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pentofuranose has the α -configuration in the solid state, the exclusive formation of the blocked 2'-deoxy- β -nucleosides is viewed to be due to a direct Walden inversion (S_N2) at the C_1 carbon by the anionic heterocyclic nitrogen. Inasmuch as the reaction mixture may contain a minor amount of positional isomers, the product is isolated from the reaction mixture in any suitable way, preferably by column chromatography. The ammonolysis is conveniently carried out by heating a solution of the 6-chloro-9-pentofuranosylpurine product in methanolic ammonia at elevated temperature, preferably about 100° C, until the reaction is complete, usually for a period of from about 5 to about 12 hours. The products of the method, 2'-deoxyadenosine and 2-chloro-2'-deoxyadenosine, are useful cytotoxic agents and are useful as intermediates for the production of 2'-deoxyadenosine analogs (Cf. Proc. Am. Assoc. Cancer Res. 1980, 71, 302; Cancer Res. 1982, 42, 3911).

The invention is illustrated, and the best mode of carrying out the same is set forth, in the following examples.

General Procedures

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

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Nuclear magnetic resonance (^1H NMR) spectra were determined at 90 MHz with a JEOL FX 900 spectrometer. The chemical-shift values are expressed in δ values (parts per million) relative to tetramethylsilane as an internal standard. Ultraviolet spectra (UV; sh = shoulder) were recorded on a Cary Model 15 spectrophotometer. Evaporations were carried out under reduced pressure with the bath temperature below 30° C.

Example 1

2,6-Dichloro-9-(2-deoxy-3,5-di-O-p-toluoyl- β -D-erythro-pentofuranosyl)-purine

a) A mixture of 2,6-dichloropurine (0.95 g, 5 mmol) and sodium hydride (50% in oil, 0.25 g, 5.2 mmol) in anhydrous CH_3CN (35 mL) was stirred at ambient temperature under a nitrogen atmosphere for 30 min. Dry, powdered 1-chloro-2-deoxy-3,5-di-O-p-toluoyl- α -D-erythro-pentofuranose (1.95 g, 5 mmol) was added portionwise with stirring, during 20 min, and stirring was continued for a further 15 h. A small amount of insoluble material was removed by filtration. Evaporation of the solvent gave an oily residue, which was purified on a silica gel column (5 X 60 cm) using toluene:acetone (9:1, v/v) as the solvent. Two

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nucleosides were isolated in the order listed: the title compound was crystalized from EtOH to yield 1.60 g (59%); mp 159-162°C [Literature mp 155-157°C].

5 b) The N-7 glycosyl isomer 2,6-dichloro-7-(2-deoxy-3,5,di-O-p-toluoyl-β-D-erythro-pentofuranosyl) purine was isolated and crystallized from EtOH to yield 0.35 g (13%); mp 141-143°C. ¹H NMR (Me₂SO-d₆: δ 6.88 (t, 1, C₁H, peak width 14.5 Hz), 7.36 and 7.90 (m, 8, Ph), 9.28 (s, 1, C₈H). Anal. Calcd for C₂₆H₂₂Cl₂N₄O₅ (541.4): C, 57.68; H, 4.09; N, 10.35. Found: C, 57.55; H, 4.00; N, 10.36.

2-Chloro-6-amino-9-(2-deoxy-β-D-erythro-pentofuranosyl)purine (2-Chloro-2'-deoxyadenosine)

15 c) A solution of the 2,6-dichloro-9-pentofuranosylpurine product of 1a) (2.50 g, 4.6 mmol) in CH₃OH/NH₃ (saturated at 0°C, 60 ml) was heated at 100°C for 5 h and the mixture was evaporated to dryness. The residue was purified on a silica gel column (5 x 40 cm) using CHCl₃:MeOH (8:2, v/v) as the solvent.

20 Crystallization of the homogeneous solid from EtOH gave 0.87 g (71% of analytically pure title compound; mp 220°C (softens), resolidifies, turns brown, does not melt below 300°C [Lit. mp 210-215°C (softens) and then solidifies and turns brown].

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Example 26-Chloro-9-(2-deoxy-3,5-di-O-p-toluoyl- β -D-erythro-pentofuranosyl)purine

5 a) In the same manner as for Example 1, reaction of the sodium salt of 6-chloropurine (J. Med. Chem. 1984, 27, 175, 0.77 g, 5 mmol and 50% NaH in oil, 0.25 g, 5.2 mmol) with 1-chloro-2-deoxy-3, 5-di-O-p-toluoyl- α -D-erythro-pentofuranose (2.0 g, 5.15 mmol) in CH₃CN (50 mL) gave 1.51 g (59%) of crystalline title
10 compound (from EtOH); mp 107-109°C. ¹H NMR (Me₂SO-d₆) δ 6.76 (t, 1, C₁H, peak width 14.0 Hz), 7.36 and 7.94 (m, 8, Ph), 8.80 (s, 1, C₂H), 9.00 (s, 1, C₁H). Anal. Calcd for C₂₆H₂₃ClN₄O₅ (506.9): C, 61.60; H, 4.57; N, 11.05. Found: C, 61.73; H, 4.72; N, 11.03.

15 b) The N-7 glycosyl isomer 6-chloro-7-(2-deoxy-3,5-di-O-p-toluoyl- β -D-erythro-pentofuranosyl)purine was isolated and crystallized from EtOH to yield 0.29 g (11%); mp 152-153°C. ¹H NMR (Me₂SO-d₆) δ 6.96 (t, 1, C₁H, peak width 14.5 Hz), 7.36
20 and 7.94 (m, 8, Ph), 8.94 (s, 1, C₂H), 9.26 (s, 1, C₈H). Anal. Calcd for C₂₆H₂₃ClN₄O₅ (506.9): C, 61.60; H, 4.57; N, 11.05. Found: C, 61.55; H, 4.49; N, 11.05.

6-Amino-9-(2-deoxy- β -D-erythro-pentofuranosyl)purine
(2'-Deoxyadenosine)

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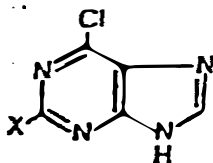
c) A solution of the 6-chloro-9-pentofuranosylpurine product of 2a) (1.01 g, 2 mmol) in MeOH/NH₃ (18 mL) was heated at 100°C for 12 h and then evaporated to dryness. The aqueous solution of the residue was extracted with CHCl₃ (2 x 25 mL), followed by ether (2 x 25 mL) and then evaporated to dryness. The residue was crystallized from water to yield 0.41 g (78%); mp 186-189°C [Lit. mp 187-189°C, and all other physicochemical properties of the title 2'-deoxyadenosine product are identical with 2'-deoxyadenosine reported in the literature].

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

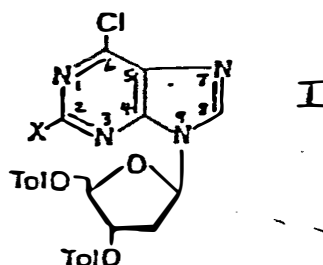
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CLAIMS

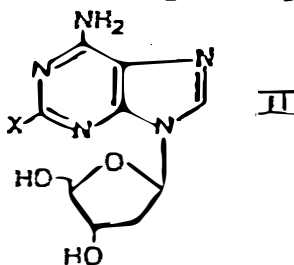
1. A method of producing 2'-deoxyadenosine compounds, comprising glycosylating a sodium salt of a purine compound having the formula



5 with 1-chloro-2-deoxy-3,5-di-O-p-toluoyl- α -D-erythro-pentofuranose, isolating the resulting 9-(2-deoxy-3,5-di-O-p-toluoyl- β -D-erythro-pentofuranosyl) purine having the formula I



and subjecting the same to ammonolysis under deblocking conditions to obtain the corresponding 2'-deoxyadenosine having the formula II



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where X is hydrogen or Cl.

2. A method according to Claim 1 where acetonitrile is employed as a solvent in the glycosylation step.

5 3. A method according to Claim 2 where the sodium salt is formed in situ at ambient temperature by reaction of the purine compound and sodium hydride.

10 4. A method according to Claim 1 where the ammonolysis is carried out by heating a solution of the 6-chloro-9-pentofuranosylpurine product in methanolic ammonia at elevated temperature.

5. A method according to Claim 1 where the purine compound is 2,6-dichloropurine.

15 6. A method according to Claim 1 where the purine compound is 6-chloropurine.

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7. 2,6-Dichloro-9-(2-deoxy-3,5-di-O-p-toluoyl- β -D-erythro-pentofuranosyl)purine.

8. 6-Chloro-9-(2-deoxy-3,5-di-O-p-toluoyl- β -D-erythro-pentofuranosyl)purine.

5 9. 2-Chloro-2'-deoxyadenosine produced by the method according to Claim 1.

10. 2'-Deoxyadenosine produced by the method according to Claim 1.



ELECTRONIC PAYMENT RECEIPT

APPLICATION #
16/199,119

RECEIPT DATE / TIME
07/07/2020 04:11:20 PM ET

ATTORNEY DOCKET #
000696US

Title of Invention

Cladribine regimen for treating progressive forms of Multiple Sclerosis

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # -

CONFIRMATION # 8647

FILED BY W. Michael Buck

PATENT CENTER # 60049787

AUTHORIZED BY Eric Myers

CUSTOMER # 151167

FILING DATE 11/23/2018

CORRESPONDENCE ADDRESS -

FIRST NAMED INVENTOR Fernando Dangond

Payment Information

PAYMENT METHOD
DA / 601920

PAYMENT TRANSACTION ID
E202077G13228820

PAYMENT AUTHORIZED BY
W. Michael Buck

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	240.00	1	240.00
TOTAL AMOUNT:				\$240.00

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National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Docket No. 000696US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
FERNANDO DANGOND

SERIAL NO. 16/199,119

FILED ON NOVEMBER 23, 2018

FOR: CLADRIBINE REGIMEN FOR
TREATING PROGRESSIVE FORMS
OF MULTIPLE SCLEROSIS

EXAMINER: ULM, JOHN D.

GROUP ART UNIT: 1649

AMENDMENT AND REQUEST FOR RECONSIDERATION

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

In response to the Non-Final Office Action dated April 14, 2020, please reconsider the application in view of the following amendment and remarks.

Amendments to the Claims begin on page 2 of this paper.

Interview Summary begins on page 15 of this paper.

Remarks begin on page 16 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings of claims in the application. Please amend the claims of the above-identified patent application as follows:

Listing of Claims:

1 (Currently Amended): A method of treating a progressive form of Multiple Sclerosis, said method comprising: orally administering Cladribine to a patient in need thereof at fixed dose per patient, per body weight and per treatment year, wherein said fixed dose is in a range of 1.5 mg/kg to 4.0 mg/kg, wherein the progressive form of Multiple Sclerosis is selected from the group consisting of Secondary Progressive Multiple Sclerosis (SPMS), Primary Progressive Multiple Sclerosis (PPMS), and Progressive Relapsing Multiple Sclerosis (PRMS), and wherein the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS).

2 (Canceled).

3 (Original): The method according to claim 1, wherein said fixed dose per patient is 1.75 mg/kg per treatment year with a maximum deviation of +/- 0.2 mg/kg.

4 (Original): The method according to claim 1, wherein said progressive form of multiple sclerosis comprises Primary Progressive Multiple Sclerosis and/or Secondary Progressive Multiple Sclerosis.

5 - 15 (Canceled).

16 (Original): The method according to claim 1, wherein said fixed dose is orally administered to said patient within two adjacent months within said treatment year.

17 – 18 (Canceled).

19 (Original): The method according to claim 16, wherein said fixed dose is orally administered to said patient within one week or two adjacent weeks at the beginning of each one of said two adjacent months.

20 (Canceled).

21 (Original): The method according to claim 16, wherein said fixed dose is orally administered to said patient within 4 to 5 days during said week, or within 4 to 5 days of each of said weeks.

22 (Original): The method according to claim 1, wherein said Cladribine is orally administered for at least three treatment years.

23 – 25 (Canceled).

26 (Original): The method according to claim 1, wherein each treatment year comprises:

(i) a treatment period of 2 months at the beginning of said treatment year, wherein said fixed dose of Cladribine is orally administered on 3 to 5 days each month at the

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beginning of each month, said fixed dose being divided into daily doses of 10 or 20 mg of Cladribine, and

(ii) a Cladribine-free period lasting 10 months, during which no Cladribine is administered.

27 (Original): The method according to claim 1, wherein said patient suffers from Primary Progressive Multiple Sclerosis and/or from Secondary Progressive Multiple Sclerosis, wherein said fixed dose per patient is 1.75 mg/kg per treatment year with a maximum deviation of ± 0.2 mg/kg, and wherein orally administering Cladribine comprises at least two treatment years.

28 (Canceled).

29 (Original): The method according to claim 1, wherein orally administering Cladribine comprises at least three treatment years,

a) wherein said fixed dose per treatment year is from 0.75 mg/kg to 2.0 mg/kg,

b) wherein the third treatment year comprises:

(i) a treatment period of 1 month or 2 months at the beginning of said treatment year, wherein said fixed dose of Cladribine is orally administered on 3 to 5 days each month at the beginning of each month, said fixed dose being divided into daily doses of 10 or 20 mg of Cladribine, and

(ii) a Cladribine-free period lasting 11 or 10 months respectively, during which no Cladribine is administered.

30 (Original): The method according to claim 1, wherein orally administering Cladribine is in one or two treatment years, optionally plus an additional subsequent treatment year, followed by at least one year in which no Cladribine is administered to said patient.

31 (Original): The method according to claim 1, wherein said Cladribine is orally administered as a liquid, a tablet, or a capsule.

32 (Canceled).

33 (Original): The method according to claim 1, wherein said Cladribine is orally administered as a tablet comprising 10 mg of Cladribine in the form of a mixture of Cladribine, 2-hydroxypropyl- β -cyclodextrin and Cladribine-2-hydroxypropyl- β -cyclodextrin-complexes, wherein the weight ratio of Cladribine to 2-hydroxypropyl- β -cyclodextrin is between about 1:10 to about 1:16.

34 (Currently Amended): A method of treating a patient diagnosed as suffering from a progressive form of Multiple Sclerosis, said method comprising:

orally administering to said patient a cumulative dose of Cladribine of about 3.5 mg/kg body weight, with a maximum deviation of ± 0.4 mg/kg, over 2 years, administered in each year as 1 treatment course of about 1.75 mg/kg ± 0.2 mg/kg per year, wherein each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year,

wherein the progressive form of Multiple Sclerosis is selected from the group consisting of Secondary Progressive Multiple Sclerosis (SPMS), Primary Progressive

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Multiple Sclerosis (PPMS), and Progressive Relapsing Multiple Sclerosis (PRMS), and wherein the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS).

35 (Original): The method according to claim 34, wherein each treatment week consists of 4 or 5 days on which said patient receives 10 mg or 20 mg of Cladribine for oral administration, depending on the body weight of the patient.

36 (Original): The method according to claim 35, wherein said patient receives the 10 mg or 20 mg of Cladribine for oral administration as a tablet or capsule.

37 (Original): The method according to claim 36, wherein said patient receives the 10 mg or 20 mg of Cladribine for oral administration as a tablet or capsule comprising 10 mg of Cladribine in the form of a mixture of Cladribine, 2-hydroxypropyl- β -cyclodextrin and Cladribine-2-hydroxypropyl- β -cyclodextrin-complexes, wherein the weight ratio of Cladribine to 2-hydroxypropyl- β -cyclodextrin is between about 1:10 to about 1:16.

38 – 39 (Canceled).

40 (Original): The method according to claim 34, where the progressive form of Multiple Sclerosis is selected from the group consisting of Primary Progressive Multiple Sclerosis and Secondary Progressive Multiple Sclerosis.

41 (Original): The method according to claim 40, wherein each treatment week consists of 4 or 5 days on which said patient receives 10 mg or 20 mg of Cladribine for oral administration.

42 (Original): The method according to claim 34, wherein said patient is between 18 and 65 years old.

43 – 47 (Canceled).

48 (Original): The method according to claim 34, wherein the patient additionally receives at least one disease modifying drug other than Cladribine.

49 (Currently Amended): The method according to claim 48, wherein said at least one disease modifying drug other than Cladribine is an interferon at least one selected from the group consisting of: Interferon beta-1a, Beta interferon-1a, Interferon beta-1b, Beta interferon-1b, and Peginterferon beta 1a, ~~Alentuzumab, Daclizumab, Dimethyl fumarate, Fingolimod, Glatiramer acetate, Natalizumab, and Teriflunomide.~~

50 (Original): The method according to claim 34, wherein after the completion of said 2 years with said 2 treatment courses, no Cladribine is administered to the patients in the subsequent 1 or 2 years following the completion of said 2 years with said 2 treatment courses.

51 (Canceled).

52 (Original): A method of treating a patient suffering from a progressive form of Multiple Sclerosis, comprising orally administering to said patient tablets or capsules containing about 10 mg of Cladribine each, wherein said tablets or capsules are administered during a treatment year comprising the following regimen:

(i) a treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on a treatment week of from 3 to up to 6 days each month;

(ii) followed by a Cladribine-free period lasting 10 months wherein no Cladribine is administered to said patient;

wherein patients having a bodyweight

-in the range of 40 to less than 50 kg are administered

1) 4 tablets or capsules (40 mg of Cladribine) in the 1st treatment week of said treatment course,

2) 4 tablets or capsules (40 mg of Cladribine) in the 2nd treatment week of said treatment course;

-in the range of 50 to less than 60 kg are administered

1) 5 tablets or capsules (50 mg of Cladribine) in the 1st treatment week of said treatment course, respectively,

2) 5 tablets or capsules (50 mg of Cladribine) in the 2nd treatment week of said treatment course;

-in the range of 60 to less than 70 kg are administered

1) 6 tablets or capsules (60 mg of Cladribine) in the 1st treatment week of said treatment course,

2) 6 tablets or capsules (60 mg of Cladribine) in the 2nd treatment week of said treatment course;

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-in the range of 70 to less than 80 kg are administered

1) 7 tablets or capsules (70 mg of Cladribine) in the 1st treatment week of said treatment course,

2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd treatment week of said treatment course;

-in the range of 80 to less than 90 kg are administered

1) 8 tablets or capsules (80 mg of Cladribine) in the 1st treatment week of said treatment course,

2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd treatment week of said treatment course;

-in the range of 90 to less than 100 kg are administered

1) 9 tablets or capsules (90 mg of Cladribine) in the 1st treatment week of said treatment course,

2) 8 tablets or capsules (80 mg of Cladribine) in the 2nd treatment week of said treatment course;

-in the range of 100 to less than 110 kg are administered

1) 10 tablets or capsules (100 mg of Cladribine) in the 1st treatment week of said treatment course,

2) 9 tablets or capsules (90 mg of Cladribine) in the 2nd treatment week of said treatment course; or

-in the range of 110 kg and above are administered

1) 10 tablets or capsules (100 mg of Cladribine) in the 1st treatment week of said treatment course,

2) 10 tablets or capsules (100 mg of Cladribine) in the 2nd treatment week of said treatment course.

