this embodiment, the about 70 mg of cladribine or pharmaceutically acceptable salt thereof administered during the first treatment course of the initial dosing regimen is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one, day two, day three and day four of the first treatment course of the initial dosing regimen, and the about 35 mg of cladribine or pharmaceutically acceptable salt thereof administered during the second treatment course of the initial dosing regimen is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one and on day two of the second treatment course of the initial dosing regimen. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-AChR antibody positive. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-MuSK antibody positive. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-LRP4 antibody positive or seronegative.

In an embodiment, in the use or the method of the invention, cladribine or a pharmaceutically acceptable salt thereof or the composition according to the invention is to be administered according to an initial dosing regimen comprising or consisting of two treatment courses, said treatment courses being separated by about a month, about 28 days, or, preferably, about 4 weeks, wherein the total administered dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 105 mg, and wherein about 35 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the first treatment course of the initial dosing regimen, and about 70 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the second treatment course of the initial dosing regimen. Preferably, in this embodiment, the about 35 mg of cladribine or pharmaceutically acceptable salt thereof administered during the first treatment course of the initial dosing regimen is administered in the form of a dosage form comprising about 17.5 mg

of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one and on day two of the first treatment course of the initial dosing regimen, and the about 70 mg of cladribine or pharmaceutically acceptable salt thereof administered during the second treatment course of the initial dosing regimen is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one, day two, day three and day four of the second treatment course of the initial dosing regimen. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-AChR antibody positive. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-MuSK antibody positive. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-LRP4 antibody positive or seronegative.

In a preferred embodiment, in the use or the method of the invention, cladribine or a pharmaceutically acceptable salt thereof or the composition according to the invention is to be administered according to an initial dosing regimen comprising or consisting of two treatment courses, separated by about a month, about 28 days, or, preferably, about 4 weeks, wherein the total administered dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 175 mg, and wherein about 87.5 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the first treatment course of the initial dosing regimen, and about 87.5 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the second treatment course of the initial dosing regimen. Preferably, in this embodiment, the about 87.5 mg of cladribine or pharmaceutically acceptable salt thereof administered during the first treatment course of the initial dosing regimen is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one, day two, day three, day four and day five of the first treatment course of the initial dosing regimen, and the about 87.5 mg of cladribine or pharmaceutically acceptable salt thereof administered during the second treatment course of the initial dosing regimen is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one, day two, day three, day four and day five of the second treatment course of the initial dosing regimen. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-AChR antibody positive. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-MuSK antibody positive. Preferably, in this embodiment, the patient in need thereof is a human

subject who has been diagnosed with gMG and who is anti-LRP4 antibody positive or seronegative.

In an embodiment, in the use or the method of the invention, cladribine or a pharmaceutically acceptable salt thereof or the composition according to the invention is to be administered according to an initial dosing regimen comprising or consisting of two treatment courses, said treatment courses being separated by about a month, about 28 days, or, preferably, about 4 weeks, wherein the total administered dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 175 mg, and wherein about 70 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 105 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the second treatment course. Preferably, in this embodiment, the about 70 mg of cladribine or pharmaceutically acceptable salt thereof administered during the first treatment course of the initial dosing regimen is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one, day two, day three and day four of the first treatment course of the initial dosing regimen, and the about 105 mg of cladribine or pharmaceutically acceptable salt thereof administered during the second treatment course of the initial dosing regimen is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one, day two, day three, day four, day five, and day six of the second treatment course of the initial dosing regimen. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-AChR antibody positive. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-MuSK antibody positive. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-LRP4 antibody positive or seronegative.

In an embodiment, in the use or the method of the invention, cladribine or a pharmaceutically acceptable salt thereof or the composition according to the invention is to be administered according to an initial dosing regimen comprising or consisting of two treatment courses, said treatment courses being separated by about a month, about 28 days, or, preferably, about 4 weeks, wherein the total administered dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 175 mg, and wherein about 105 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the first treatment course of the initial dosing regimen, and about 70 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the second treatment course

of the initial dosing regimen. Preferably, in this embodiment, the about 105 mg of cladribine or pharmaceutically acceptable salt thereof administered during the first treatment course of the initial dosing regimen is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one, day two, day three, day four, day five, and day six of the first treatment course of the initial dosing regimen, and the about 70 mg of cladribine or pharmaceutically acceptable salt thereof administered during the second treatment course of the initial dosing regimen is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one, day two, day three and day four of the second treatment course of the initial dosing regimen. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-AChR antibody positive. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-MuSK antibody positive. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-LRP4 antibody positive or seronegative.

In a preferred embodiment, in the use or the method of the invention, cladribine or a pharmaceutically acceptable salt thereof or the composition according to the invention is to be administered according to an initial dosing regimen comprising or consisting of two treatment courses, said treatment courses being separated by about a month, about 28 days, or, preferably, about 4 weeks, wherein the total administered dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 210 mg, and wherein about 105 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the first treatment course of the initial dosing regimen, and about 105 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the second treatment course of the initial dosing regimen. Preferably, in this embodiment, the about 105 mg of cladribine or pharmaceutically acceptable salt thereof administered during the first treatment course of the initial dosing regimen is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one, day two, day three, day four, day five and day six of the first treatment course of the initial dosing regimen, and the about 105 mg of cladribine or pharmaceutically acceptable salt thereof administered during the second treatment course of the initial dosing regimen is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one, day two, day three, day four, day five and day six of the second treatment course of the initial dosing regimen. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-AChR antibody positive. Preferably, in this

embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-MuSK antibody positive. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-LRP4 antibody positive or seronegative.

Based on the pharmacodynamic data of cladribine as gathered during the treatment of multiple sclerosis and contrary to other drugs known to be useful in the treatment of MG, cladribine would not appear to require continuous or regular pre-defined administration, and that further to the initial dosing regimen described herein there is no need for immediate retreatment. This is very advantageous for patients, who may benefit from months or years without signs of relapse or worsening of the disease and thus without the need for specific MG treatment or retreatment with cladribine.

Preferably, the use or the method of the invention comprises a period of at least about 6 months, at least about 12 months, at least about 24 months or at least about 36 months after the initial dosing regimen comprising two treatment courses, where neither cladribine nor a pharmaceutically salt thereof is administered.

Preferably, the invention pertains to a method of treating Myasthenia Gravis, preferably generalized Myasthenia Gravis, the use of cladribine or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of Myasthenia Gravis, cladribine or a pharmaceutically acceptable salt thereof or a composition comprising cladribine or a pharmaceutically acceptable salt thereof for its use for the treatment of Myasthenia Gravis comprising the oral administration of cladribine or a pharmaceutically acceptable salt thereof, wherein cladribine or a pharmaceutically acceptable salt thereof is to be administered according to the following sequential steps:

- (1) an initial dosing regimen comprising or consisting of two treatment courses, said treatment courses being separated by about a month, about 28 days, or, preferably, 4 weeks wherein the total administered dose of cladribine or a pharmaceutically acceptable salt thereof, administered under said initial dosing regimen is from about 35 mg to about 210 mg, of about 35 mg, of about 52.5 mg, of about 70 mg, of about 87.5 mg, of about 105 mg, of about 122.5 mg, of about 140 mg, of about 157.5 mg, of about 175 mg, of about 192.5 mg or of about 210 mg;
- (2) a period of at least about 6 months, preferably of at least about 12 months, more preferably of at least about 24 months, after the last administration of cladribine or a pharmaceutically acceptable salt thereof during the second treatment course of the

initial dosing regimen, where no cladribine or pharmaceutically acceptable salt thereof is administered.

It should however be understood that in the context of the invention, retreatment steps remain possible, preferably after the period where no cladribine is administered for long term efficacy of the treatment. It should also be recognized that certain patients may present with particularly difficult to treat cases of Myasthenia Gravis, and despite being treated according to the invention, may present with clinical signs of worsening of the disease justifying retreatment with cladribine. In view of the above, the dosage administered to an individual patient may still vary depending upon a variety of factors, including pharmacokinetic properties, patient conditions and characteristics (sex, age, body weight, health, size), and the extent of symptoms of worsening or relapse, some of which may prompt for a step of retreatment with cladribine, further to the initial dosing regimen described herein.

It was established by the inventors that the dose and schedule of this retreatment step should preferably be adapted depending on the dose of cladribine previously administered to the subject during the previous treatment period, and the period between the previous treatment period and the retreatment. In particular, it was established that any retreatment with cladribine or a pharmaceutically acceptable salt thereof to be administered less than about one year, less than about 12 months, less than about 52 weeks, or, preferably, less than about 48 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof of the last treatment period, which preferably is a treatment period in which a full dose was administered, should preferably be limited to a supplemental dose of between about 17.5 mg and about 35 mg of cladribine or a pharmaceutically acceptable salt thereof. Moreover, said supplemental dose should preferably not be administered less than half a year, less than 6 months, or, preferably, less than 24 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof of the last treatment period, which preferably is a treatment period in which a full dose was administered.

In some embodiments, a supplemental dose of between about 17.5 mg and about 35 mg of cladribine or a pharmaceutically acceptable salt thereof is administered less than about one year, less than about 12 months, less than about 52 weeks, or, preferably, less than about 48 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof of the last treatment period, which preferably is a treatment period in which a full dose was administered. Moreover, said supplemental dose should preferably not be administered less than half a year, less than 6 months, or, preferably, less than 24 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof of the last treatment period, which preferably is a treatment period in which a full dose was administered.

Preferably, the retreatment with a supplemental dose only has a single treatment course.

In an embodiment, the use or the method of the invention comprises a step of retreatment with a supplemental dose wherein the dose of cladribine or a pharmaceutically acceptable salt thereof administered during said retreatment is from about 17.5 mg to about 35 mg, preferably of about 17.5 mg or of about 35 mg. Preferably, in this embodiment, the about 17.5 mg of cladribine or pharmaceutically acceptable salt thereof administered as the supplemental dose is administered in the form of a dosage form comprising about 17.5 mg of cladribine or pharmaceutically acceptable salt thereof administered on day one of the retreatment. Preferably, in this embodiment, the about 35 mg of cladribine or pharmaceutically acceptable salt thereof administered as the supplemental dose is administered in the form of a dosage form comprising about 17.5 mg of cladribine or pharmaceutically acceptable salt thereof administered daily on day one and day two of the retreatment.

Preferably, the supplemental dose of the retreatment is administered more than about half a year, more than about 6 months, or, preferably, more than about 24 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, which preferably is a treatment period in which a full dose was administered. In other embodiments, preferably, the supplemental dose is administered at least about half a year, at least about 6 months, preferably at least about 24 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, which preferably is a treatment period in which a full dose was administered.

Preferably, the supplemental dose of the retreatment is administered less than about 12 months, less than about one year, less than about 52 weeks, or, preferably, less than about 48 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, which preferably is a treatment period in which a full dose was administered. In other embodiments, preferably, the supplemental dose is administered earlier than about one year, earlier than about 12 months, earlier than about 52 weeks, or, preferably, earlier than about 48 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, which preferably is a treatment period in which a full dose was administered.

More preferably the supplemental dose of the retreatment is administered more than about 6 months and less than about 12 months or about one year, preferably more than about 24 weeks and less than about 48 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, which preferably is a treatment period in which a full dose was administered. In other embodiments, preferably,

the supplemental dose is administered at least about 6 months and earlier than about one year, preferably at least about 24 weeks and earlier than about 48 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, which preferably is a treatment period in which a full dose was administered.

Preferably, the supplemental dose of the retreatment is administered more than about 6 months, preferably more than about 24 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, which preferably is a treatment period in which a full dose was administered. In other embodiments, preferably, the supplemental dose is administered at least about 6 months, preferably at least about 24 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, which preferably is a treatment period in which a full dose was administered.

Preferably, the supplemental dose of the retreatment is administered less than about one year, less than about 12 months, less than about 52 weeks, preferably less than about 48 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, which preferably is a treatment period in which a full dose was administered. In other embodiments, preferably, the supplemental dose is administered earlier than about one year, than about 12 months, than about 52 weeks, or, preferably, than about 48 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, which preferably is a treatment period in which a full dose was administered.

More preferably the supplemental dose of the retreatment is administered more than about 6 months and less than about 12 months or about one year, preferably more than about 24 weeks and less than about 48 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, which preferably is a treatment period in which a full dose was administered. In other embodiments, preferably, the supplemental dose is administered at least about 6 months and earlier than about 12 months or about one year, preferably at least about 24 weeks and earlier than about 48 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, which preferably is a treatment period in which a full dose was administered.

On the other hand, it was also established that a retreatment with cladribine or a pharmaceutically acceptable salt thereof to be administered not earlier than about one year, than about 12 months, than about 52 weeks, or, preferably, than about 48 weeks after the first

or last administration of cladribine or a pharmaceutically acceptable salt thereof of the last treatment period where a full dose was administered should preferably be a retreatment using a full dose, e.g., repeating the dosing and schedule used in the initial dosing regimen. Furthermore, it was also established that a retreatment with cladribine or a pharmaceutically acceptable salt thereof to be administered not earlier than about 6 months, or not earlier than about 24 weeks after the first or last administration of cladribine or a pharmaceutically acceptable salt thereof of the last treatment period where a supplemental dose was administered should preferably be a retreatment using a full dose, e.g., repeating the dosing and schedule used in the initial dosing regimen.

In an embodiment, the use or the method of the invention comprises a step of retreatment wherein the total administered dose of cladribine or a pharmaceutically acceptable salt thereof administered during said retreatment equals the total administered dose of cladribine or pharmaceutically acceptable salt thereof administered in the previous treatment period. Preferably, the retreatment with a full dose consists of two treatment courses, said treatment courses being separated by about a month, about 28 days, or, preferably, about 4 weeks.

In some embodiments, there are multiple retreatments. In some embodiments, the multiple retreatments comprise one or more retreatments with a full dose and one or more retreatments with a supplemental dose in any order.

In some embodiments, the full dose of a retreatment is administered more than about 6 months, preferably more than about 24 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof of the last treatment period, which is a treatment period where a supplemental dose was administered. In other embodiments, the full dose of a retreatment is administered at least about 6 months, preferably at least about 24 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof of the last treatment period, which is a treatment period where a supplemental dose was administered.

In some embodiments, the full dose of a retreatment is administered more than about 6 months, preferably more than about 24 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof of the last treatment period, which is a treatment period where a supplemental dose was administered. In other embodiments, the full dose of a retreatment is administered at least about 6 months, preferably at least about 24 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof of the last treatment period, which is a treatment period where a supplemental dose was administered.

In some embodiments, the full dose of a retreatment is administered (1) more than about 6 months, preferably more than about 24 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof of the last treatment period where a supplemental dose was administered or (2) more than about one year, more than about 12 months, more than about 52 weeks, or, preferably, more than about 48 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof of the last treatment period where a full dose was administered. In other embodiments, the full dose of a retreatment is administered (1) at least about 6 months, preferably at least about 24 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof of the last treatment period where a supplemental dose was administered or (2) at least about one year, at least about 12 months, at least about 52 weeks, or, preferably at least about 48 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof of the last treatment period where a full dose was administered.

In some embodiments, the full dose of a retreatment is administered (1) more than about 6 months, preferably more than about 24 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof of the last treatment period where a supplemental dose was administered or (2) more than about one year, more than about 12 months, more than about 52 weeks, or, preferably, more than about 48 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof of the last treatment period where a full dose was administered. In other embodiments, the full dose of a retreatment is administered (1) at least about 6 months, preferably at least about 24 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof of the last treatment period where a supplemental dose was administered or (2) at least about one year, at least about 12 months, at least about 52 weeks, or, preferably at least about 48 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof of the last treatment period where a full dose was administered.