53 (Original): The method according to claim 52, wherein the method further comprises at least one subsequent additional treatment year, wherein said additional treatment year is substantially identical to said treatment year.

54 (Original): The method according to claim 53, wherein said additional treatment year is directly adjacent to said treatment year, or wherein the method comprises a gap of 1 to 10 months in between the two treatment years.

55 (Canceled).

56 (Currently Amended): A method of treating a patient suffering from a progressive form of Multiple Sclerosis, wherein the progressive form of Multiple Sclerosis is selected from the group consisting of Secondary Progressive Multiple Sclerosis (SPMS), Primary Progressive Multiple Sclerosis (PPMS), and Progressive Relapsing Multiple Sclerosis (PRMS), and wherein the progressive form of Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis (ESPMS), said method comprising orally administering to said patient tablets or capsules containing about 10 mg of Cladribine each, wherein said tablets or capsules are administered during two treatment years comprising the following regimen:

- (i) a first treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month;
- (ii) followed by a first Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient;

(iii) followed by a second treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month; and

(iv) followed by a second Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient, and

wherein patients having a bodyweight

-in the range of 40 to less than 50 kg are administered

1) 4 tablets or capsules (40 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 4 tablets or capsules (40 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively:

-in the range of 50 to less than 60 kg are administered

1) 5 tablets or capsules (50 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 5 tablets or capsules (50 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively:

-in the range of 60 to less than 70 kg are administered

1) 6 tablets or capsules (60 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 6 tablets or capsules (60 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively;

-in the range of 70 to less than 80 kg are administered

1) 7 tablets or capsules (70 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

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2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively;

-in the range of 80 to less than 90 kg are administered

1) 8 tablets or capsules (80 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively;

-in the range of 90 to less than 100 kg are administered

1) 9 tablets or capsules (90 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 8 tablets or capsules (80 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively;

-in the range of 100 to less than 110 kg are administered

1) 10 tablets or capsules (100 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 9 tablets or capsules (90 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively; or

-in the range of 110 kg and above are administered

1) 10 tablets or capsules (100 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 10 tablets or capsules (100 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively.

57 (Original): The method according to claim 56, wherein said 10 mg or 20 mg of Cladribine for oral administration are administered to the patient as a tablet or capsule

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comprising 10 mg of Cladribine in the form of a mixture of Cladribine, 2-hydroxypropyl- β -cyclodextrin and Cladribine-2-hydroxypropyl- β -cyclodextrin-complexes, wherein the weight ratio of Cladribine to 2-hydroxypropyl- β -cyclodextrin is between about 1:10 to about 1:16.

58 (Original): The method according to claim 56, wherein the progressive form of Multiple Sclerosis is Primary Progressive Multiple Sclerosis.

59 (Original): The method according to claim 56, wherein the progressive form of Multiple Sclerosis is Secondary Progressive Multiple Sclerosis.

60 – 63 (Canceled).

64 (Original): The method according to claim 56, wherein the patient additionally receives at least one disease modifying drug other than Cladribine.

65 (Currently Amended): The method according to claim 64, wherein said at least one disease modifying drug other than Cladribine is an interferon at least one selected from the group consisting of: Interferon beta-1a, Beta interferon-1a, Interferon beta-1b, Beta interferon-1b, and Peginterferon beta 1a, ~~Alentuzumab, Daclizumab, Dimethyl fumarate, Fingolimod, Glatiramer acetate, Natalizumab, and Teriflunomide.~~

66 (Canceled).

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67 (Original): The method according to claim 56, wherein to the patients having completed said 2 treatment courses of one year each, no further Cladribine treatment is administered to said patients in the subsequent years 3 and 4.

68 (Original): The method according to claim 56, wherein the progressive form of Multiple Sclerosis is selected from the group consisting of Primary Progressive Multiple Sclerosis and Secondary Progressive Multiple Sclerosis.

69 – 71 (Canceled).

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INTERVIEW SUMMARY

Applicant wishes to thank Examiner Ulm for the helpful and courteous discussion with Applicant's Representative on May 15, 2020. During this discussion a proposed amendment to independent claim 1 was discussed in view of the rejections of record. The discussion mainly focused on the progression of Multiple Sclerosis and distinguishing disease states.

REMARKS

This paper responds to the April 14, 2020, Non-Final Office Action. Claims 1, 34, 49, 56, and 65 are amended. Claims 2, 5-15, 17-18, 20, 23-25, 28, 32, 38-39, 43-47, 51, 55, 60-63, 66, and 69-71 were previously cancelled. Support for the claim amendments can be found at least at p. 12, Ins. 21-22, and throughout the specification, drawings, and claims as originally filed. Upon entry of this paper, claims 1, 3-4, 16, 19, 21-22, 26-27, 29-31, 33-37, 40-42, 48-50, 52-54, 56-59, 64-65, and 67-68 are pending and under consideration. No new matter is believed to have been added by entry of this amendment. Entry and favorable reconsideration are respectfully requested.

Restriction Requirement

The restriction requirement has been made final, but no pending claims are withdrawn. In the March 9, 2020 response to the restriction requirement, Applicant elected the species of peginterferon beta 1a for search purposes only as a disease modifying drug (DMDs) other than cladribine. In the present Amendment, claims 49 and 65 are amended to delete other DMDs besides those pertaining to interferon. Therefore, the other species listed in claims 49 and 65 should be examined with the present claims to the extent that there is allowable subject matter determined.

Improper Markush Grouping

Claims 49 and 65 are rejected because they contain an improper Markush grouping. Office action, pp. 3-4. As noted above and discussed during the May 15, 2020 interview, the amendments to claims 49 and 65 obviate the rejection because the claims recite types of interferons. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 102

Claims 1, 3-4, 16, 19, 21, 22, 26, 27, 29 to 31, 33 to 36, 40, 42, 48 to 50 and 56 are rejected under 35 U.S.C. § 102(a)(1) as being anticipated by De Luca *et al.*, U.S. Pat. No. 8,377,903 (De Luca). Office Action, pp. 5-6.

Independent claims 1, 34, and 56 are newly amended herein to recite that the progressive form of MS is SPMS, PPMS, and PRMS, but not ESPMS. De Luca refers to the use of Cladribine to treat relapsing-remitting MS and early secondary progressive MS. According to the specification of the instant application, “Secondary Progressive Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis.” Specification, p. 12, lns. 21-22. De Luca states, “Approximately, half of the patients with RRMS switch to a progressive course, called SPMS, 10 years after the diseased onset.” De Luca, ¶ [0009] and specification, p. 2, lns. 17-18. The specification describes early SPMS (ESPMS) as, “some form of Multiple Sclerosis that marks some kind of transition state between the relapsing remitting forms of MS and the progressive forms of MS. This form combines the very different aspects and also very different mechanisms of both the pure relapsing remitting forms and the progressive forms of MS.” Specification, p. 4, lns 14-18. Thus, claims 1, 34, and 56, as amended herein, recite that the “progressive multiple sclerosis” refers to specific patient populations.

Furthermore, De Luca exemplified treatment of 60 patients with relapsing forms of MS with orally administered Cladribine at amounts of 1.75 mg/kg and 3.5 mg/kg. De Luca, ¶¶ [0167]-[0169]. In the present application, “preferably patients according to the invention do not suffer from RRMS and/or or ESPMS, or are not diagnosed RRMS and/or ESPMS.” Specification, p. 63, lns. 8-9. The present application appears to be the only source of clinical data showing the efficacy of Cladribine on the progressive form of MS such as SPMS or PPMS patients. The specification also indicates that Cladribine and other disease modifying

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drugs are only approved by the EMA and FDA for treatment of RRMS at present. *Id.*, p. 4, Ins. 1-12.

During the May 15, 2020 interview, the Examiner requested that Applicant clarify why PRMS is not a species of RRMS. Applicant attaches hereto a copy of webpage from the MS Association of America (<https://mymsaa.org/ms-information/overview/types/>), which describes types of MS. The webpage states:

A small percentage of individuals are initially diagnosed with a less common form of MS known as **progressive-relapsing MS (PRMS)**. This type of MS steadily worsens from the onset, but symptom flare-ups – with or without remissions – are also present. However, as the different forms of MS are further studied, redefined, and reclassified, the label of **progressive-relapsing MS** is being used less frequently.

There are also graphs in this reference that illustrate the progression of various types of MS forms, i.e. RRMS, SPMS and PPMS. Applicant submits that a person having ordinary skill in the subject art, such as a physician in the field of MS, could readily distinguish between the different forms of MS. Even though the webpage does not provide a graph for progression of PRMS, the webpage makes it clear that in PRMS, there is a constant worsening or increasing of the symptoms and/or disability over time from the onset of the PRMS (*e.g.*, as shown in the graphical display of PPMS and in the latter two thirds of the graph of SPMS). PRMS lacks the isolated relapses that leads to complete or partial remission. Instead, relapses occur on top of the more or less constantly progressing, worsening or increasing symptoms and/or disability as shown in the PPMS graphical display. PRMS appears to be similar to the second two thirds of the SPMS graphical display, but lacking the isolated relapses/remissions in the

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first third of said SPMS graphical display. Thus, PRMS has a distinct pattern of disease progression from RRMS.

Based upon the claim amendments and foregoing arguments, Applicant submits that De Luca fails to disclose the features recited at least in independent claims 1, 34, and 56. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 103

Claims 52-54, 57-59, 64, 65, 67, and 68 are rejected as obvious under 35 U.S.C. § 103 over De Luca. Office Action, pp. 7-9. Claims 49 and 65 are rejected under 35 U.S.C. § 103 over De Luca in view of the Wiles *et al.*, U.S. Pat. Pub. No. 2017/0057983 (Wiles). *Id.*, p. 9. Wiles is relied upon for the assertion that interferon beta-1a and peginterferon beta-1a are essentially interchangeable in the treatment of multiple sclerosis. It does not remedy the above-mentioned deficiencies of De Luca. Thus, Applicant submits that the applied art does not render as obvious the subject matter of the claims as amended herein. Withdrawal of the rejections is respectfully requested.

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Conclusion

This application presents allowable subject matter, and the Examiner is kindly requested to pass it to issue. Should the Examiner have any questions regarding the claims or otherwise wish to discuss this case, the Examiner is kindly invited to contact Applicant's below-signed representative, who would be happy to provide any assistance deemed necessary in speeding this application to allowance.

Respectfully Submitted,
GRÜNEBERG AND MYERS PLLC

/Kirsten Grueneberg/

Dr. Kirsten Grueneberg
Attorney of Record
Registration No. 47,297

Dr. Cory M. Valley
Registration No. 72,554

Customer Number

151167

Phone: (571) 458-7790

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TRANSMITTAL OF AN INFORMATION DISCLOSURE STATEMENT

Application No.	16/199,119
Filing Date	November 23, 2018
First Named Inventor	Fernando Dangond
Art Unit	1649
Examiner Name	ULM, JOHN D.
Attorney Docket No.	000696US
Title	Cladribine regimen for treating progressive forms of Multiple Sclerosis

Commissioner For Patents
Alexandria, VA 22313

Commissioner:

Applicant submits herewith an Information Disclosure Statement under 37 CFR 1.97. Applicant wishes to make of record the references listed on the attached form PTO-1449 and/or accompanying documents from a corresponding foreign application. Copies of the listed references are attached, except for any US patents and published US patent applications, as are either statements of relevancy or any readily available partial or full English translations of pertinent portions of any non-English language references.

Further:

- ☐ I hereby state that each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this statement.
- ☐ I hereby state that no item of information contained in the Information Disclosure Statement filed herewith was cited in a communication from a foreign patent office in a counterpart foreign application, and, to my knowledge after making reasonable inquiry, no item of information contained in this Information Disclosure Statement was known to any individual designated in 37 CFR § 1.56(c) more than three months prior to the filing of this Information Disclosure Statement.

- ☐ I hereby state that each item of information contained in this Information Disclosure Statement: (i) was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by an individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or (ii) is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

Payment

- ☐ Credit card payment is being made online (if electronically filed), or is attached hereto (if paper filed), in the amount required under 37 CFR 1.17(p).
- ☒ Deposit Account Number 601920.
- ☒ For the above-identified Deposit Account Number, the Director is hereby authorized to:
- ☒ Charge the fee identified in 37 CFR 1.17(p).
 - ☒ Charge any additional fees or underpaid fees.
 - ☒ Credit any overpayment of fee(s).

Grüneberg and Myers, PLLC

Customer No. 151167
Telephone No. 571 458 7790
Facsimile No. 571 458 7789

/Kirsten Grueneberg/

Name	Dr. Kirsten Grueneberg
Reg. No.	47,297

Name	Dr. Cory M. Valley
Reg. No.	72,554

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875				Application or Docket Number 16/199,119		Filing Date 11/23/2018		☐ To be Mailed		
ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO										
APPLICATION AS FILED - PART I										
		(Column 1)	(Column 2)							
FOR		NUMBER FILED	NUMBER EXTRA	RATE (\$)		FEE (\$)				
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))		N/A	N/A	N/A						
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))		N/A	N/A	N/A						
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))		N/A	N/A	N/A						
TOTAL CLAIMS (37 CFR 1.16(i))		minus 20 =	*	x \$100 =						
INDEPENDENT CLAIMS (37 CFR 1.16(h))		minus 3 =	*	x \$460 =						
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))		If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).								
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))										
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL						
APPLICATION AS AMENDED - PART II										
		(Column 1)	(Column 2)	(Column 3)						
AMENDMENT	07/07/2020	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)		
	Total (37 CFR 1.16(i))	* 34	Minus	** 68	= 0	x \$100 =		0		
	Independent (37 CFR 1.16(h))	* 4	Minus	*** 4	= 0	x \$460 =		0		
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
						TOTAL ADD'L FEE		0		
		(Column 1)	(Column 2)	(Column 3)						
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)		
	Total (37 CFR 1.16(i))	*	Minus	**	=	x \$0 =				
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x \$0 =				
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))									
						TOTAL ADD'L FEE				
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.						LIE				
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".						/CORALIA BETANCOURT/				
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".										
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.										

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/199,119	11/23/2018	Fernando Dangond	000696US	8647
151167	7590	05/20/2020		
Gruneberg and Myers PLLC 1775 Tysons Blvd 5th Floor Tysons, VA 22102			EXAMINER ULM, JOHN D	
			ART UNIT	PAPER NUMBER
			1649	
			NOTIFICATION DATE	DELIVERY MODE
			05/20/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

em@gandmpatent.com
kg@gandmpatent.com
patent@gandmpatent.com

<i>Applicant-Initiated Interview Summary</i>	Application No. 16/199,119	Applicant(s) Dangond et al.	
	Examiner JOHN D ULM	Art Unit 1649	AIA (FITF) Status Yes

All participants (applicant, applicants representative, PTO personnel):

(1) JOHN D. ULM. (3) ____.

(2) CORY VALLEY (Applicant's Representative). (4) ____.

Date of Interview: 15 May 2020.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☒ Yes ☐ No.

If Yes, brief description: Proposed amendment to claim 1.

Issues Discussed ☐101 ☐112 ☒102 ☐103 ☐Others

(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 1,4,16,19,21-23,26-27,29-31,33-37,40-42,48-50,52-54,56-59,64-65 and 67-68.

Identification of prior art discussed: De Luca et al. (US 8,377,903).

Substance of Interview

(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Applicant proposed avoiding De Luca et al. by limiting the claims to the treatment of PPMS, SPMS and RPMS. Applicant was advised that SPMS encompasses "early" SPMS as recited in claim 1 of De Luca patent. Applicant was further advised that the text in lines 21-22 on page 12 of the instant specification states that "early" SPMS was only excluded from SPMS as a preferable embodiment. It was suggested that Applicant amend claim 1 to expressly exclude "early" SPMS from the claimed method. Applicant was further advised that the facts of record do not appear to support a position that PRMS is not a sub-genus of RRMS, and was encouraged to provide an art-supported explanation as to the differences between these two forms of MS. It is unclear to the Examiner how a form of MS can be "relapsing" without first having undergone remission..

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☒ Attachment

/JOHN D ULM/
Primary Examiner, Art Unit 1649

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record

A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) 1.133 Interviews

Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.

All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiners responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicants correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:

- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:

- 1) A brief description of the nature of any exhibit shown or any demonstration conducted,-
- 2) an identification of the claims discussed,
- 3) an identification of the specific prior art discussed,
- 4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
- 5) a brief identification of the general thrust of the principal arguments presented to the examiner,
(The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
- 6) a general indication of any other pertinent matters discussed, and
- 7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicants record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiners version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, Interview Record OK on the paper recording the substance of the interview along with the date and the examiners initials.

Agenda

Claim Rejection – improper Markush

See proposed argument.

Claim Rejections – 35 U.S.C. § 102/103

See proposed arguments and claim amendments.

Remarks

1. Rejection – improper Markush group:
 - a. Claims 49 and 65 may be focused to peg-INF and/or INF
2. Rejections – §§ 102/103:
 - a. De Luca refers to use of Cladribine to treat relapsing-remitting MS and early secondary progressive MS. According to the specification of the instant application, “Secondary Progressive Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis.” Specification, p. 12, lns. 21-22. The proposed amendment clarifies the meaning of “progressive” MS. The applied art is clearly directed to RRMS.
 - b.

Proposed Claim Amendments

Claim 1 (Proposed Amendment): A method of treating a progressive form of Multiple Sclerosis, said method comprising: orally administering Cladribine to a patient in need thereof at fixed dose per patient, per body weight and per treatment year, wherein said fixed dose is in a range of 1.5 mg/kg to 4.0 mg/kg, wherein the progressive form of Multiple Sclerosis is selected from the group consisting of Secondary Progressive Multiple Sclerosis SPMS, Primary Progressive Multiple Sclerosis (PPMS), and Progressive Relapsing Multiple Sclerosis PRMS.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/199,119	11/23/2018	Fernando Dangond	000696US	8647
151167	7590	04/14/2020	EXAMINER	
Gruneberg and Myers PLLC			ULM, JOHN D	
1775 Tysons Blvd			ART UNIT	
5th Floor			PAPER NUMBER	
Tysons, VA 22102			1649	
			NOTIFICATION DATE	
			DELIVERY MODE	
			04/14/2020	
			ELECTRONIC	

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The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

em@gandmpatent.com
kg@gandmpatent.com
patent@gandmpatent.com

Office Action Summary

Application No.

16/199,119

Applicant(s)

Dangond et al.

Examiner

JOHN D ULM

Art Unit

1649

AIA (FITF) Status

Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 09 March 2020.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a) ☐ This action is **FINAL**.

2b) ☒ This action is non-final.

3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☒ Claim(s) 1,3-4,16,19,21-22,26-27,29-31,33-37,40-42,48-50,52-54,56-59,64-65 and 67-68 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☒ Claim(s) 1, 3-4, 16, 19, 21-22, 26-27, 29-31, 33-37, 40-42, 48-50, 52-54, 56-59, 64-65 and 67-68i is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10) ☐ The specification is objected to by the Examiner.

11) ☒ The drawing(s) filed on 28 November 2018 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some** c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

3) ☐ Interview Summary (PTO-413)

Paper No(s)/Mail Date _____.

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)

4) ☐ Other: _____.

Paper No(s)/Mail Date _____.

DETAILED ACTION

1) Claims 1, 3, 4, 16, 19, 21, 22, 26, 27, 29 to 31, 33 to 37, 40 to 42, 48 to 50, 52 to 54, 56 to 59, 64, 65, 67 and 68 are pending in the instant application.

Notice of Pre-AIA or AIA Status

2) The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Election/Restrictions

3) Applicant's election with traverse of PEG-Interferon beta-1a as the species of "disease modifying drug other than cladribine" in the reply filed on 09 March, 2020 is acknowledged. The traversal is on the ground(s) that the requirement is allegedly based upon a conclusion "that the species are exclusive, distinct, and not obvious from each other, without providing any reason or example". This is not found persuasive because, ***as stated in the original requirement***, these species are chemically distinct and, in the case of at least interferon beta-1a, Dimethyl fumarate, Glatiramer acetate and Natalizumab, are structurally and functionally unrelated and, consequently, are not obvious variants of each other based on the current record. If Applicant was aware of any common substantial structural feature that is shared between Interferon beta-1a, which is a member of the cytokine family of proteins, Dimethyl fumarate, which is a methyl ester of fumaric acid, the semi-random peptide mixture that defines Glatiramer acetate, and the monoclonal antibody Natalizumab, Applicant should have identified that feature when traversing the requirement. Conversely, Applicant was certainly entitled to identify a single grouping of patentably indistinct species wherein that grouping could include all of the alternate species recited in claims 49 and 65, with the

understanding that, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission would be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species. Applicant has chosen not to submit such evidence or identify such evidence now of record showing the species to be obvious variants, or clearly admit on the record that this is the case.

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

4) There is no information disclosure statement (IDS) of record in the instant application. Applicant is reminded of their duty to disclose to the Office all information known to the person to be material to patentability as defined in 37 CFR 1.56. As stated therein, “[e]ach individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section”. In addition, Applicant’s attention is directed to M.P.E.P. 704.10.

Improper Markush Rejection

5) Claims 49 and 65 are rejected on the basis that they each contain an improper Markush grouping of alternatives. See *In re Harnisch*, 631 F.2d 716, 721-22 (CCPA 1980) and *Ex parte Hozumi*, 3 USPQ2d 1059, 1060 (Bd. Pat. App. & Int. 1984). A Markush grouping is proper if the alternatives defined by the Markush group (i.e., alternatives from which a selection is to be made in the context of a combination or process, or alternative chemical compounds as a whole) share a “single structural similarity” and a common use. A Markush grouping meets these requirements in two

situations. First, a Markush grouping is proper if the alternatives are all members of the same recognized physical or chemical class or the same art-recognized class, and are disclosed in the specification or known in the art to be functionally equivalent and have a common use. Second, where a Markush grouping describes alternative chemical compounds, whether by words or chemical formulas, and the alternatives do not belong to a recognized class as set forth above, the members of the Markush grouping may be considered to share a “single structural similarity” and common use where the alternatives share both a substantial structural feature and a common use that flows from the substantial structural feature. See MPEP § 706.03(y).

As explained in section 3) above, the Markush grouping of alternate embodiments of “disease modifying drug other than cladribine” recited in claims 49 and 65 is improper because the alternatives defined by the Markush grouping do not share both a single structural similarity and a common use.

To overcome this rejection, Applicant may set forth each alternative (or grouping of patentably indistinct alternatives) within an improper Markush grouping in a series of independent or dependent claims and/or present convincing arguments that the group members recited in the alternative within a single claim in fact share a single structural similarity as well as a common use.

Claim Rejections - 35 USC § 102

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of

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rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

(a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale or otherwise available to the public before the effective filing date of the claimed invention.

6) Claims 1, 3, 4, 16, 19, 21, 22, 26, 27, 29 to 31, 33 to 36, 40, 42, 48 to 50 and 56 are rejected under 35 U.S.C. 102(a)(1) as being anticipated by the De Luca et al. patent (U.S. 8,377,903), which corresponds to U.S. Patent Publication U.S. 2010/0203017. The De Luca et al. patent is relied upon because the claims contained therein have of presumption of validity. The De Luca et al. patent publication is being employed a reference because the paragraphs therein are numbered, thereby facilitating the identification of those portions of the De Luca et al. patent upon which the instant rejection is based.

Claims 1, 3, 4 16 19 21 22 27 of the instant application encompass a method of treating a subject afflicted with Secondary Progressive Multiple Sclerosis (SPMS) by the oral administration thereto of 1.70 mg/kg of Cladribine (a.k.a. Mavenclad, a.k.a. Leustatin) in the first two months of a treatment year follows by ten months without the administration of Cladribine. Claims 17, 19, 20, 22 to 24, 26 and 28 of the De Luca et al. patent fairly taught such a method before the filing of the instant application.

With respect to claims 30 and 50, the text in paragraph [0042] of the De Luca et al. patent publication shows that the De Luca et al. patent fairly taught the discontinuation of treatment after any one of “about 2 years”, “about 3 years” and “about 4 years”. That text places no upper limit on how long the treatment should be discontinued.

With respect to claims 31, 33 and 37 the text in paragraph [0169] and Table 2 of the De Luca et al. patent publication, when compared to the material described in Table 12 on page 109 of the instant specification, shows that the De Luca et al. patent fairly taught the use of the 10 mg 2-CdA tablets, “as described in WO 2004/08101”, that are described in the instant specification. Other formulations are further identified in paragraphs [0055] to [0061] of the De Luca et al. patent publication.

With respect to claims 19, 21, 26, 29, 34, 35, 36 and 41, the text in paragraph [0128] of the De Luca et al. patent publication shows that the De Luca et al. patent fairly taught that “the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 5 each month during the induction period”.

With respect to claim 42, the text in paragraphs [0062] to [0071] of the De Luca et al. patent publication shows that the De Luca et al. patent fairly taught that “patients are selected from human males or females between 18 and 55 years of age”.

With respect to claim 49, the text in paragraph [0128] of the De Luca et al. patent publication shows that the De Luca et al. patent fairly taught that “[a]ccording to the invention, Cladribine can be administered alone or in combination with IFN-beta, prophylactically or therapeutically to an individual prior to, simultaneously or sequentially with other therapeutic regimens or agents (e.g. multiple drug regimens), in a therapeutically effective amount, especially therapeutic agents for the treatment of multiple sclerosis”.

All of the elements recited in the instant claims were fairly taught by the De Luca et al. patent in the context claimed by Applicant.

Claim Rejections - 35 USC § 103

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

7) Claims 52 to 54, 57 to 59, 64, 65, 67 and 68 are rejected under 35 U.S.C. 103 as being unpatentable over the De Luca et al. patent (U.S. 8,377,903), which corresponds to U.S. Patent Publication U.S. 2010/0203017. These claims only distinguish over those claims discussed above in that claims 52 and 56 set forth

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specific dosages of Cladribine to be administered in accordance with the specific body weight of a subject to be treated. The text in paragraph [0048] of the De Luca et al. patent publication shows that the De Luca et al. patent fairly taught that "[t]he dosage administered, as single or multiple doses, to an individual will vary depending upon a variety of factors, including pharmacokinetic properties, patient conditions and characteristics (sex, age, body weight, health, size), extent of symptoms, concurrent treatments, frequency of treatment and the effect desired". M.P.E.P. § 2144.05(II)(B) explains that there is a motivation to optimize result-effective variables. As stated therein:

In *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977), the CCPA held that a particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation, because "obvious to try" is not a valid rationale for an obviousness finding. In *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), the Supreme Court held that "obvious to try" was a valid rationale for an obviousness finding, for example, when there is a "design need" or "market demand" and there are a "finite number" of solutions. 550 U.S. at 421 ("The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was '[o]bvious to try.' ... When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103."). Thus, after *KSR*, the presence of a known result-effective variable would be one, but not the only, motivation for a person of ordinary skill in the art to experiment to reach another workable product or process.

The dosage of Cladribine to be administered to a subject in accordance with the therapeutic method of the De Luca et al. patent, as exemplified by claim 17 therein, is

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clearly a result-effective variable that a practitioner of the art of neurobiology would find *prima facie* obvious to optimize.

8) Claims 49 and 65 are rejected under 35 U.S.C. 103 as being unpatentable over the De Luca et al. patent (U.S. 8,377,903) as applied to claims 49 and 65 above, and further in view of the Wiles et al. patent publication (US 2017/0057983). In so far as these claims encompass a method employing Peginterferon beta 1a in place of the INF beta described in paragraph [0128] of the De Luca et al. patent publication, the text in paragraph [0497] of the Wiles et al. patent publication fairly shows that Avonex (interferon beta-1a) and Plegridy (peginterferon beta-1a) were considered to essentially be interchangeable in the art in the treatment of multiple sclerosis. Consequently, one of skill in the art would have found it *prima facie* obvious to have employed peginterferon beta-1a in place of the INF beta (a.k.a. interferon beta-1a) taught by De Luca et al.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JOHN D ULM whose telephone number is (571)272-0880. The examiner can normally be reached on 8:00 to 4:30, Monday through Friday.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JOHN D ULM/
Primary Examiner, Art Unit 1649

<i>Notice of References Cited</i>	Application/Control No. 16/199,119		Applicant(s)/Patent Under Reexamination Dangond et al.	
	Examiner JOHN D ULM		Art Unit 1649	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-8377903-B2	02-2013	De Luca; Giampiero	A61K38/215	514/46
*	B	US-20100203017-A1	08-2010	De Luca; Giampiero	A61K38/21	424/85.6
*	C	US-20170057983-A1	03-2017	Wiles; Jason Allan	C07F9/6561	1/1
	D					
	E					
	F					
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	J					
	K					
	L					
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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Giovannoni et al., Safety and efficacy of cladribine tablets in patients with relapsing–remitting multiple sclerosis: Results from the randomized extension trial of the CLARITY study, 2018, Multiple Sclerosis Journal 24(12):1594 –1604 (Year: 2018)
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

<i>Search Notes</i> 	Application/Control No. 16/199,119	Applicant(s)/Patent Under Reexamination Dangond et al.
	Examiner JOHN D ULM	Art Unit 1649

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Searched Inventor Names in PALM & NPL; Searched GOOGLE, Medline & WEST for: "cladribine", "mavenclad", "leustatin", "progressive multiple sclerosis", "interferon beta", peginterferon beta"	04/09/2020	JDU

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/JOHN D ULM/ Primary Examiner, Art Unit 1649	
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WIKIPEDIA

Human body weight

Human body weight refers to a person's mass or weight. Body weight is measured in kilograms, a measure of mass, throughout the world, although in some countries such as the United States it is measured in pounds, or as in the United Kingdom, stones and pounds. Most hospitals, even in the United States, now use kilograms for calculations, but use kilograms and pounds together for other purposes.

Strictly speaking, body weight is the measurement of weight without items located on the person. Practically though, body weight may be measured with clothes on, but without shoes or heavy accessories such as mobile phones and wallets, and using manual or digital weighing scales. Excess or reduced body weight is regarded as an indicator of determining a person's health, with body volume measurement providing an extra dimension by calculating the distribution of body weight.

Contents

Estimation in children

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- Hamwi method

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External links

Estimation in children

There are a number of methods to estimate weight in children for circumstances (such as emergencies) when actual weight cannot be measured. Most involve a parent or health care provider guessing the child's weight through weight-estimation formulas. These formulas base their findings on the child's age and tape-based systems of weight estimation. Of the many formulas that have been used for estimating body weight, some include the APLS formula, the Leffler formula, and Theron formula.^[1] There are also several types of tape-based systems for estimating children's weight, with the most well-known being the Broselow tape.^[2] The Broselow tape is based on length with weight read from the appropriate color area. Newer systems, such as the PAWPER tape, make use of a simple two-step process to estimate weight: the length-based weight estimation is modified according to the child's body habitus to increase the accuracy of the final weight prediction.^[3]

The Leffler formula is used for children 0–10 years of age.^[1] In those less than a year old it is

$$m = \frac{1}{2}a_m + 4$$

and for those 1–10 years old it is

$$m = 2a_y + 10$$

where *m* is the number of kilograms the child weighs and *a_m* and *a_y* respectively are the number of months or years old the child is.^[1]

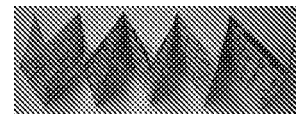
The Theron formula is

$$m = e^{0.175571a_y + 2.197099}$$

where *m* and *a_y* are as above.^[1]

Fluctuation

Body weight varies throughout the day, as the amount of water in the body is not constant. It changes frequently due to activities such as drinking, urinating, or exercise.^{[4][5]} Professional sports participants may deliberately dehydrate themselves to enter a lower weight class, a practice known as weight cutting.^[6]



An example of a half-unfolded Broselow tape

Ideal body weight

Ideal body weight (IBW) was initially introduced by Devine in 1974 to allow estimation of drug clearances in obese patients;^[7] researchers have since shown that the metabolism of certain drugs relates more to IBW than total body weight.^[8] The term was based on the use of insurance data that demonstrated the relative mortality for males and females according to different height-weight combinations.

The most common estimation of IBW is by the Devine formula; other models exist and have been noted to give similar results.^[8] Other methods used in estimating the ideal body weight are body mass index and the Hamwi method. The IBW is not the perfect fat measurement as it does not show the fat or muscle percentage in one's body. For example, athletes' results show that they are overweight when they are actually very fit and healthy. Machines like the dual-energy X-ray absorptiometry (DXA) can accurately measure the percentage and weight of fat, muscle, and bone in a body.

Devine formula

The Devine formula for calculating ideal body weight in adults is as follows:^[8]

- Male ideal body weight = 50 kilograms (110 lb) + 0.9 kilograms (2.0 lb) × (height (cm) − 152)
- Female ideal body weight = 45.5 kilograms (100 lb) + 0.9 kilograms (2.0 lb) × (height (cm) − 152)

Hamwi method

The Hamwi method is used to calculate the ideal body weight of the general adult:^[9]

- Male ideal body weight = 48 kilograms (106 lb) + 1.1 kilograms (2.4 lb) × (height (cm) − 152)
- Female ideal body weight = 45.4 kilograms (100 lb) + 0.9 kilograms (2.0 lb) × (height (cm) − 152)

Usage

Sports

Participants in sports such as [boxing](#), [mixed martial arts](#), [wrestling](#), [rowing](#), [judo](#), [Olympic weightlifting](#), and [powerlifting](#) are classified according to their body weight, measured in units of mass such as pounds or kilograms. See, e.g., [wrestling weight classes](#), [boxing weight classes](#), [judo at the 2004 Summer Olympics](#), and [boxing at the 2004 Summer Olympics](#).