Preferably, the invention pertains to a method of treating Myasthenia Gravis, preferably generalized Myasthenia Gravis, the use of cladribine or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of Myasthenia Gravis, cladribine or a pharmaceutically acceptable salt thereof or a composition comprising cladribine or a pharmaceutically acceptable salt thereof for its use for the treatment of Myasthenia Gravis comprising the oral administration of cladribine or a pharmaceutically acceptable salt thereof, wherein it is to be administered according to a dosing regimen comprising or consisting of the following steps:

- (1) an initial dosing regimen consisting of two treatment courses, said treatment courses being separated by about a month or, preferably, about 4 weeks, wherein the total administered dose of cladribine or a pharmaceutically acceptable salt thereof, administered during the initial dosing regimen is from about 35 mg to about 210 mg, of about 35 mg, of about 52.5 mg, of about 70 mg, of about 87.5 mg, of about 105 mg, of about 122.5 mg, of about 140 mg, of about 157.5 mg, of about 175 mg, of about 192.5 mg or of about 210 mg;
- (2) optionally, one or more retreatment steps in which a supplemental dose is administered, preferably administered no earlier than about 6 months and earlier than about one year, preferably no earlier than about 24 weeks and earlier than about 48 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period;
- (3) optionally, one or more retreatment steps in which a full dose is administered according to the initial dosing regimen of step (1), wherein the first dose of such retreatment step is administered at least about one year, preferably at least about 48 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, if in this last treatment period a full dose was administered, or at least about six months, preferably at least about 24 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, if in this last treatment period a supplemental dose was administered.

Preferably, the invention pertains to a method of treating Myasthenia Gravis, preferably generalized Myasthenia Gravis, the use of cladribine or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of Myasthenia Gravis, cladribine or a pharmaceutically acceptable salt thereof or a composition comprising cladribine or a pharmaceutically acceptable salt thereof for its use for the treatment of Myasthenia Gravis comprising the oral administration of cladribine or a pharmaceutically acceptable salt thereof, wherein it is to be administered according to a dosing regimen comprising or consisting of the following steps:

- (1) an initial dosing regimen consisting of two treatment courses, said treatment courses being separated by about a month or, preferably, about 4 weeks, wherein the total administered dose of cladribine or a pharmaceutically acceptable salt thereof, administered during the initial dosing regimen is from about 35 mg to about 210 mg, of about 35 mg, of about 52.5 mg, of about 70 mg, of about 87.5 mg, of about 105 mg, of about 122.5 mg, of about 140 mg, of about 157.5 mg, of about 175 mg, of about 192.5 mg or of about 210 mg;

- (2) optionally, one or more retreatment steps in which a supplemental dose is administered, preferably administered no earlier than about 6 months and earlier than about one year, preferably no earlier than about 24 weeks and earlier than about 48 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period;
- (3) optionally, one or more retreatment steps in which a full dose is administered according to the initial dosing regimen of step (1), wherein the first dose of such retreatment step is administered at least about one year, preferably at least about 48 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, if in this last treatment period a full dose was administered, or at least about six months, preferably at least about 24 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, if in this last treatment period a supplemental dose was administered.

In a preferred embodiment, the invention pertains to a method of treating Myasthenia Gravis, preferably generalized Myasthenia Gravis, the use of cladribine or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of Myasthenia Gravis, cladribine or a pharmaceutically acceptable salt thereof or a composition comprising cladribine or a pharmaceutically acceptable salt thereof for its use for the treatment of Myasthenia Gravis comprising the oral administration of cladribine or a pharmaceutically acceptable salt thereof, wherein it is to be administered according to a dosing regimen comprising or consisting of the following steps:

- (1) an initial dosing regimen consisting of two treatment courses, said treatment courses being separated by about a month or, preferably, about 4 weeks, wherein the total administered dose of cladribine or a pharmaceutically acceptable salt thereof administered during said initial dosing regimen is of about 52.5 mg, and wherein about 35 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 17.5 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the second treatment course; preferably, the about 35 mg of cladribine or pharmaceutically acceptable salt thereof administered during the first treatment course is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one and on day two of the first treatment course, and the about 17.5 mg of cladribine or pharmaceutically acceptable salt thereof administered during the second treatment course is administered in the form of a dosage form

comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered on day one of the second treatment course;

- (2) optionally, one or more retreatment steps in which a supplemental dose is administered, preferably administered no earlier than about 6 months and earlier than about one year, preferably no earlier than about 24 weeks and earlier than about 48 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period;
- (3) optionally, one or more retreatment steps in which a full dose is administered according to the initial dosing regimen of step (1), wherein the first dose of such retreatment step is administered at least about one year, preferably at least about 48 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, if in this last treatment period a full dose was administered, or at least about six months, preferably at least about 24 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, if in this last treatment period a supplemental dose was administered.

In a preferred embodiment, the invention pertains to a method of treating Myasthenia Gravis, preferably generalized Myasthenia Gravis, the use of cladribine or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of Myasthenia Gravis, cladribine or a pharmaceutically acceptable salt thereof or a composition comprising cladribine or a pharmaceutically acceptable salt thereof for its use for the treatment of Myasthenia Gravis comprising the oral administration of cladribine or a pharmaceutically acceptable salt thereof, wherein it is to be administered according to a dosing regimen comprising or consisting of the following steps:

- (1) an initial dosing regimen consisting of two treatment courses, said treatment courses being separated by about a month or, preferably, about 4 weeks, wherein the total administered dose of cladribine or a pharmaceutically acceptable salt thereof administered during said initial dosing regimen is of about 52.5 mg, and wherein about 35 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 17.5 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the second treatment course; preferably, the about 35 mg of cladribine or pharmaceutically acceptable salt thereof administered during the first treatment course is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one and on day two of the first treatment course, and the about 17.5 mg of cladribine or pharmaceutically acceptable salt thereof administered

during the second treatment course is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered on day one of the second treatment course;

- (2) optionally, one or more retreatment steps in which a supplemental dose is administered, preferably administered no earlier than about 6 months and earlier than about one year, preferably no earlier than about 24 weeks and earlier than about 48 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period;
- (3) optionally, one or more retreatment steps in which a full dose is administered according to the initial dosing regimen of step (1), wherein the first dose of such retreatment step is administered at least about one year, preferably at least about 48 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, if in this last treatment period a full dose was administered, or at least about six months, preferably at least about 24 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, if in this last treatment period a supplemental dose was administered.

In a preferred embodiment, the invention pertains to a method of treating Myasthenia Gravis, preferably generalized Myasthenia Gravis, the use of cladribine or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of Myasthenia Gravis, cladribine or a pharmaceutically acceptable salt thereof or a composition comprising cladribine or a pharmaceutically acceptable salt thereof for its use for the treatment of Myasthenia Gravis comprising the oral administration of cladribine or a pharmaceutically acceptable salt thereof, wherein it is to be administered according to a dosing regimen comprising or consisting of the following steps:

- (1) an initial dosing regimen consisting of two treatment courses, said treatment courses being separated by about a month or, preferably, about 4 weeks, wherein the total administered dose of cladribine or a pharmaceutically acceptable salt thereof administered during said initial dosing regimen is of about 105 mg, and wherein about 52.5 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 52.5 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the second treatment course; preferably, the about 52.5 mg of cladribine or pharmaceutically acceptable salt thereof administered during the first treatment course is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one, day two and day three of the first treatment

course, and the about 52.5 mg of cladribine or pharmaceutically acceptable salt thereof administered during the second treatment course is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one, day two and day three of the second treatment course;

- (2) optionally, one or more retreatment steps in which a supplemental dose is administered, preferably administered no earlier than about 6 months and earlier than about one year, preferably no earlier than about 24 weeks and earlier than about 48 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period;
- (3) optionally, one or more retreatment steps in which a full dose is administered according to the initial dosing regimen of step (1), wherein the first dose of such retreatment step is administered at least about one year, preferably at least about 48 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, if in this last treatment period a full dose was administered, or at least about six months, preferably at least about 24 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, if in this last treatment period a supplemental dose was administered.

In a preferred embodiment, the invention pertains to a method of treating Myasthenia Gravis, preferably generalized Myasthenia Gravis, the use of cladribine or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of Myasthenia Gravis, cladribine or a pharmaceutically acceptable salt thereof or a composition comprising cladribine or a pharmaceutically acceptable salt thereof for its use for the treatment of Myasthenia Gravis comprising the oral administration of cladribine or a pharmaceutically acceptable salt thereof, wherein it is to be administered according to a dosing regimen comprising or consisting of the following steps:

- (1) an initial dosing regimen consisting of two treatment courses, said treatment courses being separated by about a month or, preferably, about 4 weeks, wherein the total administered dose of cladribine or a pharmaceutically acceptable salt thereof administered during said initial dosing regimen is of about 105 mg, and wherein about 52.5 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the first treatment course, and about 52.5 mg of cladribine or pharmaceutically acceptable salt thereof is administered during the second treatment course; preferably, the about 52.5 mg of cladribine or pharmaceutically acceptable salt thereof administered during the first treatment course is administered in the form of a dosage

form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one, day two and day three of the first treatment course, and the about 52.5 mg of cladribine or pharmaceutically acceptable salt thereof administered during the second treatment course is administered in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof administered daily on day one, day two and day three of the second treatment course;

- (2) optionally, one or more retreatment steps in which a supplemental dose is administered, preferably administered no earlier than about 6 months and earlier than about one year, preferably no earlier than about 24 weeks and earlier than about 48 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period;
- (3) optionally, one or more retreatment steps in which a full dose is administered according to the initial dosing regimen of step (1), wherein the first dose of such retreatment step is administered at least about one year, preferably at least about 48 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, if in this last treatment period a full dose was administered, or at least about six months, preferably at least about 24 weeks after the first administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, if in this last treatment period a supplemental dose was administered.

In some embodiments of any of the above embodiments referring to the dosing regimen comprising or consisting of steps (1) to (3), step (2) or step (3) or both steps (2) and (3) are done, i.e. one or both of the steps are not optional. In some embodiments of any of the above embodiments referring to the dosing regimen comprising or consisting of steps (1) to (3), the steps (2) and (3) are done if clinically justified.

Preferably, in these preferred embodiments, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-AChR antibody positive. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-MuSK antibody positive or seronegative. Preferably, in this embodiment, the patient in need thereof is a human subject who has been diagnosed with gMG and who is anti-LRP4 antibody positive or seronegative.

Preferably, in the method of treating Myasthenia Gravis, use of cladribine or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of Myasthenia Gravis, cladribine or a pharmaceutically acceptable salt thereof or a composition comprising cladribine or a pharmaceutically acceptable salt thereof for its use for the treatment of

Myasthenia Gravis comprising the oral administration of cladribine or a pharmaceutically acceptable salt thereof, the maximum dose of cladribine or a pharmaceutically acceptable salt thereof administered daily is of about 17.5 mg or about 35 mg.

FURTHER EMBODIMENTS

It has been found that cladribine, or a pharmaceutically acceptable salt thereof, may be an ideal candidate for a treatment of myasthenia gravis, preferably generalized myasthenia gravis, having therapeutic advantages, such as one or more of the following:

- i) it is useful for the treatment of myasthenia gravis, preferably generalized myasthenia gravis, as a disease-modifying therapy;
- ii) it is useful for the treatment of myasthenia gravis, preferably generalized myasthenia gravis, as a steroid-sparing agent;
- iii) it has clinical benefits for myasthenia gravis patients, preferably generalized myasthenia gravis patients, by targeting B and T cell-mediated autoimmunity with a pharmacodynamic effect that lasts for long periods (e.g. it allows extended treatment-free periods where MG patients do not require intervention);
- iv) it reduces the impact, of the severity of symptoms of MG, on activities of daily living, for example, compared to placebo or to baseline, for example, as assessed by using standard scales, such as patient outcome scales, for example the MG-ADL scale;
- v) it reduces the impact of muscle weakness to effort associated with MG, for example, compared to placebo or to baseline, for example, as assessed by using standard scales, for example the QMG scale or the MGC scale;
- vi) it improves the health related quality of life, for example compared to placebo or to baseline, for example as assessed by using standard scales, for example the MG-QoL15 scale or the EQ-5D-5L scale;
- vii) it has a favorable therapeutic profile, such as a favorable safety profile or favorable benefit to risk profile.

Further embodiments of the present invention are described herein below:

(A) Embodiments:

Embodiment 1a: Cladribine, or a pharmaceutically acceptable salt thereof, for use in a treatment of myasthenia gravis, preferably generalized myasthenia gravis.

Embodiment 2a: Cladribine, or a pharmaceutically acceptable salt thereof, for use in a treatment of myasthenia gravis, preferably generalized myasthenia gravis, as a disease-modifying therapy.

Embodiment 3a: Cladribine, or a pharmaceutically acceptable salt thereof, for use in a treatment of myasthenia gravis as a steroid-sparing agent.

Embodiment 4a: Cladribine, or a pharmaceutically acceptable salt thereof, for use in a treatment for the reduction (e.g. compared to baseline or placebo) of the impact of the severity of symptoms of MG on activities of daily living [e.g. as assessed by using standard scales, such as a patient reported scale (e.g. the MG-ADL scale)].

Embodiment 5a: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to embodiment 4a, wherein activities of daily living comprise one or more selected from the group consisting of talking, chewing, swallowing, breathing, brushing teeth, combing hair, and ability to arise from a chair.

Embodiment 6a: Cladribine, or a pharmaceutically acceptable salt thereof, for use in a treatment for the reduction (e.g. compared to baseline or placebo) of the impact of muscle weakness to effort associated with MG [e.g. as assessed by using standard scales (e.g. the QMG scale or the MGC scale)].

Embodiment 7a: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to embodiment 6a, wherein muscle weakness to effort associated with MG comprises movement of body parts [e.g. ocular muscles (e.g. ptosis, double vision), bulbar muscles (e.g. swallowing 4 oz water, speech after counting aloud from 1 to 50) or limb movement (e.g. right arm outstretched, left arm outstretched, right hand grip, left hand grip, right leg outstretched, left leg outstretched), or facial muscles], [for example as assessed by using standard scales (e.g. a clinical scale, for example the QMG scale)].

Embodiment 8a: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to embodiment 6a, wherein muscle weakness to effort associated with MG comprises one or more selected from the group consisting of ptosis, double vision, neck flexion, neck extension,

shoulder abduction and hip flexion [for example as assessed by using standard scales (e.g. the MGC scale)].

Embodiment 9a: Cladribine, or a pharmaceutically acceptable salt thereof, for use in a treatment for the improvement (e.g. compared to baseline or placebo) of the health related quality of life of a MG patient [for example as assessed by using standard scales (e.g. a patient reported scale, for example the MG-QoL15r scale or the EQ-5D-5L)].

Embodiment 10a: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to embodiment 9a, wherein the health related quality of life of an MG patient comprises one or more selected from the group consisting of psychological function associated with MG, wellbeing associated with MG and social life function associated with MG [for example as assessed by using standard scales (e.g. a patient reported scale, for example the MG-QoL15r scale)].

Embodiment 11a: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to embodiment 9a, wherein the improvement (e.g. compared to baseline or placebo) of the health related quality of life of an MG patient comprises the improvement (e.g. as compared to baseline or placebo) of one or more selected from the group consisting of mobility, self-care, usual activities (e.g. work, study, housework, family or leisure activities), pain, discomfort, anxiety and depression [for example as assessed by using standard scales (e.g. a patient reported scale, for example the EQ-5D-5L scale)].

Embodiment 12a: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1a to 11a, wherein myasthenia gravis is anti-acetylcholine receptor antibody-positive myasthenia gravis.

Embodiment 13a: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1a to 11a, wherein myasthenia gravis is anti-MuSK antibody-positive myasthenia gravis.

Embodiment 14a: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1a to 11a, wherein myasthenia gravis is anti-acetylcholine receptor antibody-positive and anti-MuSK antibody-positive myasthenia gravis.

Embodiment 15a: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1a to 11a, wherein myasthenia gravis is anti-LRP4 antibody-positive myasthenia gravis.

Embodiment 16a: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1a to 11a, wherein myasthenia gravis is anti-acetylcholine receptor antibody-negative.

Embodiment 17a: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1a to 11a, wherein myasthenia gravis is anti-MuSK antibody-negative.

Embodiment 18a: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1a to 11a, wherein myasthenia gravis is anti-acetylcholine receptor antibody-negative and anti-MuSK antibody-negative.

Embodiment 19a: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1a to 11a, wherein myasthenia gravis is anti-acetylcholine receptor antibody-negative and anti-MuSK antibody-negative.