Medicine

Ideal body weight, specifically the [Devine formula](#), is used clinically for multiple reasons, most commonly in estimating renal function in drug dosing, and predicting pharmacokinetics in morbidly obese patients.^{[i0][i1]}

Average weight around the world

By region

Region	Adult population (millions)	Average weight	Overweight population / total population	Source
Africa	535	60.7 kg (133.8 lb)	28.9%	^{[12]}
Asia	2,815	57.7 kg (127.2 lb)	24.2%	^{[12]}
Europe	606	70.8 kg (156.1 lb)	55.6%	^{[12]}
Latin America and the Caribbean	386	67.9 kg (149.7 lb)	57.9%	^{[12]}
North America	263	80.7 kg (177.9 lb)	73.9%	^{[12]}
Oceania	24	74.1 kg (163.4 lb)	63.3%	^{[12]}
World	4,630	62.0 kg (136.7 lb)	34.7%	^{[12]}

By country

Country	Average male weight	Average female weight	Sample population / age range	Methodology	Year	Source
Brazil	72.7 kg (160.3 lb)	62.5 kg (137.8 lb)	20–74	Measured	2008–2009	^{[13]}
Belarus	69 kg (152.1 lb)	56 kg (123.5 lb)	18+	Measured	2008	^{[14]}
Canada	80.3 kg (177 lb)			Measured		
Chile	77.3 kg (170.4 lb)	67.5 kg (148.8 lb)	15+	Measured	2009–2010	^{[15]}
Finland	82.1 kg (181 lb)			Measured		
France	77.1 kg (170 lb)	62.7 kg (138 lb)	15+	Measured	2005	^{[16]}
Germany	82.4 kg (181.7 lb)	67.5 kg (148.8 lb)	18+	Measured	2005	^{[17]}
South Korea	68.6 kg (151.2 lb)	56.5 kg (124.6 lb)	18+	Measured	2007	^{[18]}
Sweden	81.9 kg (180.6 lb)	66.7 kg (147.0 lb)	16–84	Measured	2003–2004	^{[19]}
UK – Wales	84.0 kg (185.2 lb)	69.0 kg (152.1 lb)	16+	Measured	2009	^{[20]}
United States	88.8 kg (195.8 lb)	76.4 kg (168.4 lb)	20+	Measured	2011–2014	^{[21]}

Global statistics

Researchers at the [London School of Hygiene & Tropical Medicine](#) published a study of average weights of adult humans in the journal *BMC Public Health* and at the United Nations conference [Rio+20](#).^[22]

Rank	Country	Kilograms	Pounds	Relative size
1	Micronesia	87.398	192.68	
2	Tonga	87.344	192.56	
3	United States	81.928	180.62	
4	Samoa	78.544	173.16	
5	Kuwait	77.791	171.50	
6	Australia	77.356	170.54	
7	Malta	76.956	169.66	
8	Qatar	76.866	169.46	
9	Croatia	76.412	168.46	
10	United Kingdom	75.795	167.10	
11	UAE	75.532	166.52	
12	Greece	75.038	165.43	
13	Cyprus	74.802	164.91	
14	Egypt	74.271	163.74	
15	Barbados	73.831	162.77	
16	Belarus	73.663	162.40	
17	Bahrain	73.550	162.15	
18	Germany	73.042	161.03	
19	Solomon Islands	72.797	160.49	
20	Austria	72.743	160.37	
21	Saudi Arabia	72.638	160.14	
22	Iceland	72.584	160.02	
23	Trinidad & Tobago	72.538	159.92	
24	Argentina	72.434	159.69	
25	Bahamas	72.380	159.57	
26	Finland	72.348	159.50	
27	Israel	71.912	158.54	
28	Czech Rep.	71.640	157.94	
29	New Zealand	71.631	157.92	
30	Bulgaria	71.459	157.54	
31	Russia	71.418	157.45	
32	Slovenia	71.200	156.97	
33	Slovakia	71.060	156.66	
34	Albania	71.019	156.57	
35	Bosnia	71.001	156.53	
36	Switzerland	70.987	156.50	
37	Rep. of Moldova	70.978	156.48	
38	Venezuela	70.788	156.06	
39	Chile	70.593	155.63	
40	Georgia	70.561	155.56	
41	Spain	70.556	155.55	
42	Azerbaijan	70.484	155.39	
43	Hungary	70.443	155.30	
44	Libya	70.429	155.27	
45	Luxembourg	70.270	154.92	
46	Tajikistan	70.234	154.84	
47	Portugal	70.193	154.75	
48	Lithuania	70.153	154.66	
49	Grenada	70.139	154.63	
50	Panama	69.939	154.19	
51	Ireland	69.926	154.16	

Rank	Country	Kilograms	Pounds	Relative size
52	Canada	69.767	153.81	
53	Jordan	69.649	153.55	
54	St Vincent & Grenadines	69.590	153.42	
55	Belize	69.377	152.95	
56	Poland	69.241	152.65	
57	Macedonia	69.209	152.58	
58	Italy	69.205	152.57	
59	Jamaica	69.064	152.26	
60	Sweden	69.064	152.26	
61	Turkey	69.046	152.22	
62	Cuba	69.037	152.20	
63	Mexico	69.023	152.17	
64	Mongolia	68.910	151.92	
65	Uruguay	68.873	151.84	
66	Belgium	68.801	151.68	
67	Suriname	68.778	151.63	
68	Latvia	68.778	151.63	
69	Norway	68.774	151.62	
70	Netherlands	68.746	151.56	
71	Ukraine	68.674	151.40	
72	Guatemala	68.579	151.19	
73	Saint Lucia	68.438	150.88	
74	Armenia	68.424	150.85	
75	Nicaragua	68.415	150.83	
76	Vanuatu	68.229	150.42	
77	El Salvador	68.220	150.40	
78	Lebanon	68.170	150.29	
79	Ecuador	68.166	150.28	
80	Fiji	68.048	150.02	
81	Bolivia	68.034	149.99	
82	Dominican Rep.	67.993	149.90	
83	Denmark	67.957	149.82	
84	Costa Rica	67.853	149.59	
85	Tunisia	67.726	149.31	
86	Iran	67.608	149.05	
87	Turkmenistan	67.563	148.95	
88	Paraguay	67.445	148.69	
89	Peru	67.440	148.68	
90	Syria	67.422	148.64	
91	Guyana	67.032	147.78	
92	France	66.782	147.23	
93	Estonia	66.732	147.12	
94	Equatorial Guinea	66.451	146.50	
95	Romania	66.401	146.39	
96	Colombia	66.370	146.32	
97	Uzbekistan	66.351	146.28	
98	Kazakhstan	66.265	146.09	
99	Brazil	66.093	145.71	
100	Mauritius	66.052	145.62	
101	Iraq	66.034	145.58	
102	Lesotho	65.966	145.43	

Rank	Country	Kilograms	Pounds	Relative size
103	Honduras	65.834	145.14	
104	Oman	65.803	145.07	
105	South Africa	65.667	144.77	
106	Kyrgyzstan	65.413	144.21	
107	Botswana	65.045	143.40	
108	Cameroon	64.832	142.93	
109	Morocco	64.764	142.78	
110	South Korea	64.392	141.96	
111	Mauritania	64.179	141.49	
112	Algeria	63.639	140.30	
113	Gabon	62.845	138.55	
114	Ghana	62.491	137.77	
115	Cape Verde	62.296	137.34	
116	Papua New Guinea	62.251	137.24	
117	Swaziland	62.097	136.90	
118	Djibouti	62.015	136.72	
119	Haiti	61.698	136.02	
120	Comoros	61.044	134.58	
121	Zimbabwe	61.022	134.53	
122	Brunei	60.945	134.36	
123	Sierra Leone	60.854	134.16	
124	Nigeria	60.745	133.92	
125	Malaysia	60.682	133.78	
126	China	60.555	133.50	
127	Angola	60.387	133.13	
128	Senegal	60.373	133.10	
129	Benin	60.282	132.90	
130	Mali	60.078	132.45	
131	Yemen	59.802	131.84	
132	Philippines	59.715	131.65	
133	Namibia	59.584	131.36	
134	Sudan	59.407	130.97	
135	Togo	59.280	130.69	
136	Guinea	59.112	130.32	
137	Japan	59.017	130.11	
138	Pakistan	58.976	130.02	
139	Singapore	58.935	129.93	
140	Thailand	58.786	129.60	
141	Côte d'Ivoire	58.727	129.47	
142	Laos	58.436	128.83	
143	Chad	58.196	128.30	
144	Niger	57.933	127.72	
145	Maldives	57.647	127.09	
146	São Tomé and Príncipe	57.561	126.90	
147	Burkina Faso	57.456	126.67	
148	Congo	57.384	126.51	
149	Tanzania	57.293	126.31	
150	Gambia	57.071	125.82	
151	Uganda	57.007	125.68	
152	Afghanistan	56.935	125.52	
153	Malawi	56.681	124.96	

Rank	Country	Kilograms	Pounds	Relative size
154	Rwanda	56.635	124.86	
155	Myanmar	56.354	124.24	
156	Kenya	56.264	124.04	
157	Guinea-Bissau	56.087	123.65	
158	Mozambique	55.955	123.36	
159	Central African Rep.	55.946	123.34	
160	Zambia	55.910	123.26	
161	Cambodia	55.742	122.89	
162	Liberia	55.533	122.43	
163	Somalia	55.375	122.08	
164	Madagascar	55.157	121.60	
165	Burundi	54.127	119.33	
166	Congo	53.501	117.95	
167	Ethiopia	53.057	116.97	
168	India	52.943	116.72	
169	North Korea	52.589	115.94	
170	Indonesia	52.467	115.67	
171	Eritrea	52.041	114.73	
172	Timor-Leste	51.950	114.53	
173	Bhutan	51.142	112.75	
174	Vietnam	50.725	111.83	
175	Nepal	50.476	111.28	
176	Sri Lanka	50.421	111.16	
177	Bangladesh	49.591	109.33	
—	world average	61.997	136.68	

See also

- Anthropometry**
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- Body Mass Index (BMI)**
- Body volume index**
- Emaciation**
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- History of anthropometry**
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- List of the heaviest people**
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- Underweight**
- Weight loss and weight gain**
- Weight phobia**

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+ 1	3	☐	☒	US 20150011610 A1	PGPB	20150108	METHOD FOR ENHANCING REMYELINATION USING GLII INHIBITORS	Sal
+ 2	6	☐	☒	US 20100099608 A1	PGPB	20100422	TREATMENT OF DEMYELINATING DISORDERS WITH SOLUBLE LYMPHOTOXIN-BETA- RECEPTOR	BR
	7	☐	☒	US 20100004304 A1	PGPB	20100107	METHODS AND COMPOSITIONS FOR THE TREATMENT OF MALIGNANT MELANOMA, BREAST, PROSTATE, COLON, PAPILLARY THYROID AND PANCREATIC CANCER	Kol
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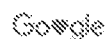
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Date	<u>L8</u>	cladribine or leustatin or mevenclad	25726	<u>L8</u>	<u>L8</u>	<u>L8</u>
Date	<u>L7</u>	15 and 11	133	<u>L7</u>	<u>L7</u>	<u>L7</u>
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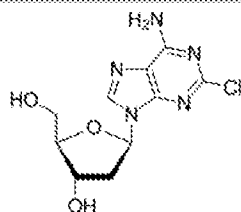
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Cladribine

Cladribine



Clinical data

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Legal status

Pharmacokinetic data

Identifiers

Chemical and physical data

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Cladribine, sold under the brand name **Leustatin** among others, is a medication used to treat hairy cell leukemia (HCL, leukemic reticuloendotheliosis), B-cell chronic lymphocytic leukemia and Relapsing-remitting Multiple Sclerosis (RRMS).^{[4][5]} Its chemical name is 2-chloro-2'-deoxyadenosine (2CdA).

As a purine analog, it is a synthetic chemotherapy agent that targets lymphocytes and selectively suppresses the immune system. Chemically, it mimics the nucleoside adenosine. However, unlike adenosine it is relatively resistant to breakdown by the enzyme adenosine deaminase, which causes it to accumulate in cells and interfere with the cell's ability to process DNA. Cladribine is taken up by cells via a transporter. Once inside a cell cladribine is activated mostly in lymphocytes, when it is triphosphorylated by the enzyme deoxyadenosine kinase (dCK). Various phosphatases dephosphorylate cladribine. Activated, triphosphorylated, cladribine is incorporated into mitochondrial and nuclear DNA, which triggers apoptosis. Non-activated cladribine is removed quickly from all other cells. This means that there is very little non-target cell loss.^{[4][6]}

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Medical uses

Cladribine is used for as a first and second-line treatment for symptomatic hairy cell leukemia and for B-cell chronic lymphocytic leukemia and is administered by intravenous or subcutaneous infusion.^{[5][7]}

Since 2017, cladribine is approved as an oral formulation (10 mg tablet) for the treatment of RRMS in Europe, UAE, Argentina, Chile, Canada and Australia. Marketing authorization for RRMS and SPMS in the US was obtained in March 2019.^{[8][9]}

Some investigators have used the parenteral formulation orally to treat patients with HCL. It is important to note that approximately 40% of oral cladribine is bioavailable orally. It used, often in combination with other cytotoxic agents, to treat various kinds of histiocytosis, including Erdheim–Chester disease^[10] and Langerhans cell histiocytosis.^[11]

Cladribine can cause fetal harm when administered to a pregnant woman and is listed by the FDA as Pregnancy Category D; safety and efficacy in children has not been established.^[7]

Adverse effects

Injectable cladribine suppresses the body's ability to make new lymphocytes, natural killer cells and neutrophils (called myelosuppression); data from HCL studies showed that about 70% of people taking the drug had fewer white blood cells and about 30% developed infections and some of those progressed to septic shock; about 40% of people taking the drug had fewer red blood cells and became severely anemic; and about 10% of people had too few platelets.^[7]

At the dosage used to treat HCL in two clinical trials, 16% of people had rashes and 22% had nausea, the nausea generally did not lead to vomiting.^[7]

In comparison, in MS, cladribine is associated with a 6% rate of severe lymphocyte suppression (lymphopenia) (levels lower than 50% of normal). Other common side effects include headache (75%), sore throat (56%), common cold-like illness (42%) and nausea (39%).^[12]

Mechanism of Action

As a purine analogue, it is taken up into rapidly proliferating cells like lymphocytes to be incorporated into DNA synthesis. Unlike adenosine, cladribine has a chlorine molecule at position 2, which renders it partially resistant to breakdown by adenosine deaminase (ADA). In cells it is phosphorylated into its toxic form, deoxyadenosine triphosphate, by the enzyme deoxycytidine kinase (DCK). This molecule is then incorporated into the DNA synthesis pathway, where it causes strand breakage. This is followed by the activation of transcription factor p53, the release of cytochrome c from mitochondria and eventual programmed cell death (apoptosis).^[13] This process occurs over approximately 2 months, with a peak level of cell depletion 4–8 weeks after treatment^[14]

Within the lymphocyte pool, cladribine targets B cells more than T cells. Both HCL and B-cell chronic lymphocytic leukaemia are types of B cell blood cancers. In MS, its effectiveness may be due to its ability to effectively deplete B cells, in particular memory B cells.^[15] In the pivotal phase 3 clinical trial of oral cladribine in MS, CLARITY, cladribine selectively depleted 80% of peripheral B cells, compared to only 40–50% of total T cells.^[16] More recently, cladribine has been shown to induce long term, selective suppression of certain subtypes of B cells, especially memory B cells.^[17]

Another family of enzymes, the 5' nucleotidase (5NCT) family, is also capable of dephosphorylating cladribine, making it inactive. The most important subtype of this group appears to be 5NCT1A, which is cytosolically active and specific for purine analogues. When DCK gene expression is expressed as a ratio with 5NCT1A, the cells with the highest ratios are B cells, especially germinal centre and naive B cells.^[17] This again helps to explain which B cells are more vulnerable to cladribine-mediated apoptosis.

Although cladribine is selective for B cells, the long term suppression of memory B cells, which may contribute to its effect in MS, is not explained by gene or protein expression. Instead, cladribine appears to deplete the entire B cell department. However, while naive B cells rapidly move from lymphoid organs, the memory B cell pool repopulates very slowly from the bone marrow.

History

Ernest Beutler and Dennis A. Carson had studied adenosine deaminase deficiency and recognized that because the lack of adenosine deaminase led to the destruction of B cell lymphocytes, a drug designed to inhibit adenosine deaminase might be useful in lymphomas. Carson then synthesized cladribine, and through clinical research at Scripps starting in the 1980s, Beutler tested it as intravenous infusion and found it was especially useful to treat hairy cell leukemia (HCL). No pharmaceutical companies were interested in selling the drug because HCL was an orphan disease, so Beutler's lab synthesized and packaged it and supplied it to the hospital pharmacy; the lab also developed a test to monitor blood levels. This was the first treatment that led to prolonged remission of HCL, which was previously untreatable.^{[18]:14–15}

In February 1991, Scripps began a collaboration with Johnson & Johnson to bring intravenous cladribine to market and by December of that year J&J had filed an NDA; cladribine was approved by the FDA in 1993 for HCL as an orphan drug.^[19] and was approved in Europe later that year.^{[20]:2}

The subcutaneous formulation was developed in Switzerland in the early 1990s and it was commercialized by Lipomed GmbH in the 2000s.^{[20]:2[21]}

Multiple sclerosis

In the mid-1990s Beutler, in collaboration with Jack Sipe, a neurologist at Scripps, ran several clinical trials exploring the utility of cladribine in multiple sclerosis, based on the drug's immunosuppressive effects. Sipe's insight into MS, and Beutler's interest in MS due to his sister's having had it, led a very productive collaboration.^{[18]:17[22]} Ortho-Clinical, a subsidiary of J&J, filed an NDA for cladribine for MS in 1997 but withdrew it in the late 1990s after discussion with the FDA proved that more clinical data would be needed.^{[23][24]}

Ivax acquired the rights for oral administration of cladribine to treat MS from Scripps in 2000.^[25] and partnered with Serono in 2002.^[24] Ivax was acquired by Teva in 2006,^{[26][27]} and Merck KGaA acquired control of Serono's drug business in 2006.^[28]

An oral formulation of the drug with cyclodextrin was developed^{[29]:16} and Ivax and Serono, and then Merck KGaA conducted several clinical studies. Merck KGaA submitted an application to the European Medicines Agency in 2009, which was rejected in 2010, and an appeal was denied in 2011.^{[29]:4–5} Likewise Merck KGaA's NDA with the FDA rejected in 2011.^[30] The concerns were that several cases of cancer had arisen, and the ratio of benefit to harm was not clear to regulators.^{[29]:54–55} The failures with the FDA and the EMA were a blow to Merck KGaA and were one of a series of events that led to a reorganization, layoffs, and closing the Swiss facility where Serono had arisen.^{[31][32]} However, several MS clinical trials were still ongoing at the time of the rejections, and Merck KGaA committed to completing them.^[30] A meta-analysis of data from clinical trials showed that cladribine did not increase the risk of cancer at the doses used in the clinical trials.^[33]

In 2015, Merck KGaA announced it would again seek regulatory approval with data from the completed clinical trials in hand,^[31] and in 2016 the EMA accepted its application for review.^[34] On June 22, 2017, the EMA's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the treatment of relapsing forms of multiple sclerosis.^[35]

Finally, after all these problems it was approved in Europe, in August 2017, for highly active RRMS.^[36]

Efficacy

Cladribine is an effective treatment for relapsing remitting MS, with a reduction in the annual rate of relapses of 54.5%.^[12] These effects may be sustained up to 4 years after initial treatment, even if no further doses are given.^[37] Thus, cladribine is considered to be a highly effective immune reconstitution therapy in MS. Similar to alemtuzumab, cladribine is given as two courses approximately one year apart. Each course consists of 4–5 tablets given over a week in the first month, followed by a second dosing of another 4–5 tablets the following month^[38] During this time and after the final dose patients are monitored for adverse effects and signs of relapse.

<https://www.merckneurology.co.uk/wp-content/uploads/2017/08/mavenclad-table-1.jpg>

Safety

Compared to alemtuzumab, cladribine is associated with a lower rate of severe lymphopenia. It also appears to have a lower rate of common adverse events, especially mild to moderate infections.^{[12][37]} As cladribine is not a recombinant biological therapy, it is not associated with the development of antibodies against the drug, which might reduce the effectiveness of future doses. Also, unlike alemtuzumab, cladribine is not associated with secondary autoimmunity.^[39]

This is probably due to the fact cladribine more selectively targets B cells. Unlike alemtuzumab, cladribine is not associated with a rapid repopulation of the peripheral blood B cell pool, which then 'overshoots' the original number by up to 30%.^[40] Instead, B cells repopulate more slowly, reaching near normal total B cells numbers at 1 year. This phenomenon and the relative sparing of T cells, some of which might be important in regulating the system against other autoimmune reactions, is thought to explain the lack of secondary autoimmunity.