Embodiment 20a: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1a to 11a, wherein myasthenia gravis is anti-LRP4 antibody-negative myasthenia gravis.

Embodiment 21a: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1a to 11a, wherein myasthenia gravis is seronegative myasthenia gravis (i.e. anti-acetylcholine receptor antibody-negative, anti-MuSK antibody-negative and anti-LRP4 antibody-negative).

Embodiment 22a: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1a to 21a, wherein myasthenia gravis is generalized myasthenia gravis.

Embodiment 23a: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1a to 21a, wherein myasthenia gravis is refractory myasthenia gravis.

Embodiment 24a: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1a to 21a, wherein myasthenia gravis is refractory generalized myasthenia gravis.

Embodiment 25a: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1a to 24a, wherein cladribine, or the pharmaceutically acceptable salt thereof, is provided as a solid dosage form (e.g. a capsule comprising minitables).

Embodiment 26a: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any of embodiments 1a to 25a, wherein the use of cladribine, or a pharmaceutically acceptable salt thereof, is concomitant with corticosteroid or AChE inhibitor treatment.

Embodiment 27a: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1a to 26a, wherein cladribine is in non-salt form (i.e. the free form).

Embodiment 28a: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1a to 27a, wherein cladribine, or the pharmaceutically acceptable salt thereof, is administered according to the dosing regimen of any one of embodiments 1c to 12c hereinbelow.

(B) Embodiments:

Embodiment 1b: A method of treatment of myasthenia gravis, preferably generalized myasthenia gravis, in a subject, in need thereof, comprising administering to said subject an effective amount of cladribine or a pharmaceutically acceptable salt thereof.

Embodiment 2b: A method of treatment of myasthenia gravis, preferably generalized myasthenia gravis, in a subject, in need thereof, comprising administering to said subject an effective amount of cladribine, or a pharmaceutically acceptable salt thereof, as a disease-modifying therapy.

Embodiment 3b: A method of treatment of myasthenia gravis, preferably generalized myasthenia gravis, in a subject, in need thereof, comprising administering to said subject an effective amount of cladribine, or a pharmaceutically acceptable salt thereof, as a steroid-sparing agent.

Embodiment 4b: A method of treatment for the reduction (e.g. compared to baseline or placebo) of the impact of the severity of symptoms of MG on activities of daily living [e.g. as assessed by using standard scales, such as a patient reported scale (e.g. the MG-ADL scale)], in a subject, in need thereof, comprising administering to said subject an effective amount of cladribine or a pharmaceutically acceptable salt thereof.

Embodiment 5b: The method according to embodiment 4b, wherein activities of daily living comprise one or more selected from the group consisting of talking, chewing, swallowing, breathing, brushing teeth, combing hair, and ability to arise from a chair.

Embodiment 6b: A method of treatment for the reduction (e.g. compared to baseline or placebo) of the impact of muscle weakness to effort associated with MG [e.g. as assessed by using

standard scales (e.g. the QMG scale or the MGC scale)], in a subject, in need thereof, comprising administering to said subject an effective amount of cladribine or a pharmaceutically acceptable salt thereof.

Embodiment 7b: The method according to embodiment 6b, wherein muscle weakness to effort associated with MG comprises movement of body parts [e.g. ocular muscles (e.g. ptosis, double vision), bulbar muscles (e.g. swallowing 4 oz water, speech after counting aloud from 1 to 50) or limb movement (e.g. right arm outstretched, left arm outstretched, right hand grip, left hand grip, right leg outstretched, left leg outstretched), or facial muscles], [for example as assessed by using standard scales (e.g. a clinical scale, for example the QMG scale)].

Embodiment 8b: The method according to embodiment 6b, wherein muscle weakness to effort associated with MG comprises one or more selected from the group consisting of ptosis, double vision, neck flexion, neck extension, shoulder abduction and hip flexion [for example as assessed by using standard scales (e.g. for example the MGC scale)].

Embodiment 9b: A method of treatment for the improvement (e.g. compared to baseline or placebo) of the health related quality of life of a MG patient [for example as assessed by using standard scales (e.g. a patient reported scale, for example the MG-QoL15r scale or the EQ-5D-5L)], in a subject, in need thereof, comprising administering to said subject an effective amount of cladribine or a pharmaceutically acceptable salt thereof.

Embodiment 10b: The method according to embodiment 9b, wherein the health related quality of life of an MG patient comprises one or more selected from the group consisting of psychological function associated with MG, wellbeing associated with MG and social life function associated with MG [for example as assessed by using standard scales (e.g. a patient reported scale, for example the MG-QoL15r scale)].

Embodiment 11b: The method according to embodiment 9b, wherein the improvement (e.g. compared to baseline or placebo) of the health related quality of life of an MG patient comprises the improvement (e.g. as compared to baseline or placebo) of one or more selected from the group consisting of mobility, self-care, usual activities (e.g. work, study, housework, family or leisure activities), pain, discomfort, anxiety and depression [for example as assessed by using standard scales (e.g. a patient reported scale, for example the EQ-5D-5L scale)].

Embodiment 12b: The method according to any one of embodiments 1b to 11b, wherein myasthenia gravis is anti-acetylcholine receptor antibody-positive myasthenia gravis.

Embodiment 13b: The method according to any one of embodiments 1b to 11b, wherein myasthenia gravis is anti-MuSK antibody-positive myasthenia gravis.

Embodiment 14b: The method according to any one of embodiments 1b to 11b, wherein myasthenia gravis is anti-acetylcholine receptor antibody-positive and anti-MuSK antibody-positive myasthenia gravis.

Embodiment 15b: The method according to any one of embodiments 1b to 11b, wherein myasthenia gravis is anti-LRP4 antibody-positive myasthenia gravis.

Embodiment 16b: The method according to any one of embodiments 1b to 11b, wherein myasthenia gravis is anti-acetylcholine receptor antibody-negative.

Embodiment 17b: The method according to any one of embodiments 1b to 11b, wherein myasthenia gravis is anti-MuSK antibody-negative.

Embodiment 18b: The method according to any one of embodiments 1b to 11b, wherein myasthenia gravis is anti-acetylcholine receptor antibody-negative and anti-MuSK antibody-negative.

Embodiment 19b: The method according to any one of embodiments 1b to 11b, wherein myasthenia gravis is anti-acetylcholine receptor antibody-negative and anti-MuSK antibody-negative.

Embodiment 20b: The method according to any one of embodiments 1b to 11b, wherein myasthenia gravis is anti-LRP4 antibody-negative myasthenia gravis.

Embodiment 21b: The method according to any one of embodiments 1b to 11b, wherein myasthenia gravis is seronegative myasthenia gravis (i.e. anti-acetylcholine receptor antibody-negative, anti-MuSK antibody-negative and anti-LRP4 antibody-negative).

Embodiment 22b: The method according to any one of embodiments 1b to 21b, wherein myasthenia gravis is generalized myasthenia gravis.

Embodiment 23b: The method according to any one of embodiments 1b to 21b, wherein myasthenia gravis is refractory myasthenia gravis.

Embodiment 24b: The method according to any one of embodiments 1b to 21b, wherein myasthenia gravis is refractory generalized myasthenia gravis.

Embodiment 25b: The method according to any one of embodiments 1b to 24b, wherein cladribine, or the pharmaceutically acceptable salt thereof, is provided as a solid dosage form (e.g. a capsule comprising minitablets).

Embodiment 26b: The method according to any one of embodiments 1b to 25b, wherein administration of cladribine, or a pharmaceutically acceptable salt thereof, is concomitant with corticosteroid or AChE inhibitor treatment.

Embodiment 27b: The method according to any one of embodiments 1b to 26b, wherein cladribine is in non-salt form (i.e. the free form).

Embodiment 28b: The method according to any one of embodiments 1b to 27b, wherein cladribine, or the pharmaceutically acceptable salt thereof, is administered according to the dosing regimen of any one of embodiments 1c to 12c hereinbelow.

(C) Embodiments:

Embodiment 1c: Cladribine, or a pharmaceutically acceptable salt thereof, for use in the treatment of Myasthenia Gravis, wherein cladribine, or a pharmaceutically acceptable salt thereof is to be administered orally according to an initial dosing regimen comprising two treatment courses, separated by about 4 weeks, wherein the total dose of cladribine, or a pharmaceutically acceptable salt thereof, administered under said initial dosing regimen is from about 35 mg to about 210 mg.

Embodiment 2c: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to embodiment 1c, wherein the total dose of cladribine, or a pharmaceutically acceptable salt thereof, administered under said initial dosing regimen is of about 35 mg, of about 52.5 mg, of about 70 mg, of about 87.5 mg, of about 105 mg, of about 122.5 mg, of about 140 mg, of about 157.5 mg, of about 175 mg, of about 192.5 mg or of about 210 mg.

Embodiment 3c: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to embodiments 1c or 2c, wherein the total dose of cladribine, or a pharmaceutically acceptable salt thereof, administered under said initial dosing regimen is of about 52.5 mg, and wherein about 35 mg of cladribine, or a pharmaceutically acceptable salt thereof, is administered during the first treatment course of the initial dosing regimen, and about 17.5 mg of cladribine, or a pharmaceutically acceptable salt thereof, is administered during the second treatment course of the initial dosing regimen.

Embodiment 4c: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to embodiment 3c, wherein, during the first treatment course of the initial dosing regimen, cladribine, or a pharmaceutically acceptable salt thereof, is administered on each of day one and two of the first treatment course in the form of a dosage form comprising about 17.5 mg

of cladribine, or a pharmaceutically acceptable salt thereof, and, during the second treatment course of the initial dosing regimen, cladribine, or a pharmaceutically acceptable salt thereof, is only administered on day one of the second treatment course in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof.

Embodiment 5c: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to embodiments 1c or 2c, wherein the total dose of cladribine, or a pharmaceutically acceptable salt thereof, administered under said initial dosing regimen is of about 105 mg, and wherein about 52.5 mg of cladribine, or a pharmaceutically acceptable salt thereof, is administered during the first treatment course of the initial dosing regimen, and about 52.5 mg of cladribine, or a pharmaceutically acceptable salt thereof, is administered during the second treatment course of the initial dosing regimen.

Embodiment 6c: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to embodiment 5c, wherein, during the first treatment course of the initial dosing regimen, cladribine, or a pharmaceutically acceptable salt thereof, is administered on each of day one, two and three of the first treatment course in the form of a dosage form comprising about 17.5 mg of cladribine, or a pharmaceutically acceptable salt thereof, and, during the second treatment course of the initial dosing regimen, cladribine, or a pharmaceutically acceptable salt thereof, is administered on each of day one, two and three of the second treatment course in the form of a dosage form comprising 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof.

Embodiment 7c: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any of the previous embodiments, wherein the use comprises a period of at least about 6 months, preferably of at least about 12 months, more preferably of at least about 24 months, after the last administration of cladribine, or a pharmaceutically acceptable salt thereof, during the second treatment course of the initial dosing regimen, where no cladribine, or a pharmaceutically acceptable salt thereof, is administered.

Embodiment 8c: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any of the previous embodiments, wherein the use further comprises after the initial dosing regimen a retreatment step wherein a supplemental dose of cladribine, or a pharmaceutically acceptable salt thereof, from about 17.5 mg to about 35 mg is administered.

Embodiment 9c: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to embodiment 8c, wherein the supplemental dose is administered no earlier than about 24 weeks and earlier than about 48 weeks after the last administration of cladribine, or a pharmaceutically acceptable salt thereof, during the last treatment period.

Embodiment 10c: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any of the previous embodiments, wherein the use further comprises after the initial dosing regimen a step of retreatment, wherein the total administered dose of cladribine, or a pharmaceutically acceptable salt thereof, administered during said retreatment equals the total administered dose of cladribine, or a pharmaceutically acceptable salt thereof, administered during the two treatment courses of the initial dosing regimen.

Embodiment 11c: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to embodiment 10c, wherein the retreatment consists of two treatment courses, said treatment courses being separated by about 4 weeks.

Embodiment 12c: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any of the previous embodiments,

wherein the initial dosing regimen consists of the two treatment courses, and

wherein the use further comprises, if clinically justified, one or more retreatment steps in which a dose of about 17.5 mg to about 35 mg of cladribine, or a pharmaceutically acceptable salt thereof, is administered no earlier than about 24 weeks and earlier than about 48 weeks after the first or last administration of cladribine, or a pharmaceutically acceptable salt thereof, during the last treatment period, and, if clinically justified, one or more retreatment steps in which the same total dose of cladribine, or a pharmaceutically acceptable salt thereof, as under the initial dosing regimen is administered at least about 48 weeks after the first or last administration of cladribine, or a pharmaceutically acceptable salt thereof, during the last treatment period, if in this last treatment period the same total dose of cladribine, or a pharmaceutically acceptable salt thereof, as under the initial dosing regimen was administered, or at least about 24 weeks after the first or last administration of cladribine, or a pharmaceutically acceptable salt thereof, during the last treatment period, if in this last treatment period a dose of about 17.5 mg to about 35 mg of cladribine, or a pharmaceutically acceptable salt thereof, was administered.

Embodiment 13c: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any of the previous embodiments, wherein cladribine, or the pharmaceutically acceptable salt thereof, is provided as a solid dosage form (e.g. a capsule comprising minitablets).

Embodiment 14c: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any of the previous embodiments, wherein myasthenia gravis is selected from the group consisting of anti-acetylcholine receptor antibody-positive myasthenia gravis, anti-MuSK antibody-positive myasthenia gravis, anti-acetylcholine receptor antibody-positive and anti-

MuSK antibody-positive myasthenia gravis, anti-LRP4 antibody-positive myasthenia gravis or seronegative myasthenia gravis.

Embodiment 15c: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any of the previous embodiments, wherein myasthenia gravis is selected from the group consisting of anti-acetylcholine receptor antibody-negative myasthenia gravis, anti-MuSK antibody-negative myasthenia gravis, anti-acetylcholine receptor antibody-negative and anti-MuSK antibody-negative myasthenia gravis, anti-LRP4 antibody-negative myasthenia gravis.

Embodiment 16c: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any of the previous embodiments, wherein myasthenia gravis is generalized myasthenia gravis.

Embodiment 17c: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any of the previous embodiments, wherein myasthenia gravis is refractory myasthenia gravis (e.g. refractory generalized myasthenia gravis).

Embodiment 18c: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any of the previous embodiments, wherein the use of cladribine, or a pharmaceutically acceptable salt thereof, is concomitant with corticosteroid or AChE inhibitor treatment.

Embodiment 19c: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any of the previous embodiments, wherein cladribine is in non-salt form (i.e. the free form).

(D) Embodiments:

Embodiment 1d: Cladribine, or a pharmaceutically acceptable salt thereof, for use in a treatment of myasthenia gravis, preferably gMG, by reconstituting the immune system to restore immune homeostasis by the repopulation of immune cells that are anti-inflammatory.

Embodiment 2d: Cladribine, or a pharmaceutically acceptable salt thereof, for use in a treatment of myasthenia gravis, preferably gMG, by modifying the immune pathology of myasthenia gravis at the level of immune cells that contribute in T/B cell interaction to drive plasmacell development.

Embodiment 3d: Cladribine, or a pharmaceutically acceptable salt thereof, for use in a treatment of myasthenia gravis, preferably gMG, by modifying the immune pathology of myasthenia gravis at the level of immune cells which are directly involved in the production of autoantibodies.

Embodiment 4d: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any of embodiments 1d to 3d, wherein myasthenia gravis is selected from the group

consisting of anti-acetylcholine receptor antibody-positive myasthenia gravis, anti-MuSK antibody-positive myasthenia gravis, anti-acetylcholine receptor antibody-positive and anti-MuSK antibody-positive myasthenia gravis, anti-LRP4 antibody-positive myasthenia gravis or seronegative myasthenia gravis.

Embodiment 5d: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any of embodiments 1d to 4d, wherein myasthenia gravis is generalized myasthenia gravis.

Embodiment 6d: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any of embodiments 1d to 4d, wherein myasthenia gravis is refractory myasthenia gravis (e.g. refractory generalized myasthenia gravis).

Embodiment 7d: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1d to 6d, wherein cladribine, or the pharmaceutically acceptable salt thereof, is administered according to the dosing regimen of any one of embodiments 1c to 12c hereinabove.

Embodiment 8d: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any of embodiments 1d to 7d, wherein cladribine is in non-salt form (i.e. the free form).

Embodiment 9d: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1d to 7d, wherein cladribine, or the pharmaceutically acceptable salt thereof, is administered according to the dosing regimen of any one of embodiments 1c to 12c hereinbelow.

(E) Embodiments:

Embodiment 1e : A solid pharmaceutical composition comprising:

- cladribine, or a pharmaceutical acceptable salt thereof; and
- at least two different fillers [i.e. a filler (e.g. a first filler), another filler (i.e. a different filler; e.g. a second filler) and optionally at least a further (i.e. one or more) filler (e.g. a third filler or a third filler and a forth filler)];

wherein at least one of said at least two different fillers (e.g. the first filler) is a sugar alcohol (e.g. mannitol (e.g. D-mannitol), xylitol or sorbitol; for example mannitol).

Embodiment 2e: A solid pharmaceutical composition according to embodiment 1e comprising:

- cladribine, or a pharmaceutical acceptable salt thereof; and

- at least two different fillers [i.e. a filler (e.g. a first filler), another filler (i.e. a different filler; e.g. a second filler) and optionally at least a further (i.e. one or more) filler (e.g. a third filler or a third filler and a forth filler)];

wherein,

at least one of said at least two different fillers is a sugar alcohol [e.g. the first filler (e.g. mannitol, xylitol and sorbitol; for example mannitol)]; and

at least one of said at least two different fillers [e.g. the second filler; i.e. a filler other than the sugar alcohol] is a cellulose derivative.

Embodiment 3e: The composition according to embodiment 1e or 2e, wherein the at least two different fillers comprise said two different fillers and at least a further filler (i.e. one or more filler; e.g. a third filler or a third filler and a forth filler).

Embodiment 4e: The composition according to any of embodiments 1e to 3e, wherein the at least two different fillers comprise said two different fillers and a further filler, wherein said further filler is a different sugar alcohol (i.e. a sugar alcohol different from that of the first filler).

Embodiment 5e: The composition according to any one of embodiments 1e to 3e, wherein the at least two different fillers comprise said two different fillers and a further filler, wherein said further filler is a sugar.

Embodiment 6e: The composition according to any one of embodiments 1e to 3e, wherein the at least two different fillers comprise said two different fillers and two or more further fillers are selected from the group consisting of a (different) sugar alcohol (i.e. a sugar alcohol different from that of the first filler), a sugar or a mixture thereof.

Embodiment 7e: The composition according to any one of embodiments 2e to 6e, wherein the cellulose derivative is selected from the group consisting of microcrystalline cellulose (e.g. Avicel®) and cellulose; for example microcrystalline cellulose.

Embodiment 8e: The composition according to any one of embodiments 1e to 7e, wherein the sugar alcohol is selected from the group consisting of mannitol (e.g. D-mannitol), xylitol, and sorbitol; for example mannitol.

Embodiment 9e: The composition according to any one of embodiments 5e to 8e, wherein the sugar is selected from the group consisting of lactose, sucrose, maltose and fructose.

Embodiment 10e: The composition according to any one of embodiments 1e to 9e, further comprising one or more (e.g. 2, 3, 4, 5 or 6) pharmaceutical excipients, for example selected from the group consisting of a glidant, a lubricant and a disintegrant.

Embodiment 11e: The composition according to any one of embodiments 1e to 10e, further comprising a glidant.

Embodiment 12e: The composition according to embodiment 11e, wherein the glidant is selected from the group consisting of magnesium oxide and colloidal silicon dioxide; for example colloidal silicon dioxide.

Embodiment 13e: The composition according to any one of embodiments 1e to 12e, further comprising a lubricant.

Embodiment 14e: The composition according to embodiment 13e, wherein the lubricant is selected from the group consisting of talc, sodium stearyl fumarate, stearic acid and salts thereof (e.g. magnesium stearate, calcium stearate); for example magnesium stearate.

Embodiment 15e: The composition according to any one of embodiments 1e to 14e, further comprising a disintegrant.

Embodiment 16e: The composition according to embodiment 15e, wherein the disintegrant is selected from the group consisting of croscarmellose sodium, sodium starch glycolate, crospovidone, starch and low-substituted hydroxypropyl cellulose; for example croscarmellose sodium.

Embodiment 17e: The composition according to any of the preceding embodiments, wherein the ratio as calculated based on % w/w of said at least two different fillers [i.e. the ratio of % w/w of one of said at least two different fillers (i.e. % weight of one of said at least two different fillers with respect to the total weight of the pharmaceutical composition, e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab) to % w/w of the other one of said at least two different fillers (% weight of other one of said at least two different fillers with respect to the total weight of the pharmaceutical composition, e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab)] is between about 1 (e.g. of sugar alcohol) : 3 [e.g. of the filler other than the sugar alcohol (i.e. second filler; e.g. cellulose derivative)] to about 1 (e.g. of sugar alcohol) : 2 [e.g. of filler other than the sugar alcohol (i.e. second filler; e.g. cellulose derivative)]; preferably about 1 (e.g. of sugar alcohol) : 2 [e.g. of filler other than the sugar alcohol (i.e. second filler; e.g. cellulose derivative)].

Embodiment 18e: The composition according to any of the preceding embodiments, wherein the ratio of the at least two different fillers selected from a sugar alcohol and a cellulose derivative is between about 1 (of sugar alcohol) : 3 (of cellulose derivative) to about 1 (of sugar alcohol) : 2 (of cellulose derivative); preferably about 1 (of sugar alcohol) : 2 (cellulose derivative), wherein the ratio is calculated based on % w/w [i.e. percentage weight with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab)].

Embodiment 19e: The composition according to any of the preceding embodiments, wherein the ratio of the at least two different fillers selected from a sugar alcohol and a cellulose derivative is between about 1 (of sugar alcohol) : 3 (of cellulose derivative) to about 1 (of sugar alcohol) : 2 (of cellulose derivative); preferably about 1 (of sugar alcohol) : 2 (cellulose derivative), wherein the ratio is calculated based on % w/w with respect to the total weight of an uncoated minitab.

Embodiment 20e: The composition according to any of the preceding embodiments, wherein the ratio of the at least two different fillers selected from a sugar alcohol (i.e. first filler) and a filler other than a sugar alcohol (i.e. second filler; e.g. cellulose derivative) is about 1 (of sugar alcohol) : 3 [of the filler other than the sugar alcohol (i.e. second filler; e.g. cellulose derivative)], wherein the ratio is calculated based on % w/w [i.e. percentage weight with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab)].

Embodiment 21e: The composition according to any of the preceding embodiments, wherein the ratio of the at least two different fillers selected from a sugar alcohol and a cellulose derivative is about 1 (of sugar alcohol) : 3 (of cellulose derivative), wherein the ratio is calculated based on % w/w [i.e. percentage weight with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab)].

Embodiment 22e: The composition according to any of the preceding embodiments, wherein the ratio of the at least two different fillers selected from a sugar alcohol and a cellulose derivative is about 1 (of sugar alcohol) : 3 (of cellulose derivative), wherein the ratio is calculated based on % w/w with respect to the total weight of an uncoated minitab.

Embodiment 23e: The composition according to any of embodiments 1e to 19e, wherein the ratio of the at least two different fillers selected from a sugar alcohol (i.e. first filler) and a filler

other than a sugar alcohol (i.e. second filler; e.g. cellulose derivative) is about 1 (of sugar alcohol) : 2 [of the filler other than the sugar alcohol (i.e. second filler; e.g. cellulose derivative)], wherein the ratio is calculated based on % w/w [i.e. percentage weight with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab)].

Embodiment 24e: The composition according to any of embodiments 1e to 19e, wherein the ratio of the at least two different fillers selected from a sugar alcohol and a cellulose derivative is about 1 (of sugar alcohol) : 2 (of cellulose derivative), wherein the ratio is calculated based on % w/w [i.e. percentage weight with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab)].

Embodiment 25e: The composition according to of embodiments 1e to 19e, wherein the ratio of the at least two different fillers selected from a sugar alcohol and a cellulose derivative is about 1 (of sugar alcohol) : 2 (of cellulose derivative), wherein the ratio is calculated based on % w/w with respect to the total weight of an uncoated minitab.

Embodiment 26e: The composition according to any of the preceding embodiments, wherein the composition is in the form of a minitab.

Embodiment 27e: The composition of embodiment 26e, wherein the minitab is film-coated.

Embodiment 28e: The composition of embodiment 27e, wherein the minitab is film-coated with a composition comprising at least one film coating agent selected from the group consisting of cellulose ethers (e.g. hypromellose, hyprollose), vinyl derivatives (e.g. polyvinyl alcohol, polyvinyl alcohol-polyethylene glycol-graft-copolymer), methacrylate aminoester copolymer, ethylacrylate-methacrylate copolymer, polyethylene glycol, maltodextrin, polydextrose, isomalt, calcium carbonate, a sugar (e.g. saccharose or glucose), a sugar alcohol (e.g. sorbitol), wax and an alginate salt (e.g. sodium alginate).

Embodiment 29e: The composition according to any of embodiments 27e or 28e, wherein the film coated minitab is titanium dioxide free film-coated.

Embodiment 30e: The composition of embodiment 27e, wherein the minitab is enteric film-coated.

Embodiment 31e: The composition of embodiment 27e, wherein the minitab is film-coated with a composition comprising at least one film enteric-coating agent selected from the group

consisting of a polymethacrylate (e.g. methacrylic acid-ethyl acrylate copolymer), a cellulose ester (for example cellulose acetate phthalate, cellulose acetate trimellitate, cellulose acetate succinate, hydroxypropylmethylcellulose acetate succinate (HPMCAS), or hydroxypropyl methylcellulose phthalate), a polyvinyl derivative (for example polyvinyl acetate phthalate) and shellac.

Embodiment 32e: The composition of embodiments 30e or 31e, wherein the enteric film coated minitabket is titanium dioxide free enteric film-coated.

Embodiment 33e: The composition according to any of the preceding embodiments, wherein the composition is in the form of a capsule (e.g. a hard capsule) comprising one or more (e.g. 1 to 50, such as 8 or 32) minitabkets.

Embodiment 34e: The composition according to any of the preceding embodiments, wherein the composition is in the form of a capsule (e.g. a hard capsule) comprising one or more minitabkets, wherein the composition comprises cladribine, or a salt thereof, in an amount of from about 2 to about 20 mg/capsule.

Embodiment 35e: The composition according to any of the preceding embodiments, wherein the composition is in the form of a capsule (e.g. a hard capsule) comprising one or more minitabkets, wherein the composition comprises cladribine, or a salt thereof, in an amount of from about 4 to about 18 mg/capsule.

Embodiment 36e: The composition according to any of the preceding embodiments, wherein the composition is in the form of a capsule (e.g. a hard capsule) comprising one or more minitabkets, wherein the composition comprises cladribine, or a salt thereof, in an amount of from about 4 to about 17 mg/capsule.

Embodiment 37e: The composition according to any of the preceding embodiments, wherein the composition is in the form of a capsule (e.g. a hard capsule) comprising one or more minitabkets, wherein the composition comprises cladribine, or a salt thereof, in an amount of about 4.3 mg/capsule, such as 4.375 mg/capsule.

Embodiment 38e: The composition according to any of the preceding embodiments, wherein the composition is in the form of a capsule (e.g. a hard capsule) comprising one or more (e.g. 8) minitabkets, wherein the composition comprises cladribine, or a salt thereof, in an amount of about 4.375 mg/capsule.

Embodiment 39e: The composition according to any of embodiments 1e to 35e, wherein the composition is in the form of a capsule (e.g. a hard capsule) comprising one or more

minitabets, wherein the composition comprises cladribine, or a salt thereof, in an amount of about 17 or 18 mg/capsule, such as 17.5 mg/capsule.

Embodiment 40e: The composition according to any of the preceding embodiments, wherein the composition is in the form of a capsule (e.g. a hard capsule) comprising one or more (e.g. 32) minitabets, wherein the composition comprises cladribine, or a salt thereof, in an amount of about 17.5 mg/capsule.

Embodiment 41e: The composition according to any of the preceding embodiments, comprising of from about 50 to about 90% per weight of the at least two different fillers [e.g. % weight of the sugar alcohol plus % weight of the filler other than the sugar alcohol (i.e. second filler; e.g. cellulose derivative) and optionally a further (i.e. one or more) filler] with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitabets, such as an uncoated minitabets).

Embodiment 42e: The composition according to any of the preceding embodiments, comprising of from about 60 to about 90% per weight of the at least two different fillers [e.g. % weight of the sugar alcohol plus % weight of the filler other than the sugar alcohol (i.e. second filler; e.g. cellulose derivative) and optionally a further (i.e. one or more) filler] with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitabets, such as an uncoated minitabets).

Embodiment 43e: The composition according to any of the preceding embodiments, comprising of from about 70 to about 90% per weight of the at least two different fillers [e.g. % weight of the sugar alcohol plus % weight of the filler other than the sugar alcohol (i.e. second filler; e.g. cellulose derivative) and optionally a further (i.e. one or more) filler] with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitabets, such as an uncoated minitabets).

Embodiment 44e: The composition according to any of the preceding embodiments, comprising of from about 80 to about 90% per weight of the at least two different fillers [e.g. % weight of the sugar alcohol plus % weight of the filler other than the sugar alcohol (i.e. second filler; e.g. cellulose derivative) and optionally a further (i.e. one or more) filler] with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitabets, such as an uncoated minitabets).

Embodiment 45e: The composition according to any of the preceding embodiments, comprising of from about 80 to about 85% per weight of the at least two different fillers [e.g. % weight of the sugar alcohol plus % weight of the filler other than the sugar alcohol (i.e. second filler; e.g. cellulose derivative) and optionally a further (i.e. one or more) filler] with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab).

Embodiment 46e: The composition according to any of the preceding embodiments, comprising about 83% (e.g. 83.2%) per weight of the at least two different fillers [e.g. % weight of the sugar alcohol plus % weight of the filler other than the sugar alcohol (i.e. second filler; e.g. cellulose derivative) and optionally a further (i.e. one or more) filler] with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab).

Embodiment 47e: The composition according to any of the preceding embodiments, comprising of from about 50 to about 90% per weight of said at least two different fillers selected from a sugar alcohol and a cellulose derivative [i.e. % weight of the sugar alcohol plus % weight of cellulose derivative)] with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab).

Embodiment 48e: The composition according to any of the preceding embodiments, comprising of from about 60 to about 90% per weight of said at least two different fillers selected from a sugar alcohol and a cellulose derivative [i.e. % weight of the sugar alcohol plus % weight of cellulose derivative)] with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab).

Embodiment 49e: The composition according to any of the preceding embodiments, comprising of from about 70 to about 90% per weight of said at least two different fillers selected from a sugar alcohol and a cellulose derivative [i.e. % weight of the sugar alcohol plus % weight of the cellulose derivative)] with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab).

Embodiment 50e: The composition according to any of the preceding embodiments, comprising of from about 80 to about 90% per weight of said at least two different fillers

selected from a sugar alcohol [i.e. % weight of the sugar alcohol plus % weight of the cellulose derivative]] with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab).

Embodiment 51e: The composition according to any of the preceding embodiments, comprising of from about 80 to about 85% per weight of said at least two different fillers selected from a sugar alcohol and a cellulose derivative [i.e. % weight of the sugar alcohol plus % weight of the cellulose derivative]] with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab).

Embodiment 52e: The composition according to any of the preceding embodiments, comprising about 83% (e.g. 83.2%) per weight of said at least two different fillers selected from a sugar alcohol and a cellulose derivative [i.e. % weight of the sugar alcohol plus % weight of the cellulose derivative]] with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab).

Embodiment 53e: The composition according to any of the preceding embodiments, comprising of from about 20% to about 85% per weight of one of said at least two different fillers (e.g. of the first filler, i.e. of the sugar alcohol) with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab).