Use in clinical practice

The decision to start cladribine in MS depends on the degree of disease activity (as measured by number of relapses in the past year and T1 gadolinium-enhancing lesions on MRI), the failure of previous disease-modifying therapies, the potential risks and benefits and patient choice.

In the UK, the National Institute for Clinical Excellence (NICE) recommends cladribine for treating highly active RRMS in adults if the persons has:

rapidly evolving severe relapsing–remitting multiple sclerosis, that is, at least 2 relapses in the previous year and at least 1 T1 gadolinium-enhancing lesion at baseline MRI or

relapsing–remitting multiple sclerosis that has responded inadequately to treatment with disease-modifying therapy, defined as 1 relapse in the previous year and MRI evidence of disease activity.^[41]

People with MS require counselling on the intended benefits of cladribine in reducing the risk of relapse and disease progression, versus the risk of adverse effects such as headaches, nausea and mild to moderate infections. Women of childbearing age also require counselling that they should not conceive while taking cladribine, due to the risk of harm to the fetus.

Cladribine, as the 10 mg oral preparation Mavenclad, is administered as two courses of tablets approximately one year apart. Each course consists of four to five treatment days in the first month, followed by an additional four to five treatment days in the second month. The recommended dose of Mavenclad is 3.5 mg/kg over 2 years, given in two treatment courses of 1.75 mg/kg/year. Therefore, the number of tablets administered on each treatment day depends on the person's weight. A full guide to the dosing strategy can be found below:

<https://www.merckneurology.co.uk/mavenclad/mavenclad-efficacy/>

After treatment, people with MS are monitored with regular blood tests, looking specifically at the white cell count and liver function. Patients should be followed up regularly by their treating neurologist to assess efficacy, and should be able to contact their MS service in the case of adverse effects or relapse. After the first two years of active treatment no further therapy may need to be given, as cladribine has been shown to be efficacious for up to last least four years after treatment. However, if patients fail to respond, options include switching to other highly effective disease-modifying therapies such as alemtuzumab, fingolimod or natalizumab.

Research directions

Cladribine has been studied as part of a multi-drug chemotherapy regimen for drug-resistant T-cell prolymphocytic leukemia.^[42]

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=> s cladribine or leustatin or "Mavenclad"

2011 CLADRIBINE
19 LEUSTATIN
12 "MAVENCLAD"

L1 2015 CLADRIBINE OR LEUSTATIN OR "MAVENCLAD"

=> s progressive multiple sclerosis

278193 PROGRESSIVE
1364036 MULTIPLE
156180 SCLEROSIS
L2 1923 PROGRESSIVE MULTIPLE SCLEROSIS
(PROGRESSIVE(W)MULTIPLE(W)SCLEROSIS)

=> s l1 (p) l2

L3 22 L1 (P) L2

=> d 1-22 ti so ab au

L3 ANSWER 1 OF 22 MEDLINE ® on STN

TI Cladribine Treatment Improved Homocysteine Metabolism and Increased Total Serum Antioxidant Activity in Secondary Progressive Multiple Sclerosis Patients.

SO Oxidative medicine and cellular longevity, (2020) Vol. 2020, pp. 1654754. Electronic Publication Date: 14 Mar 2020
Journal code: 101479826. E-ISSN: 1942-0994. L-ISSN: 1942-0994.
Report No.: PMC-PMC7103043.

AB Hyperhomocysteinemia plays a crucial role in the pathogenesis of many diseases of the central nervous system (CNS). The nervous system is particularly sensitive to high homocysteine (Hcy) level mainly due to its prooxidative and cytotoxic effects. Cladribine, a drug recently registered for the treatment of multiple sclerosis (MS), possesses additionally neuroprotective effects which are independent of its peripheral immunosuppressant action. Accumulating evidence suggests that oxidative stress and homocysteine thiolactone-mediated protein homocysteinylation play a causal role in MS. Both of these processes may be attenuated by paraoxonase 1 (PON1). Therefore, in the present study, we aimed to examine whether the beneficial effects of the drug in MS patients with a secondary progressive (SP) clinical course, treated with cladribine subcutaneously (s.c.), may be related to its ability to modify serum PON1 activity, Hcy concentration, and protein homocysteinylation, as well as to correct total antioxidant status. A total of 118 subjects were enrolled into the study: (1) patients with a SP type of MS, SP-MS (n = 40); (2) patients with a relapsing-remitting (RR) type of MS, RR-MS (n = 30); and (3) healthy people (n = 48). Patients with SP-MS were treated with cladribine. The drug was given in SP-SM patients s.c. six times every 6 weeks up to a total mean cumulative dose of 1.8 mg/kg. PON1 activity was assessed spectrophotometrically. The level of Hcy, homocysteine thiolactone (HTL) attached to plasma proteins (N-Hcy-protein), and antibodies against homocysteinylation proteins was assessed with an enzyme immunoassay. The total antioxidant activity of the serum was assessed with the ferric-reducing activity of plasma (FRAP) method. Basically, there was no difference in PON1 activity between untreated SP-MS, RR-MS, and control subjects. Serum Hcy was significantly higher in RR-MS patients (p < 0.001) and in SP-MS patients (p < 0.01) compared to the control group. The N-Hcy protein level was higher in

RR-MS patients ($p < 0.05$) in comparison to the control group. Moreover, the elevated level of antibodies against homocysteinylation proteins was observed in the serum of patients with SP-MS. The total antioxidant capacity of serum was lower in MS patients vs. the control group ($p < 0.001$). After cladribine treatment, the activity of PON1 did not change in SP-MS patients, whereas cladribine treatment decreased the level of total Hcy ($p < 0.05$). Treatment with cladribine increased the total serum antioxidant activity in SP-MS patients ($p < 0.01$). The Expanded Disability Status Scale (EDSS) score did not change in SP-MS patients. Cladribine treatment in the SP-MS group attenuates hyperhomocysteinemia-induced protein homocysteinylation (n.s.). It also stabilises the neurological condition of SP-MS patients. The stabilisation of a neurological condition observed in SP-MS patients after cladribine treatment may be partially related to its ability to reduce elevated Hcy level and to improve serum antioxidant potential.

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AU Jamroz-Wisniewska Anna; Rejdak Konrad; Beltowski Jerzy; Wojcicka Grazyna; Bartosik-Psujek Halina

L3 ANSWER 2 OF 22 MEDLINE ® on STN

TI Efficacy and Safety of Intravenous Cladribine in Patients with Rapidly Evolving or Early Secondary Progressive Multiple Sclerosis.

SO Cureus, (2020 Feb 14) Vol. 12, No. 2, pp. e6995. Electronic Publication Date: 14 Feb 2020

Journal code: 101596737. ISSN: 2168-8184. L-ISSN: 2168-8184.

Report No.: PMC-PMC7077152.

AB Background Multiple sclerosis (MS) is an autoimmune and demyelinating inflammatory disease that affects the central nervous system (CNS). The etiology of the disease remains unknown. Multiple theories highlight genetic, environmental, and infectious factors that may a role. MS is considered as the main cause of disability in young people. Cladribine, known chemically as (2-Chloro-2'-deoxyadenosine), is a purine analog chemotherapy used for hairy cell leukemia and other B-cell lymphomas. The goal of this study was to evaluate the safety and efficacy of cladribine in patients with rapidly evolving or early secondary progressive MS. Methods This observational, single-center, retrospective chart review at the MS Clinic in the Ottawa General Hospital, Ottawa, Canada. A total of 24 patients (median Expanded Disability Status Scale (EDSS) of 4.5) received cladribine (0.07 mg/kg/day) for four consecutive days every six months for ≥ 2 cycles with further cycles depending on lymphocyte recovery or disease activity to a maximum of eight cycles from 2005 until 2016 were included. Four patients who were already diagnosed with rapidly evolving or early secondary progressive multiple sclerosis (SPMS) were induced with cladribine. We evaluated relapse, EDSS, and magnetic resonance imaging (MRI) results. Results Out of 24 patients (ages ranging from 30 - 60), 80% were female. Median follow-up time was seven years. The mean relapse rate in the two years before patients were given cladribine was 1.25. Twenty patients had previously received multiple disease-modifying therapies (DMTs) (≥ 2) prior to receiving cladribine. Following cladribine, eight patients suffered 10 relapses (33.3% of the cohort). Annualized relapse rates (ARRs) were reduced from 1.25 to 0.42, which was statistically significant (p -value = 0.002). There was no mean difference in EDSS (p -value = 0.06): 16% deteriorated, 62% did not change, and 12.5% improved. New MRI activity (new T2 or Gad+ lesions) was noted in only seven of 24 patients. Conclusion Parenteral cladribine reduced the relapse rate from 1.25 to 0.42, which was statistically significant (p -value = 0.002). MRI activity in patients with rapidly evolving or early secondary progressive multiple sclerosis had a reasonable safety profile.

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AU Alshamrani Foziah; Alnajashi Hind; Almuaigel Mohammed F

L3 ANSWER 3 OF 22 MEDLINE ® on STN

TI Advances in oral immunomodulating therapies in relapsing multiple sclerosis.

SO The Lancet. Neurology, (2020 Apr) Vol. 19, No. 4, pp. 336-347. Electronic Publication Date: 11 Feb 2020

Journal code: 101139309. E-ISSN: 1474-4465. L-ISSN: 1474-4422.

AB BACKGROUND: Oral treatment options for disease-modifying therapy in relapsing multiple sclerosis have substantially increased over the past

decade with four approved oral compounds now available: fingolimod, dimethyl fumarate, teriflunomide, and cladribine. Although these immunomodulating therapies are all orally administered, and thus convenient for patients, they have different modes of action. These distinct mechanisms of action allow better adaption of treatments according to individual comorbidities and offer different mechanisms of treatment such as inhibition of immune cell trafficking versus immune cell depletion, thereby substantially expanding the available treatment options.

RECENT DEVELOPMENTS: New sphingosine-1-phosphate receptor (S1PR) modulators with more specific S1PR target profiles and potentially better safety profiles compared with fingolimod were tested in patients with relapsing multiple sclerosis. For example, siponimod, which targets S1PR1 and S1PR5, was approved in March, 2019, by the US Food and Drug Administration for the treatment of relapsing multiple sclerosis including active secondary progressive multiple sclerosis. Ozanimod, another S1P receptor modulator in the approval stage that also targets S1PR1 and S1PR5, reduced relapse rates and MRI activity in two phase 3 trials of patients with relapsing multiple sclerosis. Blocking of matrix metalloproteinases or tyrosine kinases are novel modes of action in the treatment of relapsing multiple sclerosis, which are exhibited by minocycline and evobrutinib, respectively. Minocycline reduced conversion to multiple sclerosis in patients with a clinically isolated syndrome. Evobrutinib reduced MRI activity in a phase 2 trial, and a phase 3 trial is underway, in patients with relapsing multiple sclerosis. Diroximel fumarate is metabolised to monomethyl fumarate, the active metabolite of dimethyl fumarate, reduces circulating lymphocytes and modifies the activation profile of monocytes, and is being tested in this disease with the aim to improve gastrointestinal tolerability. The oral immunomodulator laquinimod did not reach the primary endpoint of reduction in confirmed disability progression in a phase 3 trial of patients with relapsing multiple sclerosis. In a phase 2 trial of patients with primary progressive multiple sclerosis, laquinimod also did not reach the primary endpoint of a reduction in brain volume loss, as a consequence the development of this drug will probably not be continued in multiple sclerosis. **WHERE NEXT?:** Several new oral compounds are in late-stage clinical development. With new modes of action introduced to the treatment of multiple sclerosis, the question of how to select and sequence different treatments in individual patients arises. Balancing risks with the expected efficacy of disease-modifying therapies will still be key for treatment selection. However, risks as well as efficacy can change when moving from the controlled clinical trial setting to clinical practice. Because some oral treatments, such as cladribine, have long-lasting effects on the immune system, the cumulative effects of sequential monotherapies can resemble the effects of a concurrent combination therapy. This treatment scheme might lead to higher efficacy but also to new safety concerns. These sequential treatments were largely excluded in phase 2 and 3 trials; therefore, monitoring both short-term and long-term effects of sequential disease-modifying therapies in phase 4 studies, cohort studies, and registries will be necessary.

AU Copyright © 2020 Elsevier Ltd. All rights reserved.
 Derfuss Tobias; Mehling Matthias; Papadopoulou Athina; Bar-Or Amit; Cohen Jeffrey A; Kappos Ludwig

L3 ANSWER 4 OF 22 MEDLINE © on STN
 TI [New aspects of immunotherapy in multiple sclerosis].
 Neues aus der Immuntherapie bei Multipler Sklerose.
 SO Der Nervenarzt, (2018 Dec) Vol. 89, No. 12, pp. 1365-1370.
 Journal code: 0400773. E-ISSN: 1433-0407. L-ISSN: 0028-2804.
 AB The spectrum of therapeutic options for immunotherapy of multiple sclerosis is continuously broadening. After the approval of cladribine and ocrelizumab in Europe, two new drugs are now available with ocrelizumab being the first approved option for treatment of primary progressive multiple sclerosis; however, the increased use of highly effective therapies is accompanied by a rise in severe side effects. During recent months, special attention was paid to the new progressive multifocal leukoencephalopathy (PML) risk assessment in natalizumab-treated patients, cardiac side effects of fingolimod, cases of idiopathic thrombocytopenic purpura and listeria meningitis associated with alemtuzumab and cases of daclizumab-treated patients with liver

failure or encephalitis. These case reports highlight the importance of careful monitoring of all patients treated with immunomodulatory therapies.

AU Pape K; Zipp F; Bittner S

L3 ANSWER 5 OF 22 MEDLINE ® on STN

TI Disease activity in **progressive multiple sclerosis** can be effectively reduced by cladribine.

SO Multiple sclerosis and related disorders, (2018 Aug) Vol. 24, pp. 20-27.

Electronic Publication Date: 1 Jun 2018

Journal code: 101580247. E-ISSN: 2211-0356. L-ISSN: 2211-0348.

AB BACKGROUND: Evidence suggests people with non-relapsing deteriorating ("progressive") multiple sclerosis (pwPMS) may benefit from disease-modifying immune therapy (DMT). However, only one such treatment (ocrelizumab) has been licensed and is highly restricted to pwPMS suffering from the primary progressive phenotype. The difficulties assessing treatment outcome in pwPMS is one important reason for the lack of respective DMT. The concentration of neurofilaments in the cerebrospinal fluid (CSF) provides a biomarker of neuro-axonal damage, and both neurofilament light (NfL) and heavy chain (NfH) levels have been used as outcome indices and to guide treatment choices.

METHODS: We report on two pwPMS, who were treated with subcutaneous cladribine undergoing CSF NfL testing, alongside MRI and clinical follow-up, before and after treatment.

RESULTS: Cladribine treatment was well tolerated without any side effects. CSF NfL after treatment revealed significant reduction (by 73% and 80%, respectively) corroborating the MRI detectable drop in disease activity. Disability mildly progressed in one, and remained stable in the other pwPMS.

CONCLUSIONS: pwPMS with detectable disease activity (MRI, elevated NfL) should be considered for DMT. NfL appears to be a sensitive index of treatment effect in pwPMS, and may be a useful outcome in clinical trials targeting this patient group. Over and above its licensed indication (relapsing MS), cladribine may be an effective treatment option for pwPMS. Copyright © 2018. Published by Elsevier B.V.

AU Yildiz O; Giovannoni G; Malaspina A; Gnanapavan S; Mao Z; Adams A; Dubuisson N; Baker D; Allen-Philbey K; Schmierer K

L3 ANSWER 6 OF 22 MEDLINE ® on STN

TI Cladribine to treat disease exacerbation after fingolimod discontinuation in **progressive multiple sclerosis**.

SO Annals of clinical and translational neurology, (20170700) Vol. 4, No. 7, pp. 506-511. Electronic Publication Date: 17 May 2017

Journal code: 101623278. ISSN: 2328-9503. L-ISSN: 2328-9503.

Report No.: PMC-PMC5497536.

AB Rebound disease following cessation of disease modifying treatment (DMT) has been reported in people with both relapsing and **progressive multiple sclerosis** (pwRMS, pwPMS) questioning strict separation between these two phenotypes. While licensed DMT is available for pwRMS to counter rebound disease, no such option exists for pwPMS. We report on a pwPMS who developed rebound disease, with 45 Gadolinium-enhancing lesions on T1 weighted MRI brain, within 6 months after fingolimod 0.5 mg/day was stopped. Treatment with a short course of subcutaneous cladribine 60 mg led to effective suppression of inflammatory activity and partial recovery with no short-term safety issues or adverse events.

AU Alvarez-Gonzalez Cesar; Turner Benjamin P; Giovannoni Gavin; Baker David; Schmierer Klaus; Alvarez-Gonzalez Cesar; Turner Benjamin P; Giovannoni Gavin; Schmierer Klaus; Adams Ashok; Mathews Joela

L3 ANSWER 7 OF 22 MEDLINE ® on STN

TI Impact of cladribine therapy on changes in circulating dendritic cell subsets, T cells and B cells in patients with multiple sclerosis.

SO Journal of the neurological sciences, (2013 Sep 15) Vol. 332, No. 1-2, pp. 35-40. Electronic Publication Date: 6 Jul 2013

Journal code: 0375403. E-ISSN: 1878-5883. L-ISSN: 0022-510X.

AB BACKGROUND: Cladribine causes sustained reduction in peripheral T and B

cell populations while sparing other immune cells. We determined two populations of dendritic cells (DCs): namely CD1c(+)/CD19(-) (myeloid DCs) and CD303(+)/CD123(+) (plasmacytoid DCs), CD19(+) B lymphocytes, CD3(+) T lymphocytes and CD4(+) or CD8(+) subpopulations in patients with multiple sclerosis after cladribine therapy.

METHODS: We examined 50 patients with secondary progressive multiple sclerosis (SP MS) according to McDonalds et al.'s criteria, 2001 [15]. Blood samples were collected before the initiation of cladribine therapy and after 1st, 2nd, 3th, 4th and 5th courses of treatment. DC subsets, T and B cells were analyzed by flow cytometry.