Embodiment 54e: The composition according to any of the preceding embodiments, comprising of from about 20% to about 40% per weight of one of said at least two different fillers (e.g. of the first filler, i.e. of the sugar alcohol) with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab).

Embodiment 55e: The composition according to any of the preceding embodiments, comprising of from about 25% to about 30% per weight of one of said at least two different fillers (e.g. of the first filler, i.e. of the sugar alcohol) with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab).

Embodiment 56e: The composition according to any of the preceding embodiments, comprising about 27% (e.g. 27.2%) per weight of one of said at least two different fillers (e.g.

of the first filler, i.e. of the sugar alcohol) with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab).

Embodiment 57e: The composition according to any of the preceding embodiments, comprising of from about 40% to about 85% per weight of one of said at least two different fillers [e.g. the filler other than the sugar alcohol (i.e. second filler; e.g. cellulose derivative)] with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab).

Embodiment 58e: The composition according to any of the preceding embodiments, comprising of from about 50% to about 60% per weight of one of the at least two different fillers [e.g. the filler other than the sugar alcohol (i.e. second filler; e.g. cellulose derivative)] with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab).

Embodiment 59e: The composition according to any of the preceding embodiments, comprising about 56% per weight of one of the at least two different fillers [e.g. the filler other than the sugar alcohol (i.e. second filler; e.g. cellulose derivative)] with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab).

Embodiment 60e: The composition according to any of the preceding embodiments, comprising of from about 0.5% to about 3% per weight of the glidant with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab), for example about 1% per weight of the glidant with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab).

Embodiment 61e: The composition according to any of the preceding embodiments, comprising of from about 0.5% to about 5% per weight of the lubricant with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab), for example about 3% per weight of the lubricant with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab).

Embodiment 62e: The composition according to any of the preceding embodiments, comprising of from about 0.5% to about 10% per weight of the disintegrant with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab), for example about 5% per weight of the disintegrant with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab).

Embodiment 63e: The composition according to any of the preceding embodiments, comprising of from about 3% to about 20% per weight of cladribine, or a pharmaceutical acceptable salt thereof, with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab).

Embodiment 64e: The composition according to any of the preceding embodiments, comprising of from about 5% to about 10% per weight of cladribine, or a pharmaceutical acceptable salt thereof, with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab).

Embodiment 65e: The composition according to any of the preceding embodiments, comprising of from about 6% to about 8% per weight of cladribine, or a pharmaceutical acceptable salt thereof, with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab).

Embodiment 66e: The composition according to any of the preceding embodiments, comprising about 7.8% per weight of cladribine, or a pharmaceutical acceptable salt thereof, with respect to the total weight of the pharmaceutical composition (e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab).

Embodiment 67e: The composition according to any of the preceding embodiments, wherein the sugar alcohol, for example mannitol (e.g. D-mannitol), has a particle size that is characterized by a Dv50 of from about 50 to about 200 μm , such as of about 100 to about 200 μm , for example of from about 100 to about 150 μm (e.g. as measured by laser diffraction).

Embodiment 68e: The composition according to any of the preceding embodiments, wherein cladribine, or a pharmaceutical acceptable salt thereof, is micronized.

Embodiment 69e: The composition according to embodiment 68e, wherein the micronized cladribine, or a pharmaceutical acceptable salt thereof, has a primary particle size that is characterized by a Dv90 of from about 2 μm to about 30 μm , for example of from about 2 μm to about 10 μm (e.g. as measured by laser diffraction).

Embodiment 70e: The composition according to any of the preceding embodiments, wherein cladribine is in its free form.

Embodiment 71e: The composition according to any of the preceding embodiments, wherein cladribine is in crystalline form, for example, cladribine is in crystalline anhydrous form (e.g. polymorph A1).

Embodiment 72e: The composition according to any of the preceding embodiments, which is:

- cyclodextrin free; or
- cyclodextrin free and sugar free,

wherein, when said composition is in the form of (i) a minitabket or (ii) a capsule comprising the minitabket, and said minitabket or capsule is film coated, the film coating optionally comprises a sugar.

Embodiment 73e: The composition according to any of the preceding embodiments, which is obtained by direct compression.

Embodiment 74e: A pharmaceutical preparation comprising the solid pharmaceutical composition according to any of embodiments 1e to 73e.

Embodiment 75e: The pharmaceutical preparation according to embodiment 74e, which is a pharmaceutical preparation for oral administration.

Embodiment 76e: The pharmaceutical preparation according to embodiments 74e or 75e, which is an immediate release pharmaceutical preparation.

Embodiment 77e: A method for preparing the composition according to any of embodiments 1e to 72e, comprising direct compression.

Embodiment 78e: The method according to embodiment 77e, further comprising a tableting step to make a tablet or minitabket.

Embodiment 79e: The method according to embodiment 78e, further comprising

- i) a coating step after the step of tableting; and
- ii) optionally, the step of filing the minitables obtained into capsules.

Embodiment 80e: Cladribine, or a pharmaceutically acceptable salt thereof, for use in a treatment of myasthenia gravis, according to any of embodiments 1a to 28a, wherein cladribine, or a pharmaceutically acceptable salt thereof, is provided as a solid dosage form comprising a composition according to any of embodiments 1e to 73e.

Embodiment 81e: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to embodiment 80e, wherein the solid dosage form is administered according to the dosing regimen of any one of embodiments 1c to 12c.

Embodiment 82e; The composition according to any of embodiments 1e to 73e, for use in a treatment of myasthenia gravis, according to any of embodiments 1a to 28a.

Embodiment 83e; The composition according to any of embodiments 1e to 73e for use according to embodiment 82e, which is administered according to the dosing regimen of any of embodiments 1c to 12c.

Embodiment 84e: Cladribine, or a pharmaceutically acceptable salt thereof, for use in a treatment of myasthenia gravis, according to any of embodiments 1a to 28a, wherein cladribine, or a pharmaceutically acceptable salt thereof, is provided as pharmaceutical preparation according to any of embodiments 74e to 76e.

Embodiment 85e: Cladribine, or a pharmaceutically acceptable salt thereof, for use in a treatment of myasthenia gravis, according to embodiment 84e, wherein the pharmaceutical preparation is administered according to the dosing regimen of any one of embodiments 1c to 12c.

Embodiment 86e; The pharmaceutical preparation according to any of embodiments 74e to 76e, for use in a treatment of myasthenia gravis, according to any of embodiments 1a to 28a.

Embodiment 87e; The pharmaceutical preparation according to any of embodiments 74e to 76e, for use according to embodiment 86e, wherein the pharmaceutical preparation is administered according to the dosing regimen of any one of embodiments 1c to 12c.

Embodiment 88e: A method of treatment of myasthenia gravis, according to any of embodiments 1b to 28b, wherein cladribine, or a pharmaceutically acceptable salt thereof, is provided as a solid dosage form comprising a composition according to any of embodiments 1e to 73e.

Embodiment 89e: A method of treatment of myasthenia gravis, according to embodiment 88e, wherein the solid dosage form is administered according to the dosing regimen of any one of embodiments 1c to 12c or according to the dosing regimen of any one of claims 1 to 12.

Embodiment 90e: A method of treatment of myasthenia gravis, according to any of embodiments 1b to 28b, wherein cladribine, or a pharmaceutically acceptable salt thereof, is provided as a pharmaceutical preparation according to any of embodiments 74e to 76e.

Embodiment 91e: A method of treatment of myasthenia gravis, according to embodiment 90e, wherein the pharmaceutical preparation is administered according to the dosing regimen of any one of embodiments 1c to 12c or according to the dosing regimen of any one of claims 1 to 12.

Embodiment 92e: Cladribine, or a pharmaceutically acceptable salt thereof, for use in a treatment of myasthenia gravis, according to any of embodiments 1d to 7d, wherein cladribine, or a pharmaceutically acceptable salt thereof, is provided as a solid dosage form comprising a composition according to any of embodiments 1e to 73e.

Embodiment 93e: Cladribine, or a pharmaceutically acceptable salt thereof, for use according to embodiment 92e, wherein the solid dosage form is administered according to the dosing regimen of any one of embodiments 1c to 12c.

Embodiment 94e: The composition according to any of embodiments 1e to 73e, for use in a treatment of myasthenia gravis, according to any of embodiments 1d to 7d.

Embodiment 95e: The composition according to any of embodiments 1e to 73e for use according to embodiment 94e, which is administered according to the dosing regimen of any of embodiments 1c to 12c.

Embodiment 96e: Cladribine, or a pharmaceutically acceptable salt thereof, for use in a treatment of myasthenia gravis, according to any of embodiments 1d to 7d, wherein cladribine, or a pharmaceutically acceptable salt thereof, is provided as pharmaceutical preparation according to any of embodiments 74e to 76e.

Embodiment 97e: Cladribine, or a pharmaceutically acceptable salt thereof, for use in a treatment of myasthenia gravis, according to embodiment 96e, wherein the pharmaceutical preparation is administered according to the dosing regimen of any one of embodiments 1c to 12c.

Embodiment 98e; The pharmaceutical preparation according to any of embodiments 74e to 76e, for use in a treatment of myasthenia gravis, according to any of embodiments 1d to 7d.

Embodiment 99e; The pharmaceutical preparation according to any of embodiments 74e to 76e, for use according to embodiment 98e, wherein the pharmaceutical preparation is administered according to the dosing regimen of any one of embodiments 1c to 12c.

It has been found that solid pharmaceutical compositions according to embodiments, described herein above and in Examples below, can be easily manufactured into solid dosage forms, for example solid dosage forms that are cyclodextrin free. These solid dosage forms are particularly well suited to the oral administration of cladribine. The solid pharmaceutical compositions herein disclosed can be easily manufactured into solid dosage forms, such as minitablets (e.g. a capsule comprising one or more minitablet). These solid dosage forms are robust solid dosage forms [e.g. as regards one or more properties selected from the group consisting of stability, desired dissolution profile (e.g. immediate release) and content uniformity]. The pharmaceutical compositions herein disclosed have the technological properties for being manufactured at an industrial scale (e.g. having one or more technological properties, for example, selected from flowability, compaction, or content uniformity). The minitablets, as herein disclosed, are uniform in content. Furthermore, the minitablets, as herein disclosed, have suitable properties, for example, selected from the group consisting of hardness, disintegration, friability, dissolution profile (e.g. immediate release) and stability. A capsule comprising said minitablets are uniform in content. Such capsule has suitable properties, for example, selected from the group consisting of disintegration, dissolution profile (e.g. immediate release) and stability.

In a further embodiment, one or more of the aforementioned Embodiments further comprises one or more, preferably one or two, additional characteristics as described in the specification of the instant invention and/or as described in one or more of patent claims 1-26.

EXAMPLE

The efficacy and safety of oral Cladribine administration for the treatment of MG according to the invention can be assessed for example following the protocol below.

Example 1

A phase 3, randomized, double-blind, placebo-controlled clinical study is undertaken to assess the efficacy and safety of a solid oral dosage form of cladribine compared with placebo in participants with generalized Myasthenia Gravis.

The purpose of this clinical study is to demonstrate the efficacy and safety of a new oral cladribine formulation and dosing regimen, in participants with gMG in comparison to placebo, the sustained efficacy, the need for retreatment, and the long-term safety of oral cladribine in gMG.

This is a randomized, double-blind, placebo-controlled, 3-arm, 3-period, study and it is divided into 3 periods as follows:

- In the double-blind placebo-controlled (DBPC) period, eligible participants are randomized 1:1:1 to receive either cladribine high dose, cladribine low dose, or placebo.
- In the blinded extension (BE) period, participants initially randomized to placebo are rerandomized to receive cladribine (high or low dose); participants who received cladribine in the DBPC period are allocated to receive placebo and may be eligible to receive a supplemental dose of cladribine, based on clinical need: clinical criteria triggering a required supplemental dose retreatment includes loss of MG-ADL improvement previously obtained, an observed increase of MG-ADL, or the total MG-ADL score is ≥ 6 .
- In the retreatment (RT) period, participants may be retreated with cladribine (supplemental dose or a full dose equal to the previous treatment dose), if clinically justified.

In all cases, the full dose of product is administered as 2 treatment courses separated by 4 weeks.

In the context of the study, cladribine is administered in the form of solid oral dosage forms. For this purpose, two dose strengths (4.375 mg and 17.5 mg) of cladribine capsules were manufactured from a common blend. The blend was compressed into minitables, with a core minitab weight of 7 mg, resulting in 0.546 mg of cladribine per minitab. Each minitab was consequently coated with Opadry TF 276U White (TiO₂ Free). Coated minitables (weighing 7.91 mg) from the selected batches were hand filled into capsules made of HPMC to meet the dose strength criteria; 8 mini-tablets per capsule for 4.375 mg dose strength and 32 mini-tablet per capsule for 17.5 mg dose strength.

The formulation of the blend used in the minitables is indicated in Table 1a below:

Component	%w/w
Cladribine	7.8
Pearlitol SD200 (mannitol)	27.2
Avicel PH102 (microcrystalline cellulose)	56.0
Ac-Di-Sol (croscarmellose sodium)	5.0
Aerosil 200 (pyrogenic silica)	1.0
Magnesium Stearate	3.0

Table 1a

In the 24-week DBPC period, the product (i.e. either cladribine low dose, cladribine high dose or placebo) is administered as 2 separate treatment courses: the first treatment course starting on day 1 and the second treatment course starting at the beginning of week 5, that is to say on day 1 of week 5. In the context of the study, a treatment course typically consists of a period of time of at least one day or of several consecutive days (depending on the dose to be administered) of daily administration of the medicinal product.

In the context of this particular study, the term “cladribine high dose”, when used in reference to the DBPC period, refers to a total administered dose of 105 mg of cladribine, in the form of a solid dosage formulation, by the end of the DBPC period. It should be understood that the total administered dose corresponds to the dose of the active principle cladribine administered during the DBPC period, that is to say the sum of the active principle cladribine comprised in the pharmaceutical dosage forms administered during the first and second treatment course of the DBPC period.

The first and the second treatment course are separated by 4 weeks, that is to say that day 1 of treatment course 2 occurs 4 weeks after day 1 of treatment course 1. In other embodiments, day 1 of treatment course 1 corresponds to the first day of week 1 and day 1 of treatment course 2 correspond to the first day of week 5 of the DBPC period.

In practice, as the treatment is administered in the form of oral dosage forms comprising each a fixed dose of cladribine of 17.5 mg, and since the total administered dose is administered

according to a schedule comprising 2 treatment courses separated by 4 weeks, the dosing regimen of the cladribine high dose is administered according to a schedule comprising two 3-days treatment courses where:

- Course 1 corresponds to the administration of a solid dosage form comprising 17.5 mg of cladribine on day 1, on day 2, and on day 3 of treatment course 1 that is to say of week 1 of the DBPC period;
- Course 2 corresponds to the administration of a solid dosage form comprising 17.5 mg of cladribine on day 1, on day 2 and on day 3 of treatment course 2 that is to say on week five of the DBPC period.

Similarly, the term “cladribine low dose” when used in reference to the DBPC period, refers to a total administered dose of 52.5 mg of cladribine, in the form of a solid dosage formulation, by the end of the DBPC period.

In practice, as the treatment is administered in the form of oral dosage forms comprising each a fixed dose of cladribine of 17.5 mg, and since the patients need to be blinded to their treatment to fulfill the requirement of proper randomization, solid dosage forms comprising no active ingredient (placebo) are introduced in the schedule. The dosing regimen of the cladribine low dose is thus administered according to a schedule comprising two 3-days treatment courses where:

- Course 1 corresponds to the administration of a solid dosage form comprising 17.5 mg of cladribine on day 1 and on day 2, and the administration of a solid dosage form comprising no active principle (placebo) on day 3 of treatment course 1 that is to say of week 1 of the DBPC period;
- Course 2 corresponds to the administration of a solid dosage form comprising 17.5 mg of cladribine on day 1, and the administration of a solid dosage form comprising no active principle (placebo) on day 2 and on day 3 of treatment course 2, that is to say of week five of the DBPC period.

A rich PK analysis is planned during the DBPC period to assess the need for dose modification in the cladribine high dose and cladribine low dose groups.

In the 24-week BE period, gMG patients initially randomized to placebo are rerandomized to receive cladribine high dose or cladribine low dose, while gMG patients initially randomized to cladribine high dose or cladribine low dose are allocated to receive placebo. During the BE period, participants who received cladribine in the DBPC period will be eligible for retreatment if clinically justified.

In the context of this particular study, the term “cladribine high dose”, when used in reference to the BE period, refers to the same dose and treatment schedule as used for the “cladribine high dose” treatment regimen in the DBCP period (as possibly modified after the rich PK analysis). Similarly, the term “cladribine low dose”, when used in reference to the BE period, refers to the same dose and treatment schedule as used for the “cladribine low dose” treatment regimen in the DBCP period (as possibly modified after the rich PK analysis).

Thus, in practice, as the treatment is administered in the form of oral dosage forms comprising each a fixed dose of cladribine of 17.5 mg, and since the total administered dose is administered according to a schedule comprising 2 treatment courses separated by 4 weeks, the dosing regimen of the cladribine high dose is administered according to a schedule comprising two 3-days treatment courses where:

- Course 1 corresponds to the administration of a solid dosage form comprising 17.5 mg of cladribine on day 1, on day 2, and on day 3 of treatment course 1 that is to say of week 1 of the BE period;
- Course 2 corresponds to the administration of a solid dosage form comprising 17.5 mg of cladribine on day 1, on day 2 and on day 3 of treatment course 2 that is to say on week five of the BE period.

Regarding the cladribine low dose, in practice, as the treatment is administered in the form of oral dosage forms comprising each a fixed dose of cladribine of 17.5 mg, and since the patients need to be blinded to their treatment to fulfill the requirement of proper randomization, a solid dosage form comprising no active ingredient (placebo) is introduced in the schedule. The dosing regimen of the cladribine low dose is thus administered according to a schedule comprising two 3-days treatment courses where:

- Course 1 corresponds to the administration of a solid dosage form comprising 17.5 mg of cladribine on day 1 and on day 2, and the administration of a solid dosage form comprising no active principle (placebo) on day 3 of treatment course 1 that is to say of week 1 of the BE period;
- Course 2 corresponds to the administration of a solid dosage form comprising 17.5 mg of cladribine on day 1, and the administration of a solid dosage form comprising no active principle (placebo) on day 2 and on day 3 of treatment course 2, that is to say of week five of the BE period.

In the 24-week BE period, gMG patients initially randomized during DBPC period to cladribine high dose or cladribine low dose are allocated to receive placebo but may further be retreated if clinically justified. The retreatment will consist of:

- A cladribine supplemental dose if the participant has received the last tablet from the initial cladribine treatment dose ≥ 24 weeks and < 48 weeks ago (i.e. during the DBPC period), or
- Placebo if the participant has initiated cladribine during the BE period.

In such case, the terms cladribine supplemental dose refer to an administered dose of cladribine of 17.5 mg. For the purpose of the clinical trial and in particular in order to ensure that patients remain blinded to the treatment actually received, the cladribine supplemental dose is administered according to a regimen of two 3-day treatment courses separated by 4 weeks (with a total dose of 17.5 mg administered during these two 3-day treatment courses), where:

- Course 1: oral cladribine 17.5 mg on Day 1, placebo on Days 2 and 3 of course 1;
- Course 2: placebo on Days 1, 2 and 3 of course 2.

The supplemental dose may be increased to 35 mg cladribine if clinically justified.

In the 96-week RT period, gMG patients are retreated if clinically justified with the following retreatment options based on prior received cladribine doses: cladribine high dose, cladribine low dose, or a cladribine supplemental dose.

The retreatment administered during the RT period can consist of:

- cladribine low dose, if the last tablet of last cladribine low dose was received ≥ 48 weeks ago or the last tablet of the last cladribine supplemental dose was received ≥ 24 weeks ago, or
- cladribine high dose, if the last tablet of last cladribine high dose was received ≥ 48 weeks ago or the last tablet of the last cladribine supplemental dose was received ≥ 24 weeks ago, or
- a cladribine supplemental dose, if the last tablet of last cladribine high or low dose was received between 24 weeks and < 48 weeks ago.

With respect to the retreatment administered during the RT, the terms “cladribine low dose”, “cladribine high dose” and “cladribine supplemental dose” refer to the same dose and similar treatment schedules as used during the DBCP period and the BE period.

In the context of the clinical trial, the terms “if clinically justified” is meant as indicating a worsening of the disease, i.e. MG, and/or of the symptoms associated with MG. Clinical criteria triggering a required retreatment as per protocol during the BE period and the RT period are as follows (any of the following may apply):

- Loss of MG-ADL improvement (i.e. a decrease of at least 2 points) previously obtained, evidence over 3 consecutive visits;
- Increase of MG-ADL of at least 2 points from any prior visit separated by at least 4 weeks;
- An increase of MG-ADL by 1 point over 3 consecutive visits;
- Total MG-ADL score ≥ 6 , with $> 50\%$ of the score obtained by non-ocular muscles.

The Myasthenia Gravis Activities of Daily Living scale or MG-ADL is an 8-item patient reported scale that assesses MG symptoms and their impact on daily activities (Wolfe 1999). The scale evaluates the capacity to perform different activities of daily living such as talking, chewing, swallowing, breathing, brushing teeth/combining hair, or arising from a chair. The scale also assesses double vision and eyelid drooping. Each item is measured on a 4-point Likert Scale from 0 (=normal) to 3 (=most severe). The total score can range from 0 to 24, with higher total scores indicating greater symptom severity and impairment. Assessing MG-ADL does not require any equipment. The scoring of MG ADL should be performed by the Evaluating Investigator (or a Qualified Evaluating Designee).

In addition, a participant needs to fulfill all of the following criteria to be eligible for cladribine retreatment:

- Has an ALC
 - o $\geq 800/\text{mm}^3$ (i.e. Grade 1 or better) for a full dose of cladribine, or
 - o $\geq 500/\text{mm}^3$ (i.e. Grade 2 or better) for a cladribine supplemental dose.
- Has Grade 1 or better in the following hematology assessments:
 - o Hemoglobin levels suggestive of anemia (hemoglobin value $\geq 10.0 \text{ g/dL}$ or $\geq 6.2 \text{ mmol/L}$ or $\geq 100 \text{ g/L}$)
 - o Neutrophil count ($\geq 1500/\text{mm}^3$ or $\geq 1.5 \times 10^9/\text{L}$)

- o Platelet count ($\geq 75,000/\text{mm}^3$ or $\geq 75.0 \times 10^9 /\text{L}$)
- Has Grade 1 or better in the following chemistry assessments:
 - o ALT ($\leq 3.0 \times \text{ULN}$ of the laboratory reference range)
 - o AST ($\leq 3.0 \times \text{ULN}$ of the laboratory reference range)
 - o ALP ($\leq 2.5 \times \text{ULN}$ of the laboratory reference range)
 - o Total bilirubin ($\leq 1.5 \times \text{ULN}$ of the laboratory reference range)
- Does not have any severe or opportunistic infection, including viral hepatitis (HBV, HCV), HIV or TB.
- Is not pregnant or breastfeeding.

The clinical study includes the collection of biological tissue samples in order to gather PK, PD and safety data. After review of PK, PD and safety data from this group of patients, a decision can be made to switch to an alternative dosing regimen.

The alternative dosing regimens comprise alternative “high dose” and “low dose” cladribine regimen where the total administered dose differs, but the solid dosage form used is the same as the one described herein, i.e. hard capsule filled with minitablets comprising cladribine up to an amount of 17.5 mg of cladribine. Furthermore, the regimen schedules are similar in that the doses, i.e. the high dose cladribine and the low dose cladribine are administered to the patients according to a schedule comprising two courses of one or several consecutive days, said courses being separated of 4 weeks.

A first alternative dosing regimen is an alternative cladribine high dose regimen wherein the total administered dose is of 175 mg cladribine, and the schedule of administration comprises two 5-day treatment courses separated by 4 weeks with:

- Course 1: Oral cladribine 17.5 mg on Days 1, 2, 3, 4, and 5;
- Course 2: Oral cladribine 17.5 mg on Days 1, 2, 3, 4, and 5.

A second alternative dosing regimen is an alternative cladribine high dose regimen wherein the total administered dose is of 210 mg cladribine, and the schedule of administration comprises two 6-day treatment courses separated by 4 weeks with:

- Course 1: Oral cladribine 17.5 mg on Days 1, 2, 3, 4, 5, and 6;
- Course 2: Oral cladribine 17.5 mg on Days 1, 2, 3, 4, 5, and 6.

A third alternative dosing regimen is an alternative cladribine low dose regimen wherein the total administered dose is of 87.5 mg cladribine, and the schedule of administration comprises two 5-day treatment courses separated by 4 weeks with:

- Course 1: Oral cladribine 17.5 mg on Days 1, 2, and 3, placebo on Days 4 and 5;
- Course 2: Oral cladribine 17.5 mg on Days 1, and 2, placebo on Days 3, 4 and 5.

A fourth alternative dosing regimen is an alternative cladribine high dose regimen wherein the total administered dose is of 105 mg cladribine, and the schedule of administration comprises two 6-day treatment courses separated by 4 weeks with:

- Course 1: Oral cladribine 17.5 mg on Days 1, 2, and 3, placebo on Days 4, 5, and 6;
- Course 2: Oral cladribine 17.5 mg on Days 1, 2, and 3, placebo on Days 4, 5, and 6.

A fifth alternative dosing regimen is an alternative cladribine supplemental dose wherein the total administered dose is of 35 mg cladribine, and the schedule of administration comprises two 5-day treatment courses separated by 4 weeks with:

- Course 1: oral cladribine 17.5 mg on Day 1 and 2, placebo on Days 3, 4, and 5;
- Course 2: placebo on Days 1, 2, 3, 4, and 5.

A sixth alternative dosing regimen is an alternative cladribine supplemental dose wherein the total administered dose is of 35 mg cladribine, and the schedule of administration comprises two 6-day treatment courses separated by 4 weeks with:

- Course 1: oral cladribine 17.5 mg on Day 1 and 2, placebo on Days 3, 4, 5, and 6;
- Course 2: placebo on Days 1, 2, 3, 4, 5, and 6.

With respect to the treatment and dosing regimen, efficacy assessments are made using established assessments MG-ADL (for Myasthenia Gravis Activities of Daily Living), MGC, (for Myasthenia Gravis Composite) and QMG (Quantitative Myasthenia Gravis), and quality of life measured using MG-QoL15r and EQ-5D-5L.

The Quantitative Myasthenia Gravis scale or QMG is clinician scale which quantifies disease severity based on impairments of body functions and structures (defined by the International Classification of Functioning, Disability and Health – WHO 2001; Barohn 1998). The QMG consists of 13 items that assess ocular, bulbar, and limb function. 6 out of the 13 items are timed tests of endurance measured in seconds. Each item has a possible score from 0 to 3, with a total possible score of 39, where higher total scores indicate more severe impairments.

It is based on quantitative testing of specific muscle groups assessing limb function. Minimal equipment is required such as spirometer, mouthpieces that fit the spirometer, nose clips, stopwatch, cups and water for swallowing tests, goniometer, dynamometer, and is based on the trained rater's examination. The scoring of QMG should be performed by the Evaluating Investigator (or a Qualified Evaluating Designee).

The Myasthenia Gravis Composite scale or MGC has 10 items and combines a trained rater's examination and PRO items (Burns 2010.). Each item is scored on an ordinal scale with 4 possible categories. The impairments that need to be examined by the Evaluating Investigator (or a Qualified Evaluating Designee) include ptosis or upward gaze, double vision, eye closure, neck flexion, shoulder abduction, and hip flexion. The PRO items within MGC cover talking, chewing, swallowing, and breathing. The maximum total possible score is 50, with higher total scores reflecting more severe impairments. The scoring of MGC should be performed by the Evaluating Investigator (or a Qualified Evaluating Designee).

The Myasthenia Gravis 15-Item Quality of Life Scale or MG-QoL15r is a health-related quality of life measure for patients with MG (Burns 2016). It addresses MG-specific psychological, wellbeing and social functioning. The questionnaire is completed by the patient and each item is measured on a 3-point Likert scale from 0 (=Not at all) to 2 (=very much). A total score can range from 0 to 30, with a lower score indicating a better quality of life. The MG-QoL15r is helpful in informing the clinician about the patient's perception of the extent of and dissatisfaction with MG-related dysfunction (Burns 2016).

The EuroQoL 5 Dimension 5 Levels or EQ-5D is a standardized instrument (EuroQoL Research Foundation) developed as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments. The EQ-5D-5L was introduced in 2009 to improve the instrument's sensitivity and to reduce ceiling effects, as compared to the EQ-5D-3L (Herdman 2011). The EQ-5D-5L essentially consists of 2 pages: the EQ-5D descriptive system and the EQ-VAS, which are completed by the patient. The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The levels of the five dimensions can be combined into a 5-digit number that describes the patient's health state. EQ-5D-5L health states, defined by the EQ-5D-5L descriptive system, may be converted into a single health utility index value using country specific value sets. Health utility values facilitate the calculation of quality-adjusted life years that are used to inform pharmacoeconomic evaluations of health care interventions.

The EQ-VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labeled “the best health you can imagine” and “the worst health you can imagine”. This information can be used as a quantitative measure of health as judged by the individual respondents. Higher scores on both EQ-5D-5L health utility values and EQ-VAS represent a better Health-related quality of life (HRQoL).

Example 2

The process flow for blending, direct compression and coating for all blend examples (i.e. blend-1, blend-2, blend-3, blend-4, as described herein below) is depicted in Figure 2 and was identical for all direct compressed mini-tablets. Commercially available cladribine (free form, CAS Number 4291-63-8) in crystalline form (anhydrous polymorphic form A1) was used. The utilized excipients where of pharmaceutical grade and were commercially available.

According to the process flow described in Figure 2, the formulation of four different blend compositions (i.e. Blend-1, Blend-2, Blend-3 and Blend-4, as detailed below) were manufactured (Table 1). A multi-step blending process as depicted above was chosen in order to ensure maximal dispersion of the drug substance. Initially, cladribine and microcrystalline cellulose are sieved sequentially and blended for 7 minutes at 20 rpm in a 10 L intermediate bulk container utilizing a Pharmatech blender. Subsequently, all other excipients besides magnesium stearate were sieved and added to the cladribine-microcrystalline cellulose blend and blending was continued for an additional 5 min at 20rpm. Last, magnesium stearate was sieved to the blend and mixed for 2 min at 20 rpm. The blend was later compressed by means of direct compression using a rotary die tablet press with a 2 mm 24-multi-tip tooling. The formulation of each of the four different blend compositions (i.e. Blend-1, Blend-2, Blend-3 and Blend-4, as detailed below) prepared according to the above process, was used in the preparation of minitables with a height and diameter of 2 mm.

Table 1: Composition of Blends 1-4

Material	Blend-1 (%)	Blend-2 (%)	Blend-3 (%)	Blend-4 (%)
Cladribine	7.8	7.8	7.8	7.8
Pearlitol SD200	64.7	-	20.0	27.2
Pardeck M200	-	64.7		
Avicel PH102	20.0	20.0	64.0	56.0
Ac-Di-Sol	5.0	5.0	5.0	5.0

Aerosil 200	0.5	0.5	0.5	1.0
Magnesium Stearate	2.0	2.0	2.7	3.0

Pearlitol SD 200/ mannitol; Parteck M200/ mannitol; Avicel PH102 / microcrystalline cellulose ; Ac-Di-Sol / croscarmellose sodium ; Aerosil 200 / fumed silica; % = percentage weight of component by total weight of composition (i.e. % w/w).