RESULTS: During cladribine treatment the myeloid DCs CD1c(+)/CD19(-) did not change ($p=0.73175$), and the plasmacytoid DCs CD303(+)/CD123(+) significantly increased ($p=0.00034$) which resulted in significant changes in the ratio of myeloid DCs to plasmacytoid DCs ($p=0.00273$). During therapy, B lymphocyte CD19(+) significantly decreased ($p=0.00005$) and significant changes in CD4(+) cells ($p=0.00191$), changes in CD8(+) cells ($p=0.05760$) and significant changes in CD3(+) ($p=0.01822$) were found.

CONCLUSIONS: We noticed significant trend to increase the CD303(+) circulating the dendritic cells. This population produces large amounts of IFN-alfa. We found significant and rapid decrease in B cells and CD4(+) Th cells. Our results suggest two possible ways of beneficial cladribine influence on immune system in MS. Induction of IFN-alfa producing cells and their predominance over BDCA-1(+) DCs, which are associated with cytotoxic response. Additionally, cladribine could influence two populations of lymphocytes: B cells and Th lymphocytes responsible for induction of immune response against myelin antigens. Copyright © 2013 Elsevier B.V. All rights reserved.

AU Mitosek-Szewczyk Krystyna; Tabarkiewicz Jacek; Wilczynska Barbara; Lobejko Katarzyna; Berbecki Jerzy; Nastaj Marcin; Dworzanska Ewa; Kolodziejczyk Beata; Stelmasiak Zbigniew; Rolinski Jacek

L3 ANSWER 8 OF 22 MEDLINE ® on STN
TI New oral drugs for multiple sclerosis.
SO Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, (2009 Oct) Vol. 30 Suppl 2, pp. S179-83. Ref: 20
Journal code: 100959175. E-ISSN: 1590-3478. L-ISSN: 1590-1874.
AB Disease-modifying treatments are now available in relapsing-remitting and secondary progressive multiple sclerosis (MS), and their beneficial effects have been shown in several clinical studies. However, as these treatments are only partially effective in halting the MS disease process and are frequently associated with side effects and suboptimal patient adherence, new oral therapeutic approaches are warranted. This review focuses on advances in current and novel oral treatment approaches for MS. Several pivotal reports have provided promising results for new oral therapies evaluating the safety and efficacy of new agents including fingolimod, fumaric acid, cladribine, teriflunomide and laquinimod.
AU Gasperini Claudio; Ruggieri S

L3 ANSWER 9 OF 22 MEDLINE ® on STN
TI Recent clinical trials of cladribine in hematological malignancies and autoimmune disorders.
SO Reviews on recent clinical trials, (2006 Jan) Vol. 1, No. 1, pp. 15-34. Ref: 150
Journal code: 101270873. ISSN: 1574-8871. L-ISSN: 1574-8871.
AB The purine nucleoside analog - cladribine (2-chlorodeoxyadenosine, 2-CdA) is a cytotoxic agent with high activity in lymphoid and myeloid malignancies. It is also an effective drug in some autoimmune disorders. 2-CdA is usually administered intravenously in continuous or 2-hour infusion. Recently however, new formulation of this agent has been developed for subcutaneous and oral administration. 2-CdA is widely established as first line standard treatment for hairy cell leukemia. Moreover several clinical trials have demonstrated that this agent, used alone or in combination with other cytotoxic drugs, showed good efficacy and acceptable toxicity profile in the treatment of chronic lymphocytic leukemia, Waldenstrom macroglobulinemia, low-grade non-Hodgkin's lymphoma and acute myeloid leukemia. Moreover, some studies indicate that 2-CdA

has some activity in progressive multiple sclerosis and other autoimmune disorders including autoimmune hemolytic anemia, rheumatoid arthritis, systemic lupus erythematosus, psoriasis and in patients with refractory factor VIII inhibitors. This review article will summarize the results of recent clinical trials with 2-CdA in hematological malignancies, multiple sclerosis and other autoimmune diseases.

AU Robak Tadeusz; Wierzbowska Agnieszka; Robak Ewa

L3 ANSWER 10 OF 22 MEDLINE ® on STN

TI Cladribine.

SO BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy, (1997 May) Vol. 7, No. 5, pp. 386-93.

Journal code: 9705305. ISSN: 1173-8804. L-ISSN: 1173-8804.

AB Cladribine is a novel drug that selectively depletes lymphocytes and may be able to destroy the activated immunocytes that damage the central nervous system in multiple sclerosis. Our initial controlled studies have shown a beneficial, although temporary, dose-related effect of cladribine on the course of chronic progressive multiple sclerosis. Peak improvement in median Scripps Neurological Rating Scale (SNRS) neurological performance scores, followed by gradual decline, occurred at month 14 after initiation of treatment with a 2.8 mg/kg total dose and at month 7 after initiation of treatment with a 1.4 mg/kg total dose. A marked decrease in the presence of enhanced magnetic resonance imaging lesions was observed at both dose levels. Adverse effects are also dose-related. Mild segmental herpes zoster or transient marrow suppression occurred in some patients treated at the higher total dose, whereas no problems of this kind were observed at the lower total dose. It is our hope that studies that are presently under way will establish cladribine as a practical therapeutic option for patients with all non-benign forms of multiple sclerosis.

AU Romine J S; Sipe J C; Koziol J A; Zyroff J; McMillan R; Beutler E

L3 ANSWER 11 OF 22 MEDLINE ® on STN

TI Purine nucleoside analogs as immunosuppressive and antineoplastic agents: mechanism of action and clinical activity.

SO Current medicinal chemistry, (2006) Vol. 13, No. 26, pp. 3165-89.

Journal code: 9440157. ISSN: 0929-8673. L-ISSN: 0929-8673.

AB The purine nucleoside analogs (PNA) form an important group of cytotoxic drugs active in the treatment of neoplastic and autoimmune diseases. Three of them, fludarabine (FA), cladribine (2-chlorodeoxyadenosine, 2-CdA) and pentostatin (2'-deoxycoformycin, DCF) have established clinical activity in hematological malignancies and have been approved by FDA. These drugs are also investigated in some autoimmune disorders. Recently four novel PNA: clofarabine (CAFdA), nelarabine, immucillin H (BCX-1777, forodesine) and 8-chloroadenosine (8-Cl-Ado) have been synthesized and introduced into clinical trials. All these drugs have chemical structure similar to adenosine or guanosine, however, the mechanism of their action is different. FA, 2-CdA and CAFdA mainly require phosphorylation by deoxynucleoside salvage pathways. The cytotoxic effect exerts the triphosphate metabolites, which are incorporated into DNA, and finally lead to programmed cell death. In contrast, DCF does not need to be phosphorylated and results in an increase of plasma deoxyadenosine (dAdo) levels and intracellular deoxyadenosine triphosphate (dATP). Nelarabine is an arabinosylguanine (ara-G) prodrug, which after conversion to ara-G is phosphorylated to ara-G triphosphate (ara-GTP). Accumulation of ara-GTP finally leads to apoptosis. Forodesine is a purine nucleoside phosphatase (PNP) inhibitor which blocks intracellular deoxyguanine (dGuo) cleaving to guanine (Guo), but instead converts it to deoxyguanosine triphosphate (dGTP), and similarly to other PNA resulting in apoptosis. 8-chloroadenosine (8-Cl-Ado) is a ribonucleoside analog. The mechanism of its action is quite different from other PNA and remains poorly understood. However, it is known that the drug inhibits RNA synthesis, but not DNA. These agents have significant cytotoxic activity against lymphoid and myeloid malignant cells. Moreover, they have deleterious effects on the normal resting lymphocytes. They result in prolonged lymphocyte depletion especially in the CD4 subset of T-cells. Several clinical trials have demonstrated that PNA used alone or in combination with other cytotoxic drugs or monoclonal antibodies shows good efficacy and acceptable toxicity profile in the treatment of lymphoid malignancies. 2-CdA and DCF are drugs of choice in the treatment of hairy cell leukemia.

FA and 2-CdA have significant clinical activity in low-grade non-Hodgkin's lymphoma and chronic lymphocytic leukemia. 2-CdA exhibits some activity in **progressive multiple sclerosis** and other autoimmune disorders. This review will summarize current knowledge concerning the mechanism of action, pharmacological properties, clinical activity and toxicity of PNA accepted for use in clinical practice as well as new agents available for clinical trials.

AU Robak Tadeusz; Lech-Maranda Ewa; Korycka Anna; Robak Ewa

L3 ANSWER 12 OF 22 MEDLINE ® on STN

TI Cladribine followed by autologous stem-cell transplantation in **progressive multiple sclerosis**.

SO Internal medicine journal, (2004 Jan-Feb) Vol. 34, No. 1-2, pp. 66-9.

Journal code: 101092952. ISSN: 1444-0903. L-ISSN: 1444-0903.

AB We studied the safety of autologous peripheral blood stem-cell transplantation (PBSCT) in four patients with **progressive multiple sclerosis**. Clinical and magnetic resonance imaging outcomes were secondary end-points. Cladribine administration preceded filgrastim-primed PBSC collection, aiming for lymphocyte depletion. Conditioning was with antithymocyte globulin and cyclophosphamide. The procedure was well tolerated, but without obvious clinical benefit. The study was terminated when other therapeutic options with lower morbidity became available.

AU Grigg A; Tubridy N J; Szer J; Mitchell P; Butzkueven H; Shuttleworth P; Kilpatrick T

L3 ANSWER 13 OF 22 MEDLINE ® on STN

TI Effect of immunosuppressive cladribine treatment on serum leucocytes system in two-year clinical trial in patients with chronic **progressive multiple sclerosis**.

SO Medical science monitor : international medical journal of experimental and clinical research, (2001 Jan-Feb) Vol. 7, No. 1, pp. 93-8.

Journal code: 9609063. ISSN: 1234-1010. L-ISSN: 1234-1010.

AB BACKGROUND: Multiple sclerosis is presumably cell-mediated autoimmune disorder with immune abnormalities as presence of activated T-cells and increase interleukin 2 (IL-2) and soluble IL-2 receptor (sIL-2R) levels in central nervous system and peripheral blood of patients. The aim of immunosuppressive treatment is to diminish such activation. The aim of this study was to evaluate the influence of immunosuppressive cladribine treatment with total dose of 2.1 mg/kg b.w. administered in 7 cycles for 12 months, on serum leucocytes in 34 chronic **progressive multiple sclerosis** (CPMS) patients observed for 2 years as well as IL-2 and sIL-2R serum levels assessed before and right after the treatment.

MATERIAL AND METHODS: The study was designed as a randomised, placebo-controlled, double-blind trial. The patients were divided in two groups: group I, cladribine-treated, n = 34; group II, placebo-treated, n = 35. Group III were healthy controls, n = 20. Leucocyte levels were determined with flow-cytometry. IL-2 and sIL-2R levels were assessed with enzyme-linked immunosorbent assay.

RESULTS: Statistically significant gradual decrease of lymphocyte level was observed from 7th week to 12th month after the beginning of treatment. During the following 12 months, lymphocyte levels remained decreased in comparison to baseline. Mean values of IL-2 and sIL-2R levels measured 12 months after the treatment were found to be lowered by 20% (p. = 0.01) and by 24% (p. = 0.0005), respectively.

CONCLUSION: The results obtained indicate fast and long-lasting decrease of serum leucocyte level and suppressive influence of cladribine treatment on immune processes in multiple sclerosis patients.

AU Janiec K; Wajgt A; Kondera-Anasz Z

L3 ANSWER 14 OF 22 MEDLINE ® on STN

TI The effect of cladribine on T(1) 'black hole' changes in progressive MS.

SO Journal of the neurological sciences, (2000 May 01) Vol. 176, No. 1, pp. 42-4.

Journal code: 0375403. ISSN: 0022-510X. L-ISSN: 0022-510X.

AB We compared the changes of the volumes of T(1)-hypointense lesions seen on

the magnetic resonance imaging scans of the brain from 159 **progressive multiple sclerosis (MS)** patients who were enrolled in a double-blind, placebo-controlled trial assessing the efficacy of two doses of **cladribine**. Although in patients treated with **cladribine** there was a tendency to have a lower increase of T(1)-hypointense lesion volumes than those treated with placebo, no statistically significant effect of **cladribine** on T(1)-hypointense lesion accumulation was found over the one-year double-blind phase. Furthermore, no significant treatment effect was also detected in a subset of 22 patients who received placebo during the double-blind phase of the study and **cladribine** during the subsequent one-year open-label phase. We conclude that **cladribine** does not have a major impact on the mechanisms leading to severe tissue destruction in **progressive MS**.

AU Filippi M; Rovaris M; Rice G P; Sormani M P; Iannucci G; Giacomotti L; Comi G

L3 ANSWER 15 OF 22 MEDLINE ® on STN

TI The **cladribine** trial in secondary **progressive multiple sclerosis**: A reanalysis.

SO Neuroepidemiology, (2000 Mar-Apr) Vol. 19, No. 2, pp. 109-12.
Journal code: 8218700. ISSN: 0251-5350. L-ISSN: 0251-5350.

AB In a recent communication, Goodin [1] analyzes several clinical trials to point out serious flaws in both design and interpretation that may invalidate the conclusions that are drawn. We agree with Goodin [1] that the design of clinical studies, particularly of a disease as complex as multiple sclerosis, is extremely difficult. Indeed, a perfectly designed and executed clinical study is a goal that is never achieved because of the problems inherent in providing care to patients while attempting to evaluate a therapeutic modality. Specifically, in the study of multiple sclerosis, none of the clinical trials of the use of interferons could be considered fully satisfactory: blinding is actually impossible because of the symptoms that are experienced by patients when they receive active drug but not when they receive placebo. It is quite fashionable and not at all difficult to find problems in the conduct of clinical studies; indeed, if all clinical studies with flaws were discarded, there would be no acceptable clinical studies.

AU Beutler E; Koziol J A

L3 ANSWER 16 OF 22 MEDLINE ® on STN

TI Safety and tolerability of subcutaneous **cladribine** therapy in **progressive multiple sclerosis**.

SO The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques, (1998 Nov) Vol. 25, No. 4, pp. 295-9.
Journal code: 0415227. ISSN: 0317-1671. L-ISSN: 0317-1671.

AB OBJECTIVE: To evaluate the safety and tolerability of subcutaneous (s.c.) **cladribine** therapy in patients with chronic **progressive multiple sclerosis (CPMS)**, and to evaluate the effects on lymphocyte subsets.

BACKGROUND: **Cladribine**, a synthetic antineoplastic agent with immunosuppressive effects, may favourably affect the course of CPMS. However results of a previous reported clinical trial showed significant myelosuppression in some patients.

DESIGN/METHODS: 19 patients with severe (mean extended disability status score [EDSS] = 6.7) CPMS were treated on a compassionate basis with **cladribine** 0.07 mg/kg/day s.c. for 5 days per cycle, repeated every 4 weeks for a total of 6 cycles. Patients underwent clinical evaluation, EDSS, and hematologic analysis before, during, and following therapy.

RESULTS: The treatment was very well tolerated with no clinically significant side effects observed. Between baseline and the end of cycle 6, mean decreases were noted in absolute lymphocyte count from 1697 to 463 ($p = 0.000012$), CD4 count from 865 to 187 ($p = 0.0000008$), CD8 from 418 to 165 ($p = 0.005$) and CD19 from 197 to 26 ($p = 0.000002$). Platelet, granulocyte and RBC counts were unaffected. Approximately one year after completion of therapy, some recovery of CD4 and CD8 counts had occurred although both counts remained suppressed compared to baseline (302 and 227 respectively); the CD19 count had recovered essentially to normal by one year. EDSS scores post-therapy revealed some deterioration in 8 patients and stable scores in the remaining 11. Global patient evaluations of the

treatment were mixed.

CONCLUSIONS: Cladribine therapy, at lower doses than previously reported, was remarkably well tolerated in CPMS, with no significant myelosuppression. Profound effects occurred in total lymphocyte count and CD4, CD8 and CD19 subsets.

AU Selby R; Brandwein J; O'Connor P

L3 ANSWER 17 OF 22 MEDLINE @ on STN

TI Development of cladribine treatment in multiple sclerosis.

SO Multiple sclerosis (Houndmills, Basingstoke, England), (1996 Jul) Vol. 1, No. 6, pp. 343-7.

Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

AB Cladribine is a new type of drug with properties of selective lymphocyte suppression that appear to favorably alter the clinical course of progressive multiple sclerosis (MS). The history of the development of cladribine treatment in chronic progressive MS is discussed, and the application of cladribine treatment to progressive multiple sclerosis in a double-blind, placebo crossover study is reviewed. Cladribine selectively targets both resting and dividing lymphocytes and may be able to destroy the activated lymphocytes that induce CNS demyelination, thus producing stabilization or improvement in chronic MS. Although the role of cladribine has not yet been fully defined, additional studies are underway to evaluate the efficacy and safety of cladribine in both progressive MS and relapsing-remitting MS.

AU Sipe J C; Romine J S; Koziol J A; McMillan R; Zyroff J; Beutler E

L3 ANSWER 18 OF 22 MEDLINE @ on STN

TI A comparison of two neurologic scoring instruments for multiple sclerosis.

SO Journal of neurology, (1996 Mar) Vol. 243, No. 3, pp. 209-13.

Journal code: 0423161. ISSN: 0340-5354. L-ISSN: 0340-5354.

AB We examined the degree of association between two neurologic impairment scales, the Extended Disability Status Scale (EDSS) and the Scripps Neurologic Rating Scale (SNRS), with data from a randomized, double-blind, placebo-controlled clinical trial assessing the safety and efficacy of cladribine as treatment for chronic progressive multiple sclerosis (MS). We found that the EDSS and SNRS were not strongly correlated within individual patients, contrary to expectation; moreover, in 9 of the 48 evaluable patients, the directions of their changes from baseline values were not mutually consistent. The scales were differentially sensitive to clinical changes over time, with the EDSS indicating a more abrupt, and the SNRS a more gradual, change in the clinical course of disease. The validity of different impairment scales, and their sensitivity to detect clinical changes, should be formally assessed in future clinical trials using these scales as outcome measures.

AU Koziol J A; Frutos A; Sipe J C; Romine J S; Beutler E

L3 ANSWER 19 OF 22 MEDLINE @ on STN

TI The treatment of chronic progressive multiple sclerosis with cladribine.

SO Proceedings of the National Academy of Sciences of the United States of America, (1996 Feb 20) Vol. 93, No. 4, pp. 1716-20.

Journal code: 7505876. ISSN: 0027-8424. L-ISSN: 0027-8424.

Report No.: PMC-PMC40008.