All blends were analyzed for bulk and tapped density according to European Pharmacopoeia Edition 11.5 [hereinbelow and hereinafter also referred to as "Pharm. Eur.", unless otherwise stated] 2.9.34 and the Carrs index and Hausner ratio was calculated using the formulas below:

$$\text{Hausner ratio} = \frac{\text{untapped bulk volume}}{\text{final tapped bulk volume}}$$

$$\text{Carr index} = \frac{100 (\text{untapped bulk volume} - \text{final tapped bulk volume})}{\text{Untapped bulk volume}}$$

In addition, the particle size distribution of the final blend was measured according to Pharm. Eur. 2.9.38 by utilizing a sieving tower with the following used sieve mesh sizes:

Used sieves : 63, 90, 125, 180, 250, 355, 500 µm.

Powder fractions were analyzed by means of analytical sieving according to Pharm. Eur. 2.9.38 are depicted as D90, D50 and D10 in µm and fines (below 63 µm) in percent (%). Whereas, the fines refers to the weight of particles <63 µm relative to the overall mass of analyzed powder given in percent (% weight/weight).

Minitablets were encapsulated using a standard automatic encapsulation equipment, which is capable of handling the encapsulation of minitables.

Blend-1 :

The bulk and tapped density of the final blend was measured as 0.47 g/mL and 0.62 g/mL, respectively. Carrs index and Hausner ratio values were calculated as 23 and 1.30 and the flow of the blend was categorized as acceptable.

The particle size distribution of the blend was analyzed and results are depicted in Table 2 below.

Table 2: Particle size distribution of Blend-1, determined by analytical sieving according to Pharm. Eur. 2.9.3

	Blend-1
D90 (µm)	229
D50 (µm)	138
D10 (µm)	70
Fines % (Less than 63 µm)	7.84

µm: micrometer; %: Percent

Compression of the blend was not possible, due to very high ejection forces (>800N) on the tablet press at the start. The ejection force was at the high limit point of the equipment and resulted in automatic stop of the compression. i.e. minitablets with a diameter of 2 mm and a height of 2mm of this blend were not obtainable.

Blend-2:

The bulk and tapped density of the final blend was measured as 0.48 g/mL and 0.62 g/mL, respectively. Carrs index and Hausner ratio values were calculated as 23 and 1.30 and the flow of the blend was categorized as acceptable.

The particle size distribution of the blend was analyzed and results are depicted in Table 3 below.

Table 3: Particle size distribution of Blend-2, determined by analytical sieving according to Pharm. Eur. 2.9.3

	Blend-2
D90 (µm)	N/A
D50 (µm)	245
D10 (µm)	97
Fines % (Less than 63 µm)	3.86

µm: micrometer; %: Percent; N/A: Not applicable

During compression high ejection forces of the tablets from the dies were observed and resulted in the automatic discontinuation of the tableting process. Albeit that compression was feasible for a few minutes and that some minitablets were obtained, the formulation was deemed not appropriate. Nevertheless, the obtained minitablets were analyzed for Content uniformity according to Pharm. Eur. 2.9.40. and showed, as per Table 4, a low variability and match of theoretical and measured content.

Table 4: Analytical results for Content Uniformity according to Pharm. Eur. 2.9.40 for Blend-2, wherein mg/dose referring to the measured content and %LC referring to the quotient of measured content and theoretical content which is based on label claim 4.375mg.

No.	mg/dose	%LC
1	4.4271	101.191
2	4.4244	101.129
3	4.4214	101.061
4	4.3803	100.121
5	4.3518	99.47
6	4.4918	102.67
7	4.5316	103.579
8	4.4914	102.661
9	4.4437	101.57
10	4.3116	98.551
Minimum		98.6
Maximum		103.6
Mean		101.2
AV		3.7

mg: milligram; AV: Acceptance value according to Pharm. Eur. 2.9.40.; No.: Number; %LC: Percentage of active ingredient based on Label Claim, wherein Label Claim refers to the intended dose per capsule (e.g. 4.375 mg).

Blend-3:

The bulk and tapped density of the final blend was measured as 0.39 g/mL and 0.51 g/mL, respectively. Carrs index and Hausner ratio values were calculated as 22 and 1.28 and the flow of the blend was categorized as acceptable.

The particle size distribution of the blend was analyzed and results are depicted in Table 5 below.

Table 5: Particle size distribution of Blend-3, determined by analytical sieving according to Pharm. Eur. 2.9.3

	Blend-3
D90 (µm)	188
D50 (µm)	106
D10 (µm)	24
Fines % (Less than 63 µm)	26.32

µm: micrometer; %: Percent

This formulation significantly improved the processability and compression was possible without signs of too high ejection forces. Mini tablets of diameter and height of 2 mm, respectively, were obtained with various compression forces e.g. about 6 kN to 7.4 kN by using a standard rotary tablet press.

Table 5: Results from mini-tablet compression of Blend-3

Tooling size (mm)		2mm round multitap (24 tips)
Target Mini tablet Weight		7.0 mg
Mini tablet weight (mg) (5 mini tablets used)	Minimum	34
	Maximum	38
	Mean (n=10)	35.4
	SD	1.17
	RSD (%)	3.32
Thickness (mm)	Minimum	2.11
	Maximum	2.15
	Mean (n=10)	2.13
	SD	0.01
	RSD (%)	0.69
Hardness (N) Pharm. Eur. 2.9.8.	Minimum	12.7
	Maximum	15.8
	Mean (n=10)	14.27
	SD	0.93
	RSD (%)	6.54
Maximum disintegration time (sec) n(=6)*		< 10
Friability (%) Pharm. Eur. 2.9.7.		0.20

Tensile Strength (Mpa)	2.08
Accor. to Pitt K, et al. (J. Pharm. Pharmacol. 41(5):289-92)	

*Disintegration was tested by placing one mini tablet in a glass vial containing 10 mL room temperature ($23^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$) water and gently shaking until mini tablet fully disintegrated. The maximum was reported. RPM: Rounds per minute; SD: standard Deviation; RSD: Relative standard deviation; Mpa: Megapascal; N: Newton; kN: Kilonewton; mm: millimeter; mg: milligramm; %: Percent; Pharm. Eur.: European Pharmacopoeia Edition 11.5; sec: seconds; n: number of samples.

Despite the advancements made with regards to ejection forces, feeder frame blockage and the respective compression operation, the process yielded also some broken minitables (diameter and height 2 mm, respectively). In addition, rat holes were observed in the hopper of the tablet press indicating poor flowability, which would require frequent manual intervention.

Since this tablet defect has a direct impact on the content uniformity of the dosage form, a further optimization of the blend (also towards better flowability) was undertaken to obtain a minitab with better properties.

The minitables were analyzed for their content uniformity at the start, middle and end of the compression process according to Pharm. Eur. 2.9.40. The results indicated that the anticipated amount of drug substance was present, and the observed variability was low as depicted in Table 7 below.

Table 6: Analytical results for Content Uniformity according to Pharm. Eur. 2.9.40 for Blend-3 for three time points of the compression process, wherein mg/dose referring to the measured content and %LC referring to the quotient of measured content and theoretical content which is based on label claim 4.375mg.

No.	Start		Middle		End	
	mg/dose	%LC	mg/dose	%LC	mg/dose	%LC
1	4.4669	102.101	4.1794	95.529	4.3177	98.690
2	4.4170	100.960	4.1899	95.769	4.1641	95.179
3	4.3925	100.400	4.2932	98.130	4.2849	97.941
4	4.3724	99.941	4.3203	98.750	4.4664	102.089
5	4.4656	102.071	4.4271	101.191	4.5089	103.061
6	4.3999	100.569	4.2901	95.059	4.3671	99.819

7	4.6414	106.089	4.1943	95.870	4.4297	101.250
8	4.4371	101.419	4.3715	99.920	4.3733	99.961
9	4.487	102.560	4.1808	95.561	4.3523	99.481
10	4.298	98.240	4.2573	97.310	4.3864	100.261
Minimum		98.2		95.5		95.2
Maximum		106.1		101.2		103.1
Mean		101.435		97.609		99.773
AV		4.9		5.6		5.3

mg: Milligram; AV: Acceptance value according to Pharm. Eur. 2.9.40.; No.: Number; %LC: Percentage of active ingredient based on Label Claim, wherein Label Claim refers to the intended dose per capsule (e.g. 4.375mg).

The obtained minitables (diameter and height 2 mm, respectively) were coated with Opadry TF White 276U180005 by means of fluid bed coating with a Wurster insert using the process parameters outlined in Table 8 below.

First Opadry TF White 276U180005 coating and purified water were dispensed to obtain a solid content of 12%, following supplier instructions. An empty bowl was pre-warmed for 10 minutes using an inlet temperature of 65°C for 10 minutes at 165 m³/h and the mini tablet cores were loaded into the bowl and pre-warmed utilizing the same parameters until a product temperature of 50°C was reached. Coating was applied utilizing the below target parameters.

Table 7: Process parameters for the coating process of mini-tablets made from Blend-3

Spraying Phase	
Inlet air volume (m ³ /h)	165 (175 at increased spray rate)
Inlet air temperature (°C)	60-70
Spray rate (g/min)	6.0 (12.0 after 30 min)
Atomising air pressure (bar)	2.0
Drying Phase	
Inlet air volume (m ³ /h)	135
Inlet air temperature (°C)	30
Duration	15
Cooling Phase	
Inlet air volume (m ³ /h)	125
Inlet air temperature (°C)	20
Target Product temperature (°C)	≤30

m³/h : cubic meter per hour; °C : Degree Celsius; g : gram; min : minute

After coating of the Opadry TF White 276U180005 as per above process, the 2mm minitables were again analyzed for their content at the two manufactured dose strengths of 4.375 mg and 17.5 mg. The observed variability of mini tablet content was low and the mean drug substance content in agreement with the expected theoretical amount as outlined in the Table 9 below.

Table 8: Analytical results for Content Uniformity according to Pharm. Eur. 2.9.40 for low (8 count, 4.375 mg) and high (32 count, 17.5 mg) dose capsules, manufactured from Blend-3, wherein mg/dose referring to the measured content and %LC referring to the quotient of measured content and theoretical content which is based on label claim 4.375 mg respectively 17.5 mg.

No.	8 count (4.375 mg)		32 count (17.5 mg)	
	mg/dose	%LC	mg/dose	%LC
1	4.2213	96.487	17.613	100.646
2	4.2769	97.758	17.2923	98.813
3	4.2986	98.254	17.3403	99.087
4	4.4206	101.042	17.1683	98.105
5	4.2451	97.031	17.3592	99.195
6	4.4314	101.289	17.1472	97.984
7	4.2013	96.03	16.9294	96.739
8	4.4762	102.313	17.1805	98.174
9	4.2735	97.68	17.0006	97.146
10	4.3400	99.2	17.5771	100.441
Minimum		96.0		96.7
Maximum		102.3		100.6
Mean		98.708		98.633
AV		5.2		3.1

mg: milligram; AV: Acceptance value according to Pharm. Eur. 2.9.40.; No.: Number; %LC: Percentage of active ingredient based on Label Claim, wherein Label Claim refers to the intended dose per capsule (e.g. 4.375mg).

Afterwards hydroxypropylmethylcellulose (HPMC) hard capsules of size 0 (length: 21.70 mm, diameter: 7.65 mm) were hand filled with 8 (4.375 mg dose strength) and 32 (17.5 mg dose strength) mini tablets, respectively, for the assessment of dissolution behavior. For the

assessment of the dissolution apparatus II (Paddle) with 50 mM potassium dihydrogen phosphate buffer pH 6.8 was used according to Pharm. Eur. 2.9.3. One capsule was added to 500mL buffer, which was stirred with 75 rpm at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. Samples of 5 mL were taken at 10, 15, 20, 30, 45 and 60 minutes. The taken sample volume was not replaced. The sample solution was filtered through a $0.45\ \mu\text{m}$ nylon syringe tip filter prior analysis. Dissolution results are depicted in Figures 4 and 5 below.

In addition, the capsules of both dosage strengths were analyzed by means of High Performance Liquid chromatography for any potential degradation products, which showed that the total of all impurities was below 0.05%.

Disintegration testing (according to Pharm. Eur. 2.9.1) was performed on both dose strengths. Both showed a disintegration of ≤ 15 minutes and no significant difference between both dose strengths were observed, as shown in Table 10 below.

Table 10: Disintegration time of low (4.375 mg) and high dose capsules (17.5 mg) prepared from Blend-3, according to Pharm. Eur. 2.9.1

	4.375 mg	17.5 mg
Disintegration time	3.72 minutes	3.25 minutes

Blend-4:

Table 11: Composition of cladribine capsules based on Blend-4

Material	blend-4 (%)
Cladribine	7.8
Pearlitol SD200	27.2
Parteck M200	
Avicel PH102	56.0
Ac-Di-Sol	5.0
Aerosil 200	1.0
Magnesium	3.0
Total tablet core	100
Coating	13% of tablet core weight
Hard capsule	1 piece

The bulk and tapped density of the final blend was measured as 0.42 g/mL and 0.50 g/mL, respectively. Carrs index and Hausner ratio values were calculated as 17 and 1.20 and the flow of the blend was categorized as acceptable.

The particle size distribution of the blend was analyzed and results are depicted in Table 12 below. **Error! Reference source not found.**

Table 12: Particle size distribution of Blend-4, determined by analytical sieving according to Pharm. Eur. 2.9.3

	Blend-4
D90 (µm)	216
D50 (µm)	119
D10 (µm)	33
Fines % (Less than 63 µm)	19.32

µm: micrometer; %: Percent

During tableting, the blend was compressed to minitablets of 2 mm diameter and height, respectively, without any observed problems. Mini tablets of diameter and height of 2 mm, respectively, were obtained with various compression forces e.g. about 6 kN to 7.4 kN using a standard rotary tablet press.

Table 13: Results from mini-tablet compression of Blend-4

Tooling size (mm)		2mm round multitap (24 tips)
Target Mini tablet Weight		7.0 mg
Mini tablet weight (mg) (5 mini tablets used)	Minimum	34
	Maximum	36
	Mean (n=10)	34.9
	SD	0.74
	RSD (%)	2.11
Thickness (mm)	Minimum	1.93
	Maximum	1.95
	Mean (n=10)	1.94
	SD	0.01
	RSD (%)	0.42
Hardness (N)	Minimum	18
	Maximum	24
	Mean (n=10)	20
	SD	1.63
	RSD (%)	8.16

Maximum disintegration time (sec) (n=6)*	15
Friability (%) Pharm. Eur. 2.9.7.	0.016
Tensile Strength (Mpa) Accor. to Pitt K, et al. (J Pharm Pharmacol 41(5):289-92	3.25

*Disintegration was tested by placing one mini tablet in a glass vial containing 10 mL room temperature water and gently shaking until mini tablet fully disintegrated. The maximum was reported. RPM: Rounds per minute; SD: standard Deviation; RSD: Relative standard deviation; Mpa: Megapascal; N: Newton; kN: Kilonewton; mm: Millimeter; mg: milligramm; %: Percent; Pharm. Eur.: European Pharmacopoeia Edition 11.5; sec: seconds; n: number of samples.

The minitables were analyzed for content uniformity at the start, middle and end of compression process according to Pharm. Eur. 2.9.40. Results are shown in Table 14.

Table 14: Analytical results for Content Uniformity according to Pharm. Eur. 2.9.40 for blend-4 for three time points of the compression process, wherein mg/dose referring to the measured content and %LC referring to the quotient of measured content and theoretical content which is based on label claim 4.375mg.

No.	Start		Middle		End	
	mg/dose	%LC	mg/dose	%LC	mg/dose	%LC
1	4.417	100.960	4.41	100.800	4.129	94.377
2	4.414	100.891	4.348	99.383	4.175	95.429
3	4.340	99.200	4.387	100.274	4.166	95.223
4	4.462	101.989	4.234	96.777	4.256	97.280
5	4.45	101.714	4.257	97.303	4.126	94.309
6	4.409	100.777	4.162	95.131	4.212	96.274
7	4.438	101.440	4.268	97.554	4.493	102.697
8	4.404	100.663	4.191	95.794	4.122	94.217
9	4.327	98.903	3.116	71.223	4.221	96.480
10	4.415	100.914	4.323	98.811	4.226	96.594
Minimum		98.9		71.2		94.2
Maximum		102.0		100.8		102.7
Mean		100.745		95.305		96.288

AV		2.4		24		8.2
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mg: milligram; AV: Acceptance value according to Pharm. Eur. 2.9.40.; No.: Number; %LC:

Percentage of active ingredient based on Label Claim, wherein Label Claim refers to the intended dose per capsule (e.g. 4.375mg).

Since in the middle an outlier with 71% was identified, a stage 2 testing according to Pharm. Eur. 2.9.40 was conducted as shown in Table 15 below.

Table 15: Stage two testing for Content Uniformity of the "middle" data point from mini-tablet compression of blend-4 (see Table), wherein mg/dose referring to the measured content and %LC referring to the quotient of measured content and theoretical content which is based on label claim 4.375mg.

No.	mg/dose	%LC	No.	mg/dose	%LC	No.	mg/dose	%LC
1	4.41	100.800	11	4.262	97.417	21	4.164	95.177
2	4.348	99.383	12	4.306	98.423	22	4.261	97.394
3	4.387	100.274	13	4.144	94.720	23	4.168	95.269
4	4.234	96.777	14	4.292	98.103	24	4.13	94.400
5	4.257	97.303	15	4.146	94.766	25	4.376	100.023
6	4.162	95.131	16	4.174	95.406	26	4.185	95.657
7	4.268	97.554	17	4.298	98.240	27	4.257	97.303
8	4.191	95.794	18	4.204	96.091	28	4.114	94.034
9	3.116	71.223	19	4.295	98.171	29	4.305	98.400
10	4.323	98.811	20	4.144	94.720	30	4.323	98.811
Minimum		71.2						
Maximum		100.8						
Mean		96.186						
AV according to Pharm. Eur. 2.9.40		24 (stage 1), 12.5 (stage 2)						

mg: milligram; AV: Acceptance value according to Pharm. Eur. 2.9.40.; No.: Number; %LC:

Percentage of active ingredient based on Label Claim, wherein Label Claim refers to the intended dose per capsule (e.g. 4.375mg).

The core minitables (diameter and height 2 mm, respectively) were also coated using the Opadry TF White 276U180005 film coating by utilizing a fluid bed coater with Wurster insert, by analogous procedure to that described above for Blend-3. Subsequently, the coated minitables were also encapsulated [i.e. hydroxypropylmethylcellulose (HPMC) hard capsules of size 0 (length: 21.70 mm, diameter: 7.65 mm)] by means of counting using an encapsulation machine.

A final representative sample of the coated minitablen batch was taken and analyzed for content uniformity according to Pharm. Eur. 2.9.40 as outlined in Table 16 below.

Table 16 : Analytical results for Content Uniformity according To Pharm. Eur. 2.9.40 for Blend-4, wherein mg/dose referring to the measured content and %LC referring to the quotient of measured content and theoretical content which is based on label claim 4.375mg.

No.	mg/dose	%LC
1	4.172	95.360
2	4.148	94.811
3	4.38	100.114
4	4.242	96.960
5	4.12	94.171
6	4.27	97.600
7	4.345	99.314
8	4.185	95.657
9	4.307	98.446
10	4.221	96.480
Minimum		94.2
Maximum		100.1
Mean		96.891
AV according to Pharm. Eur. 2.9.40		6.3

mg: milligram; AV: Acceptance value according to Pharm. Eur. 2.9.40.; No.: Number; %LC: Percentage of active ingredient based on Label Claim, wherein Label Claim refers to the intended dose per capsule (e.g. 4.375mg).

After encapsulation of the coated minitables, the capsules dissolution was measured according to Pharm. Eur. 2.9.3. using apparatus I with a 40 mesh basket equipped with low-evaporative cover. The dissolution media was a 50 mM phosphate dihydrogen phosphate buffer at pH 6.8. The capsules were dissolved in 500mL buffer, which was stirred at 100 rpm for 60 minutes followed by 200 rpm until 75 minutes. Samples of 5 mL were taken at 5, 10, 15, 20, 30, 45, 60 and 75 minutes. Samples were filtered through a 0.45 µm nylon syringe tip filter prior analysis using. The sample volume was not replaced. Dissolution resulted in 100% dissolved drug substance. Results are depicted in Figures 7 and 8.

In addition, the capsules were analyzed for assay and degradation products. The results, as per Table 17, indicated that the expected drug substance content was achieved with about 100% and that no degradation of the drug substance occurred during manufacture.

Table 17: Analytical results for assay of low and high dose capsules produced from Blend-4.

	4.375 mg capsule	17.5 mg capsule
	%LC	%LC
Replicate 1	100.33	100.63
Replicate 2	100.52	100.76
Mean	100.4	100.7
%RSD	0.1	0.1

mg: milligram; %RSD: Relative Standard deviation in percent; %LC: Percentage of active ingredient based on Label Claim, wherein Label Claim refers to the intended dose per capsule (e.g. 4.375mg or 17.5mg).

Also, the disintegration according to Pharm. Eur. 2.9.1 of the capsules was measured and identified to be well ≤ 15 minutes. Results are shown in Table 18.

Table 18: Disintegration time of low (4.375 mg) and high dose capsules (17.5 mg) prepared from Blend-4, according to Pharm. Eur. 2.9.1

	4.375 mg capsule	17.5 mg capsule
Disintegration time	4.28 minutes	3.58 minutes

The film-coated tablets of Blend-4 were analyzed for the drug substance polymorph and the drug substance Cladribine was confirmed to remain unchanged as Form A1.

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CLAIMS

1. A method of treating Myasthenia Gravis, in a patient in need thereof, comprising orally administering cladribine or a pharmaceutically acceptable salt thereof to the patient according to an initial dosing regimen comprising two treatment courses, separated by about 4 weeks, wherein the total dose of cladribine or a pharmaceutically acceptable salt thereof, administered under said initial dosing regimen is from about 35 mg to about 210 mg.
2. Cladribine or a pharmaceutically acceptable salt thereof, for its use in treating Myasthenia Gravis in a patient in need thereof, wherein cladribine or said pharmaceutically acceptable salt thereof is to be administered orally according to an initial dosing regimen comprising two treatment courses, separated by about 4 weeks, wherein the total dose of cladribine or a pharmaceutically acceptable salt thereof, administered under said initial dosing regimen is from about 35 mg to about 210 mg.
3. The method of claim 1 or cladribine or a pharmaceutically acceptable salt thereof for the use according to claim 2, wherein the total dose of cladribine or a pharmaceutically acceptable salt thereof, administered under said initial dosing regimen is of about 35 mg, of about 52.5 mg, of about 70 mg, of about 87.5 mg, of about 105 mg, of about 122.5 mg, of about 140 mg, of about 157.5 mg, of about 175 mg, of about 192.5 mg or of about 210 mg.
4. The method of claim 1 or 3 or cladribine or a pharmaceutically acceptable salt thereof for the use according to claim 2 or 3, wherein the total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 52.5 mg, and wherein about 35 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first treatment course of the initial dosing regimen, and about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the second treatment course of the initial dosing regimen.
5. The method of claim 4 or cladribine or a pharmaceutically acceptable salt thereof for the use according to claim 4, wherein, during the first treatment course of the initial dosing regimen, cladribine or a pharmaceutically acceptable salt thereof is administered on each of day one and two of the first treatment course in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof, and, during

the second treatment course of the initial dosing regimen, cladribine or a pharmaceutically acceptable salt thereof is only administered on day one of the second treatment course in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof.

6. The method of claim 1 or 3 or cladribine or a pharmaceutically acceptable salt thereof for the use according to claim 2 or 3, wherein the total dose of cladribine or a pharmaceutically acceptable salt thereof administered under said initial dosing regimen is of about 105 mg, and wherein about 52.5 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the first treatment course of the initial dosing regimen, and about 52.5 mg of cladribine or a pharmaceutically acceptable salt thereof is administered during the second treatment course of the initial dosing regimen.
7. The method of claim 6 or cladribine or a pharmaceutically acceptable salt thereof for the use according to claim 6, wherein, during the first treatment course of the initial dosing regimen, cladribine or a pharmaceutically acceptable salt thereof is administered on each of day one, two and three of the first treatment course in the form of a dosage form comprising about 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof, and, during the second treatment course of the initial dosing regimen, cladribine or a pharmaceutically acceptable salt thereof is administered on each of day one, two and three of the second treatment course in the form of a dosage form comprising 17.5 mg of cladribine or a pharmaceutically acceptable salt thereof.
8. The method according to any of the previous claims or cladribine or a pharmaceutically acceptable salt thereof for the use according to any of the previous claims, wherein the method or use comprises a period of at least about 6 months, preferably of at least about 12 months, more preferably of at least about 24 months, after the last administration of cladribine or a pharmaceutically acceptable salt thereof during the second treatment course of the initial dosing regimen, where no cladribine or a pharmaceutically acceptable salt thereof is administered.
9. The method according to any of the previous claims or cladribine or a pharmaceutically acceptable salt thereof for the use according to any of the previous claims, wherein the method or use further comprises after the initial dosing regimen a retreatment step wherein a supplemental dose of cladribine or a pharmaceutically acceptable salt thereof from about 17.5 mg to about 35 mg is administered.

10. The method according to claim 9 or cladribine or a pharmaceutically acceptable salt thereof for the use according to claim 9, wherein the supplemental dose is administered no earlier than about 24 weeks and earlier than about 48 weeks after the last administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period.
11. The method according to any of the previous claims or cladribine or a pharmaceutically acceptable salt thereof for the use according to any of the previous claims, wherein the method or use further comprises after the initial dosing regimen a step of retreatment wherein the total administered dose of cladribine or a pharmaceutically acceptable salt thereof administered during said retreatment equals the total administered dose of cladribine or a pharmaceutically acceptable salt thereof administered during the two treatment courses of the initial dosing regimen.
12. The method according to claim 11 or cladribine or a pharmaceutically acceptable salt thereof for the use according to claim 11, wherein the retreatment consists of two treatment courses, said treatment courses being separated by about 4 weeks.
13. The method according to any of the previous claims or cladribine or a pharmaceutically acceptable salt thereof for the use according to any of the previous claims,

 wherein the initial dosing regimen consists of the two treatment courses, and

 wherein the method or use further comprises, if clinically justified, one or more retreatment steps in which a dose of about 17.5 mg to about 35 mg of cladribine or a pharmaceutically acceptable salt thereof is administered no earlier than about 24 weeks and earlier than about 48 weeks after the first or last administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, and, if clinically justified, one or more retreatment steps in which the same total dose of cladribine or a pharmaceutically acceptable salt thereof as under the initial dosing regimen is administered at least about 48 weeks after the first or last administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, if in this last treatment period the same total dose of cladribine or a pharmaceutically acceptable salt thereof as under the initial dosing regimen was administered, or at least about 24 weeks after the first or last administration of cladribine or a pharmaceutically acceptable salt thereof during the last treatment period, if in this last treatment period a dose of about 17.5 mg to about 35 mg of cladribine or a pharmaceutically acceptable salt thereof was administered.

14. The method according to any of the previous claims, or cladribine or a pharmaceutically acceptable salt thereof for the use according to any of the previous claims, wherein cladribine, or the pharmaceutically acceptable salt thereof, is formulated as a solid dosage form (e.g. as a capsule comprising minitablets).
15. The method according to any of the previous claims, or cladribine or a pharmaceutically acceptable salt thereof for the use according to any of the previous claims, wherein myasthenia gravis is selected from the group consisting of anti-acetylcholine receptor antibody-positive myasthenia gravis, anti-MuSK antibody-positive myasthenia gravis, anti-acetylcholine receptor antibody-positive and anti-MuSK antibody-positive myasthenia gravis, anti-LRP4 antibody-positive myasthenia gravis or seronegative myasthenia gravis.
16. The method according to any of the previous claims, or cladribine or a pharmaceutically acceptable salt thereof for the use according to any of the previous claims, wherein myasthenia gravis is generalized myasthenia gravis.
17. The method according to any of the previous claims, or cladribine or a pharmaceutically acceptable salt thereof for the use according to any of the previous claims, wherein myasthenia gravis is refractory myasthenia gravis (e.g. refractory generalized myasthenia gravis).
18. The method according to any of the previous claims, wherein cladribine is in non-salt form (i.e. the free form).
19. A method of treatment of generalized myasthenia gravis, in a subject, in need thereof, comprising administering to said subject an effective amount of cladribine or a pharmaceutically acceptable salt thereof.
20. A method of treatment of myasthenia gravis, preferably generalized myasthenia gravis, in a subject, in need thereof, comprising administering to said subject an effective amount of cladribine, or a pharmaceutically acceptable salt thereof, as a disease-modifying therapy or as a steroid-sparing agent.

21. A method of treatment for the reduction (e.g. compared to baseline or placebo) of the impact of the severity of symptoms of MG on activities of daily living [e.g. as assessed by using standard scales, such as a patient reported scale (e.g. the MG-ADL scale)], in a subject, in need thereof, comprising administering to said subject an effective amount of cladribine or a pharmaceutically acceptable salt thereof.
22. A method of treatment for the reduction (e.g. compared to baseline or placebo) of the impact of muscle weakness to effort associated with MG [e.g. as assessed by using standard scales (e.g. the QMG scale or the MGC scale)], in a subject, in need thereof, comprising administering to said subject an effective amount of cladribine or a pharmaceutically acceptable salt thereof.
23. A method of treatment for the improvement (e.g. compared to baseline or placebo) of the health related quality of life of a MG patient [for example as assessed by using standard scales (e.g. a patient reported scale, for example the MG-QoL15r scale or the EQ-5D-5L)], in a subject, in need thereof, comprising administering to said subject an effective amount of cladribine or a pharmaceutically acceptable salt thereof.
24. The method according to any claims 20 to 23, wherein cladribine, or the pharmaceutically acceptable salt thereof, is administered according to the dosing regimen of any one of claims 1 to 13.
25. The method according to any of the previous claims, wherein administration of cladribine, or a pharmaceutically acceptable salt thereof, is concomitant with corticosteroid or AChE inhibitor treatment.
26. A solid pharmaceutical composition comprising:
 - cladribine, or a pharmaceutical acceptable salt thereof; and
 - at least two different fillers [i.e. a filler (e.g. a first filler), another filler (i.e. a different filler; e.g. a second filler) and optionally at least a further (i.e. one or more) filler (e.g. a third filler or a third filler and a forth filler)];

wherein at least one of said at least two different fillers (e.g. the first filler) is a sugar alcohol (e.g. mannitol (e.g. D-mannitol), xylitol or sorbitol; for example mannitol).

27. The composition according to claim 26, wherein the ratio as calculated based on % w/w of said at least two different fillers [i.e. the ratio of % w/w of one of said at least two different fillers (i.e. % weight of one of said at least two different fillers with respect to the total weight of the pharmaceutical composition, e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab) to % w/w of the other one of said at least two different fillers (% weight of other one of said at least two different fillers with respect to the total weight of the pharmaceutical composition, e.g. with respect to the total weight of a pharmaceutical composition in the form of a minitab, such as an uncoated minitab)] is between about 1 (e.g. of sugar alcohol) : 3 [e.g. of the filler other than the sugar alcohol (i.e. second filler; e.g. cellulose derivative)] to about 1 (e.g. of sugar alcohol) : 2 [e.g. of filler other than the sugar alcohol (i.e. second filler; e.g. cellulose derivative)]; preferably about 1 (e.g. of sugar alcohol) : 2 [e.g. of filler other than the sugar alcohol (i.e. second filler; e.g. cellulose derivative)].
28. The composition according to claims 26 or 27, wherein the composition is in the form of a capsule (e.g. a hard capsule) comprising one or more (e.g. 1 to 50, such as 8 or 32) minitabs (e.g. wherein the composition comprises cladribine, or a salt thereof, in an amount of about 17.5 mg/capsule).
29. The composition according to any one of claims 27 to 29, wherein cladribine, or a pharmaceutical acceptable salt thereof, is micronized [e.g. micronized cladribine, or a pharmaceutical acceptable salt thereof, has a primary particle size that is characterized by a Dv90 of from about 2 μm to about 30 μm , for example of from about 2 μm to about 10 μm (e.g. as measured by laser diffraction)].