AB A 2-year, placebo-controlled, double-blind, crossover study was started in 1992 to evaluate cladribine, an immunosuppressive drug, in the treatment of chronic progressive multiple sclerosis. In the first year patients were given cladribine 0.10 mg/kg per day for 7 days as four monthly courses for a total of 2.8 mg/kg or placebo. During the second year patients treated with placebo during the first year were given i.v. infusions of 0.10 mg, 0.05 mg, and 0.05 mg of cladribine per kg of body weight per day for 7 consecutive days in three successive monthly courses, for a total dose of 1.4 mg/kg. Patients who had been treated previously with cladribine were crossed over to placebo. Analysis of the results revealed a favorable influence on the neurological performance scores, both in the Kurtz extended disability status and the Scripps neurological rating scale, and on MRI findings in patients treated with cladribine. In the first year the most striking finding was that while clinical deterioration continued in the placebo-treated patients, the condition of patients who received cladribine stabilized or even improved slightly.

Toxicity and therapeutic response were dose-related.
 AU Beutler E; Sipe J C; Romine J S; Koziol J A; McMillan R; Zyroff J

L3 ANSWER 20 OF 22 MEDLINE ® on STN
 TI The treatment of multiple sclerosis: current and future.
 SO Current opinion in neurology, (1995 Jun) Vol. 8, No. 3, pp. 200-9. Ref: 87
 Journal code: 9319162. ISSN: 1350-7540. L-ISSN: 1350-7540.
 AB During the past year observations have been published that might lead to further improvement in the design of future clinical trials. At the same time, results of clinical trials have become available that suggest that a number of treatments could be of benefit in the care of patients in the various phases of multiple sclerosis. Future multiple sclerosis clinical trials should involve a blinded investigator restricted to assessing the clinical outcome variables, and because current evidence suggests that magnetic resonance imaging gives an objective and sensitive reflection of the biological evolution of the disease, such scanning should also be included. The use of a composite outcome variable in a trial of chronic progressive multiple sclerosis should also be considered in order to increase the percentage of patients reaching the clinical endpoint. In 1994 recommendations were published for the selection of relapsing-remitting patients for treatment with interferon beta-1b; furthermore, large and well performed clinical trials demonstrated that interferon beta-1a and copolymer-1 are also partially effective, though not curative, for these patients. Two smaller studies suggested that low-dose methotrexate and cladribine might have a beneficial effect on the course of the disease in patients with secondary chronic progressive multiple sclerosis, the former drug probably being less toxic. Unfortunately, therapeutic perspectives for patients with primary progressive multiple sclerosis are less promising at present. Several studies suggest that 4-aminopyridine and tizanidine have therapeutic potential for symptomatic treatment; the former by improving neurological deficits, the latter by relieving troublesome spasticity.(ABSTRACT TRUNCATED AT 250 WORDS)
 AU Polman C H; Hartung H P

L3 ANSWER 21 OF 22 MEDLINE ® on STN
 TI [Cladribine in chronic progressive multiple sclerosis].
 Cladribin bei chronisch progredienter multipler Sklerose.
 SO Der Nervenarzt, (1995 Apr) Vol. 66, No. 4, pp. 299-303.
 Journal code: 0400773. ISSN: 0028-2804. L-ISSN: 0028-2804.
 AU Weilbach F X; Hartung H P

L3 ANSWER 22 OF 22 MEDLINE ® on STN
 TI Cladribine in treatment of chronic progressive multiple sclerosis.
 SO Lancet (London, England), (1994 Jul 02) Vol. 344, No. 8914, pp. 9-13.
 Journal code: 2985213R. ISSN: 0140-6736. L-ISSN: 0140-6736.
 AB Chronic progressive multiple sclerosis (MS) is a severely disabling demyelinating disease in which autoimmune processes seem to have a major role. The nucleoside drug cladribine is a potent lympholytic agent with few side-effects. We have studied its efficacy and safety in a randomised double-blind trial. 51 patients (48 entered as matched pairs) received four monthly courses of 0.7 mg/kg cladribine or placebo (saline) given through a surgically implanted central line. Neurologists with no knowledge of which medication the patient was receiving examined the patients monthly and noted two rating scale scores (Kurtzke and Scripps). Cerebrospinal fluid and brain magnetic resonance imaging (MRI) examinations were done at 6 and 12 months. Average neurological scores, demyelinated volumes on MRI, and concentrations of oligoclonal bands in cerebrospinal fluid were stable or improved in the patients receiving cladribine but continued to deteriorate in patients on placebo. Mean paired (placebo minus matched cladribine) differences at 12 months relative to baseline were 1.0 (SE 0.4) for the Kurtzke scores, -13.9 (2.3) for the Scripps scores, 4.57 (1.17) mL for demyelinated volumes, and 7.3 (3.3) arbitrary units for concentrations of oligoclonal bands. Cladribine was generally well tolerated and clinically significant toxicity occurred in only 1 patient, in whom severe marrow suppression developed with complete recovery after several months. 1 patient died of newly acquired hepatitis B, an event unlikely to be related to

cladribine. We conclude that the immunosuppressive drug cladribine influences favourably the course of chronic progressive MS.
AU Sipe J C; Romine J S; Koziol J A; McMillan R; Zyroff J; Beutler E

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	9.90	10.08

STN INTERNATIONAL LOGOFF AT 16:55:05 ON 09 APR 2020

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application Number	16/199,119
Filing Date	November 23, 2018
First Named Inventor	Fernando Dangond
Art Unit	1649
Examiner Name	ULM, JOHN D
Attorney Docket No.	000696US
Title	Cladribine regimen for treating progressive forms of Multiple Sclerosis

RESTRICTION RESPONSE

Commissioner for Patents
Alexandria, Virginia 22313

Commissioner:

In response to the Restriction Requirement dated January 17, 2020, the Applicant elects as a species **Peginterferon beta 1a, with traverse**. Claims 1, 3-4, 16, 19, 21-22, 26-27, 29-31, 33-37, 40-42, 48-50, 52-54, 56-59, 64-65, and 67-68 read on the elected species.

Remarks begin on page 2 of this paper.

REMARKS

Election of Species

The Examiner is requiring an election of species from ten different species of “disease modifying drug other than cladribine” listed in at least claims 49 and 65, which are as follows:

Interferon beta-1a, Beta interferon-1a,

Interferon beta-1b, Beta interferon-1b,

Peginterferon beta 1a,

Alemtuzumab,

Daclizumab,

Dimethyl fumarate,

Fingolimod,

Glatiramer acetate,

Natalizumab, and

Teriflunomide.

The applicant provisionally elects **Peginterferon beta 1a, with traverse**, for search purpose only. The claims readable on the elected species include claims 1, 3-4, 16, 19, 21-22, 26-27, 29-31, 33-37, 40-42, 48-50, 52-54, 56-59, 64-65, and 67-68.

The Examiner asserts that the above species are independent or distinct because they allegedly have mutually exclusive characteristics, are chemically distinct, and not obvious variants of each other. The Examiner therefore asserts that there is a search and examination burden. However, the Examiner is making a conclusory statement that the species are exclusive, distinct, and not obvious from each other, without providing any reason or example. *See* MPEP 803. As such, the Examiner has not fully met his burden of showing that

the species are independent or distinct. Withdrawal of the Restriction Requirement is respectfully requested.

Conclusion

The applicant therefore respectfully requests examination on the merits and prompt notice thereof.

Grüneberg and Myers, PLLC		/Kirsten Grueneberg/	
Customer No. 151167		Name	Dr. Kirsten Grueneberg
Telephone No. 571 458 7790		Reg. No.	47,297
Facsimile No. 571 458 7789		Name	Eric Myers
		Reg. No.	68,546

Electronic Acknowledgement Receipt

EFS ID:	38811917
Application Number:	16199119
International Application Number:	
Confirmation Number:	8647
Title of Invention:	Cladribine regimen for treating progressive forms of Multiple Sclerosis
First Named Inventor/Applicant Name:	Fernando Dangond
Customer Number:	151167
Filer:	Eric J.I. Myers/W. Michael Buck
Filer Authorized By:	Eric J.I. Myers
Attorney Docket Number:	000696US
Receipt Date:	09-MAR-2020
Filing Date:	23-NOV-2018
Time Stamp:	17:35:31
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2020-03-09-Response-to-RR-as-filed.pdf	223258	yes	4
			ec39bc96b016fc7b3d12166e8fe57e3b8a168c5a		

Multipart Description/PDF files in .zip description			
Document Description	Start	End	
Transmittal Letter	1	1	
Response to Election / Restriction Filed	2	2	
Applicant Arguments/Remarks Made in an Amendment	3	4	

Warnings:

Information:

Total Files Size (in bytes):	223258
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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Docket No. 000696US

GRÜNEBERG
MYERS
P L L C

ATTORNEYS AT LAW

Application of Fernando Dangond

Serial No.: 16/199,119

Filed on: November 23, 2018

Examiner: ULM, JOHN D

Group Art Unit: 1629

For: Cladribine regimen for treating progressive forms of Multiple Sclerosis

Commissioner for Patents
Alexandria, Virginia 22313

Commissioner:

The following papers are attached herewith:

RESTRICTION RESPONSE

Please charge additional fee(s) or underpayment of fee(s) to Deposit Account No. 601920 under 37 CFR 1.16 and 1.17, and please credit any overpayment of fee(s) to Deposit Account No. 601920. If these papers are not considered timely, then Applicants hereby petition under 37 CFR 1.136 for any necessary extension of time, further authorizing any necessary extension of time fees to be charged to Deposit Account No. 601920.

Respectfully Submitted,
GRÜNEBERG AND MYERS PLLC

/Kirsten Grueneberg/

Customer Number

151167

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Dr. Kirsten Grueneberg
Attorney of Record
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Eric Myers
Registration No. 68,546



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/199,119	11/23/2018	Fernando Dangond	000696US	8647
151167	7590	01/17/2020		
Gruneberg and Myers PLLC			EXAMINER	
1775 Tysons Blvd			ULM, JOHN D	
5th Floor				
Tysons, VA 22102			ART UNIT	PAPER NUMBER
			1649	
			NOTIFICATION DATE	DELIVERY MODE
			01/17/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

em@gandmpatent.com
kg@gandmpatent.com
patent@gandmpatent.com

Office Action Summary

Application No.

16/199,119

Applicant(s)

Dangond et al.

Examiner

JOHN D ULM

Art Unit

1649

AIA (FITF) Status

Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on _____.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
- 2a) ☐ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

- 5) ☒ Claim(s) 1,3-4,16,19,21-22,26-27,29-31,33-37,40-42,48-50,52-54,56-59,64-65 and 67-68 is/are pending in the application.
- 5a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 6) ☐ Claim(s) _____ is/are allowed.
- 7) ☐ Claim(s) _____ is/are rejected.
- 8) ☐ Claim(s) _____ is/are objected to.
- 9) ☒ Claim(s) 1,3-4,16,19,21-22,26-27,29-31,33-37,40-42,48-50,52-54,56-59,64-65 and 67-68 are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some** c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date _____.
- 3) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____.
- 4) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3, 4, 16, 19, 21, 22, 26, 27, 29 to 31, 33 to 37, 40 to 42, 48 to 50, 52 to 54, 56 to 59, 64, 65, 67 and 68 are pending in the instant application. Claims 2, 5 to 15, 17, 18, 20, 23 to 25, 28, 32, 38, 39, 43 to 47, 51, 55, 60 to 63, 66 and 69 to 71 have been canceled as requested by Applicant in the correspondence filed 19 February of 2019.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Election/Restrictions

Claims 1, 3, 4, 16, 19, 21, 22, 26, 27, 29 to 31, 33 to 37, 40 to 42, 48 to 50, 52 to 54, 56 to 59, 64, 65, 67 and 68 are generic to the ten different species of "disease modifying drug other than cladribine" listed in claims 49 and 65. The species are independent or distinct because as disclosed the different species have mutually exclusive characteristics for each identified species. In addition, these species are chemically distinct and, in the case of at least Interferon beta-1a, Dimethyl fumarate, Glatiramer acetate and Natalizumab, are structurally and functionally unrelated and, consequently, are not obvious variants of each other based on the current record. As a result, there is a search and examination burden for these patentably distinct species because there is no reasonable expectation that a prior art reference which anticipates one embodiment of the claimed method will anticipate or render obvious one or more of the alternate drug combinations encompassed by the instant claims.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species, for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or a grouping of patentably indistinct species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species** or grouping of patentably indistinct species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art,

the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be corrected in compliance with 37 CFR 1.48(a) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. A request to correct inventorship under 37 CFR 1.48(a) must be accompanied by an application data sheet in accordance with 37 CFR 1.76 that identifies each inventor by his or her legal name and by the processing fee required under 37 CFR 1.17(i).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JOHN D ULM whose telephone number is (571)272-0880. The examiner can normally be reached on 8:00 to 4:30, Monday through Friday.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JOHN D ULM/
Primary Examiner, Art Unit 1649



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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/199,119	11/23/2018	Fernando Dangond	000696US

CONFIRMATION NO. 8647

PUBLICATION NOTICE



OC000000108723105

151167
Gruneberg and Myers PLLC
1775 Tysons Blvd
5th Floor
Tysons, VA 22102

Title:Cladribine regimen for treating progressive forms of Multiple Sclerosis

Publication No.US-2019-0167707-A1

Publication Date:06/06/2019

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently <http://www.uspto.gov/patft/>.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently <https://portal.uspto.gov/pair/PublicPair>. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101



United States Patent and Trademark Office

Office of the Chief Financial Officer

April 02, 2019

151167
GRUNEBERG AND MYERS PLLC
Attn: KIRSTEN GRUENEBERG
1775 TYSONS BOULEVARD
5th FLOOR
TYSONS, VA 22102

Dear Sir/Madam,

The United States Patent and Trademark Office (USPTO) has reviewed your refund request for Reference Number **16199119** - Refund Request ID **REFND-20190319-00007**. Below is the current status of your refund request assigned to the following processing area: Office of Patent Application Processing

Fee code	Decision	Decision Reason(s)	Refund Amount
1202	Dismissed	Other - The Office received your preliminary amendment 02/19/2019 and adjusted the claims accordingly. However, The Office calculated the claims as presented at filing. The Office cannot refund excess claim fees that were properly paid merely because the applicant cancels or amends the excess claims prior to the first Office action. No refund will be made once the fee for claims is properly paid, even though claims are later canceled, unless a petition for express abandonment under 37 CFR 1.138(d) is granted. See MPEP 711.01.	\$0.00

Please refer to the following page to review the detailed dismissal reason(s).

You will receive a separate decision letter for any additional fee codes assigned to other processing areas, if applicable. Decisions may be subject to change if an error is identified.

For questions related to this refund request, contact the Office of Patent Application Processing at (703) 756-1158.

Thank you,
Refund Branch

Enclosure: Refund Dismissal Reason(s)

Refund Dismissal Reason(s) for fee code 1202:

- Other - The Office received your preliminary amendment 02/19/2019 and adjusted the claims accordingly. However, The Office calculated the claims as presented at filing. The Office cannot refund excess claim fees that were properly paid merely because the applicant cancels or amends the excess claims prior to the first Office action. No refund will be made once the fee for claims is properly paid, even though claims are later canceled, unless a petition for express abandonment under 37 CFR 1.138(d) is granted. See MPEP 711.01.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875						Application or Docket Number 16/199,119	
APPLICATION AS FILED - PART I							
(Column 1)		(Column 2)		SMALL ENTITY		OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	300
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	660
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760
TOTAL CLAIMS (37 CFR 1.16(j))	34	minus 20 = * 14				x 100 =	1400
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4	minus 3 = * 1				x 460 =	460
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
				TOTAL		TOTAL	3580
* If the difference in column 1 is less than zero, enter "0" in column 2.							
APPLICATION AS AMENDED - PART II							
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY	
AMENDMENT A		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=	x	=
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x	=
	Application Size Fee (37 CFR 1.16(s))						
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	
(Column 1)		(Column 2)		(Column 3)		OTHER THAN SMALL ENTITY	
AMENDMENT B		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=	x	=
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x	=
	Application Size Fee (37 CFR 1.16(s))						
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3. ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.							



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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
16/199,119	11/23/2018	1629	7140	000696US	34	4

151167
Gruneberg and Myers PLLC
1775 Tysons Blvd
5th Floor
Tysons, VA 22102

CONFIRMATION NO. 8647
UPDATED FILING RECEIPT



Date Mailed: 02/26/2019

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Fernando Dangond, Weston, MA;
Matthias Dotzauer, Erzhausen, GERMANY;

Applicant(s)

Merck Patent GmbH, Darmstadt, GERMANY;

Assignment For Published Patent Application

Merck Patent GmbH, Darmstadt, GERMANY

Power of Attorney: The patent practitioners associated with Customer Number 151167

Domestic Priority data as claimed by applicant

This appln claims benefit of 62/590,442 11/24/2017

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 12/17/2018

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/199,119**

Projected Publication Date: 06/06/2019

Non-Publication Request: No

Early Publication Request: No

Title

Cladribine regimen for treating progressive forms of Multiple Sclerosis

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
FERNANDO DANGOND

SERIAL NO. 16/199,119

FILED ON NOVEMBER 23, 2018

FOR: CLADRIBINE REGIMEN FOR
TREATING PROGRESSIVE FORMS
OF MULTIPLE SCLEROSIS

EXAMINER:

GROUP ART UNIT: 1629

RESPONSE TO NOTICE TO FILE MISSING PARTS

Commissioner for Patents
Alexandria, Virginia 22313

Commissioner:

In response to the Notice to File Missing Parts of December 19, 2018, Applicant submits the attached Preliminary Amendment to reduce the number of claims, thereby reducing the amount of excess claims fees.

The Notice to File Missing Parts dated December 19, 2018, states that excess claim fees totaling \$5560 are outstanding. Applicants submit herewith a Preliminary Amendment to reduce the number of claims, and a Request for Refund for excess claim fees previously deducted from the undersigned's Deposit Account. Specifically, \$4800 for 48 claims in excess of 20 and \$460 for 1 extra independent claim were deducted from the undersigned's Deposit Account on January 3, 2019, without a response to the Notice of December 19, 2018, having been filed.

With the entry of the attached Preliminary Amendment, the excess claims fees total \$1,400 for claims in excess of 20 and \$460 for 1 extra independent claim. Accordingly,

Application No. 16/199,119

Reply to Notice to File Missing Parts dated December 19, 2018

Applicants are owed a refund in the amount of \$3,400.00 and respectfully request that the same be credited to the undersigned's Deposit Account.

No new matter would be added to this application by entry of Applicants' amended claims.

Applicants submit that this application is now in condition for examination on the merits and early notification of such action is earnestly solicited.

Respectfully Submitted,
GRÜNEBERG AND MYERS PLLC

/Kirsten Grueneberg/

Dr. Kirsten Grueneberg
Attorney of Record
Registration No. 47,297

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151167

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application Number	16/199,119
Filing Date	November 23, 2018
First Named Inventor	Fernando Dangond
Art Unit	1629
Examiner Name	
Attorney Docket No.	000696US
Title	Cladribine regimen for treating progressive forms of Multiple Sclerosis

PRELIMINARY AMENDMENT

Commissioner for Patents
Alexandria, Virginia 22313

Commissioner:

Prior to an action on the merits, please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 15 of this paper.

IN THE CLAIMS

Please amend the claims as follows:

1 (Original): A method of treating a progressive form of Multiple Sclerosis, said method comprising: orally administering Cladribine to a patient in need thereof at fixed dose per patient, per body weight and per treatment year, wherein said fixed dose is in a range of 1.5 mg/kg to 4.0 mg/kg.

2 (Canceled)

3 (Original): The method according to claim 1, wherein said fixed dose per patient is 1.75 mg/kg per treatment year with a maximum deviation of +/- 0.2 mg/kg.

4 (Original): The method according to claim 1, wherein said progressive form of multiple sclerosis comprises Primary Progressive Multiple Sclerosis and/or Secondary Progressive Multiple Sclerosis.

5 - 15 (Canceled)

16 (Original): The method according to claim 1, wherein said fixed dose is orally administered to said patient within two adjacent months within said treatment year.

17 – 18 (Canceled)

19 (Original): The method according to claim 16, wherein said fixed dose is orally administered to said patient within one week or two adjacent weeks at the beginning of each one of said two adjacent months.

20 (Canceled)

21 (Original): The method according to claim 16, wherein said fixed dose is orally administered to said patient within 4 to 5 days during said week, or within 4 to 5 days of each of said weeks.

22 (Original): The method according to claim 1, wherein said Cladribine is orally administered for at least three treatment years.

23 – 25 (Canceled)

26 (Original): The method according to claim 1, wherein each treatment year comprises:

- (i) a treatment period of 2 months at the beginning of said treatment year, wherein said fixed dose of Cladribine is orally administered on 3 to 5 days each month at the beginning of each month, said fixed dose being divided into daily doses of 10 or 20 mg of Cladribine, and
- (ii) a Cladribine-free period lasting 10 months, during which no Cladribine is administered.

27 (Original): The method according to claim 1, wherein said patient suffers from Primary Progressive Multiple Sclerosis and/or from Secondary Progressive Multiple Sclerosis, wherein said fixed dose per patient is 1.75 mg/kg per treatment year with a maximum deviation of ± 0.2 mg/kg, and wherein orally administering Cladribine comprises at least two treatment years.

28 (Canceled)

29 (Original): The method according to claim 1, wherein orally administering Cladribine comprises at least three treatment years,

a) wherein said fixed dose per treatment year is from 0.75 mg/kg to 2.0 mg/kg,

b) wherein the third treatment year comprises:

(i) a treatment period of 1 month or 2 months at the beginning of said treatment year, wherein said fixed dose of Cladribine is orally administered on 3 to 5 days each month at the beginning of each month, said fixed dose being divided into daily doses of 10 or 20 mg of Cladribine, and

(ii) a Cladribine-free period lasting 11 or 10 months respectively, during which no Cladribine is administered.

30 (Original): The method according to claim 1, wherein orally administering Cladribine is in one or two treatment years, optionally plus an additional subsequent treatment year, followed by at least one year in which no Cladribine is administered to said patient.

31 (Original): The method according to claim 1, wherein said Cladribine is orally administered as a liquid, a tablet, or a capsule.

32 (Canceled)

33 (Original): The method according to claim 1, wherein said Cladribine is orally administered as a tablet comprising 10 mg of Cladribine in the form of a mixture of Cladribine, 2-hydroxypropyl- β -cyclodextrin and Cladribine-2-hydroxypropyl- β -cyclodextrin-complexes, wherein the weight ratio of Cladribine to 2-hydroxypropyl- β -cyclodextrin is between about 1:10 to about 1:16.

34 (Original): A method of treating a patient diagnosed as suffering from a progressive form of Multiple Sclerosis, said method comprising orally administering to said patient a cumulative dose of Cladribine of about 3.5 mg/kg body weight, with a maximum deviation of ± 0.4 mg/kg, over 2 years, administered in each year as 1 treatment course of about 1.75 mg/kg ± 0.2 mg/kg per year, wherein each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year.

35 (Original): The method according to claim 34, wherein each treatment week consists of 4 or 5 days on which said patient receives 10 mg or 20 mg of Cladribine for oral administration, depending on the body weight of the patient.

36 (Original): The method according to claim 35, wherein said patient receives the 10 mg or 20 mg of Cladribine for oral administration as a tablet or capsule.

37 (Original): The method according to claim 36, wherein said patient receives the 10 mg or 20 mg of Cladribine for oral administration as a tablet or capsule comprising 10 mg of Cladribine in the form of a mixture of Cladribine, 2-hydroxypropyl- β -cyclodextrin and Cladribine-2-hydroxypropyl- β -cyclodextrin-complexes, wherein the weight ratio of Cladribine to 2-hydroxypropyl- β -cyclodextrin is between about 1:10 to about 1:16.

38 – 39 (Canceled)

40 (Original): The method according to claim 34, where the progressive form of Multiple Sclerosis is selected from the group consisting of Primary Progressive Multiple Sclerosis and Secondary Progressive Multiple Sclerosis.

41 (Original): The method according to claim 40, wherein each treatment week consists of 4 or 5 days on which said patient receives 10 mg or 20 mg of Cladribine for oral administration.

42 (Original): The method according to claim 34, wherein said patient is between 18 and 65 years old.

43 – 47 (Canceled)

48 (Original): The method according to claim 34, wherein the patient additionally receives at least one disease modifying drug other than Cladribine.

49 (Original): The method according to claim 48, wherein said at least one disease modifying drug other than Cladribine is at least one selected from the group consisting of:

Interferon beta-1a, Beta interferon-1a,

Interferon beta-1b, Beta interferon-1b,

Peginterferon beta 1a,

Alemtuzumab,

Daclizumab,

Dimethyl fumarate,

Fingolimod,

Glatiramer acetate,

Natalizumab, and

Teriflunomide.

50 (Original): The method according to claim 34, wherein after the completion of said 2 years with said 2 treatment courses, no Cladribine is administered to the patients in the subsequent 1 or 2 years following the completion of said 2 years with said 2 treatment courses.

51 (Canceled)

52 (Original): A method of treating a patient suffering from a progressive form of Multiple Sclerosis, comprising orally administering to said patient tablets or capsules containing about 10 mg of Cladribine each, wherein said tablets or capsules are administered during a treatment year comprising the following regimen:

(i) a treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on a treatment week of from 3 to up to 6 days each month;

(ii) followed by a Cladribine-free period lasting 10 months wherein no Cladribine is administered to said patient;

wherein patients having a bodyweight

-in the range of 40 to less than 50 kg are administered

1) 4 tablets or capsules (40 mg of Cladribine) in the 1st treatment week of said treatment course,

2) 4 tablets or capsules (40 mg of Cladribine) in the 2nd treatment week of said treatment course;

-in the range of 50 to less than 60 kg are administered

1) 5 tablets or capsules (50 mg of Cladribine) in the 1st treatment week of said treatment course, respectively,

2) 5 tablets or capsules (50 mg of Cladribine) in the 2nd treatment week of said treatment course;

-in the range of 60 to less than 70 kg are administered

1) 6 tablets or capsules (60 mg of Cladribine) in the 1st treatment week of said treatment course,

2) 6 tablets or capsules (60 mg of Cladribine) in the 2nd treatment week of said treatment course;

-in the range of 70 to less than 80 kg are administered

1) 7 tablets or capsules (70 mg of Cladribine) in the 1st treatment week of said treatment course,

2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd treatment week of said treatment course;

-in the range of 80 to less than 90 kg are administered

1) 8 tablets or capsules (80 mg of Cladribine) in the 1st treatment week of said treatment course,

2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd treatment week of said treatment course;

-in the range of 90 to less than 100 kg are administered

1) 9 tablets or capsules (90 mg of Cladribine) in the 1st treatment week of said treatment course,

2) 8 tablets or capsules (80 mg of Cladribine) in the 2nd treatment week of said treatment course;

-in the range of 100 to less than 110 kg are administered

1) 10 tablets or capsules (100 mg of Cladribine) in the 1st treatment week of said treatment course,

2) 9 tablets or capsules (90 mg of Cladribine) in the 2nd treatment week of said treatment course; or

-in the range of 110 kg and above are administered

1) 10 tablets or capsules (100 mg of Cladribine) in the 1st treatment week of said treatment course,

2) 10 tablets or capsules (100 mg of Cladribine) in the 2nd treatment week of said treatment course.

53 (Original): The method according to claim 52, wherein the method further comprises at least one subsequent additional treatment year, wherein said additional treatment year is substantially identical to said treatment year.

54 (Original): The method according to claim 53, wherein said additional treatment year is directly adjacent to said treatment year, or wherein the method comprises a gap of 1 to 10 months in between the two treatment years.

55 (Canceled)

56 (Original): A method of treating a patient suffering from a progressive form of Multiple Sclerosis, said method comprising orally administering to said patient tablets or capsules containing about 10 mg of Cladribine each, wherein said tablets or capsules are administered during two treatment years comprising the following regimen:

(i) a first treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month;

(ii) followed by a first Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient;

(iii) followed by a second treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month; and

(iv) followed by a second Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient, and

wherein patients having a bodyweight

-in the range of 40 to less than 50 kg are administered

1) 4 tablets or capsules (40 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 4 tablets or capsules (40 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively:

-in the range of 50 to less than 60 kg are administered

1) 5 tablets or capsules (50 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 5 tablets or capsules (50 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively:

-in the range of 60 to less than 70 kg are administered

1) 6 tablets or capsules (60 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 6 tablets or capsules (60 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively;

-in the range of 70 to less than 80 kg are administered

1) 7 tablets or capsules (70 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively;

-in the range of 80 to less than 90 kg are administered

1) 8 tablets or capsules (80 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively;

-in the range of 90 to less than 100 kg are administered

1) 9 tablets or capsules (90 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 8 tablets or capsules (80 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively;

-in the range of 100 to less than 110 kg are administered

1) 10 tablets or capsules (100 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 9 tablets or capsules (90 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively; or

-in the range of 110 kg and above are administered

1) 10 tablets or capsules (100 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 10 tablets or capsules (100 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively.

57 (Original): The method according to claim 56, wherein said 10 mg or 20 mg of Cladribine for oral administration are administered to the patient as a tablet or capsule comprising 10 mg of Cladribine in the form of a mixture of Cladribine, 2-hydroxypropyl- β -cyclodextrin and Cladribine-2-hydroxypropyl- β -cyclodextrin-complexes, wherein the weight ratio of Cladribine to 2-hydroxypropyl- β -cyclodextrin is between about 1:10 to about 1:16.

58 (Original): The method according to claim 56, wherein the progressive form of Multiple Sclerosis is Primary Progressive Multiple Sclerosis.

59 (Original): The method according to claim 56, wherein the progressive form of Multiple Sclerosis is Secondary Progressive Multiple Sclerosis.

60 – 63 (Canceled)

64 (Original): The method according to claim 56, wherein the patient additionally receives at least one disease modifying drug other than Cladribine.

65 (Original): The method according to claim 64, wherein said at least one disease modifying drug other than Cladribine is at least one selected from the group consisting of:

Interferon beta-1a, Beta interferon-1a,

Interferon beta-1b, Beta interferon-1b,

Peginterferon beta 1a,

Alemtuzumab,

Daclizumab,

Dimethyl fumarate,

Fingolimod,

Glatiramer acetate,

Natalizumab, and

Teriflunomide.

66 (Canceled)

67 (Original): The method according to claim 56, wherein to the patients having completed said 2 treatment courses of one year each, no further Cladribine treatment is administered to said patients in the subsequent years 3 and 4.

68 (Original): The method according to claim 56, wherein the progressive form of Multiple Sclerosis is selected from the group consisting of Primary Progressive Multiple Sclerosis and Secondary Progressive Multiple Sclerosis.

69 – 71 (Canceled)

REMARKS/ARGUMENTS

Claim Status and Amendments

Claims 2, 5-15, 17-18, 20, 23-25, 28, 32, 38, 39, 43-47, 51, 55, 60-63, 66, and 69-71
have been canceled without prejudice.

No new matter is added.

An action on the merits is respectfully requested.

Grüneberg and Myers, PLLC

/Kirsten Grueneberg/

Customer No. 151167

Name Dr. Kirsten Grueneberg

Telephone No. 571 458 7790

Reg. No. 47,297

Facsimile No. 571 458 7789

Electronic Acknowledgement Receipt

EFS ID:	35194341
Application Number:	16199119
International Application Number:	
Confirmation Number:	8647
Title of Invention:	Cladribine regimen for treating progressive forms of Multiple Sclerosis
First Named Inventor/Applicant Name:	Fernando Dangond
Customer Number:	151167
Filer:	Eric J.I. Myers/Malika Ash Shakur
Filer Authorized By:	Eric J.I. Myers
Attorney Docket Number:	000696US
Receipt Date:	19-FEB-2019
Filing Date:	23-NOV-2018
Time Stamp:	18:37:54
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2019-02-19-Response-to-NTFMP-as-filed.pdf	797154	yes	20
			7d420c965380cd7f1e505df26e20879c392cfac		

	Multipart Description/PDF files in .zip description		
	Document Description	Start	End
	Transmittal Letter	1	2
	Refund Request	3	3
	Applicant Response to Pre-Exam Formalities Notice	4	5
	Preliminary Amendment	6	6
	Claims	7	19
	Applicant Arguments/Remarks Made in an Amendment	20	20
Warnings:			
Information:			
Total Files Size (in bytes):		797154	
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.			

Docket No. 000696US

GRÜNEBERG
MYERS
P L L C

ATTORNEYS AT LAW

Application of Fernando Dangond

Serial No.: 16/199,119

Filed on: November 23, 2018

Examiner:

Group Art Unit: 1629

For: Cladribine regimen for treating progressive forms of Multiple Sclerosis

Commissioner for Patents
Alexandria, Virginia 22313

Commissioner:

The following papers are attached herewith:

**FEE TRANSMITTAL; REQUEST FOR REFUND; RESPONSE TO NOTICE TO FILE MISSING
PARTS; PRELIMINARY AMENDMENT**

Please charge additional fee(s) or underpayment of fee(s) to Deposit Account No. 601920 under 37 CFR 1.16 and 1.17, and please credit any overpayment of fee(s) to Deposit Account No. 601920. If these papers are not considered timely, then Applicants hereby petition under 37 CFR 1.136 for any necessary extension of time, further authorizing any necessary extension of time fees to be charged to Deposit Account No. 601920.

Respectfully Submitted,
GRÜNEBERG AND MYERS PLLC

/Kirsten Grueneberg/

Customer Number

151167

Phone: (571) 458-7790

Fax: (571) 458-7789

Dr. Kirsten Grueneberg
Attorney of Record
Registration No. 47,297

FEE TRANSMITTAL	Application Number	16/199,119
	Filing Date	November 23, 2018
	First Named Inventor	Fernando Dangond
	Art Unit	1629
	Examiner Name	
☒ No fee required	Attorney Docket No.	000696US
☐ Total payment \$ _____	Title	Cladribine regimen for treating progressive forms of Multiple Sclerosis

- ☐ Applicant asserts small entity status, 37 CFR 1.27
- ☐ Applicant asserts micro entity status, 37 CFR 1.29 (Form PTO/SB/15 or equivalent enclosed or already submitted)
- ☐ Track 1 Prioritized Examination

Claims Fees:

Total: (34- 71) × \$100 \$ _____

Independent: (4- 4) × \$460 \$ _____

☐ Multiple dependency \$820 \$ _____

☐ Late filing declaration \$160 \$ _____

☐ Non-electronic filing fee \$400 \$ _____

☐ Non-English translation \$140 \$ _____

☐ Terminal Disclaimer \$ 160 \$ _____

☐ RCE – 1st Request \$1300 \$ _____

☐ RCE – 2nd or Subseq. \$1900 \$ _____

☐ Notice of Appeal \$ 800 \$ _____

☐ Appl'n Size (____pp.-100)/50 ×\$ 400 \$ _____

Extension Fees under 37 CFR 1.136(a) and 1.17(a), see petition filed herewith, if applicable:

☐ Within first month \$ 200 \$ _____

☐ Within second month \$ 600 \$ _____

☐ Within third month \$1400 \$ _____

☐ Within fourth month \$2200 \$ _____

☐ Within fifth month \$3000 \$ _____

Other:

☐ _____ \$ _____

☐ _____ \$ _____

☐ _____ \$ _____

☐ _____ \$ _____

Payment in the amount of \$ _____ paid by:

- ☐ Credit Card (online if electronically filed, or attached if paper filed)
- ☒ Deposit Account No. **601920**.

- ☒ Please charge additional fee(s) or underpayment of fee(s) to Deposit Account No. **601920** under 37 CFR 1.16 and 1.17, and please credit any overpayment of fee(s) to Deposit Account No. **601920**.

- ☒ If these papers are not considered timely, then Applicants hereby petition under 37 CFR 1.136 for any necessary extension of time, further authorizing any necessary extension of time fees to be charged to Deposit Account No. **601920**.

Respectfully Submitted,
GRÜNEBERG AND MYERS PLLC

/Kirsten Grueneberg/

Customer Number

151167

Phone: (571) 458-7790

Fax: (571) 458-7789

Dr. Kirsten Grueneberg
Registration No. 47,297

REQUEST FOR REFUND

Reference # (Patent #, Application #, Trademark Serial #, Registration #, etc.)		Title of Invention or Mark Information	
16/199,119		Cladribine regimen for treating progressive forms of Multiple Sclerosis	
Attorney Docket # (if applicable)	Payment Date (mm/dd/yyyy)	Refund Request Amount	
000696US	01/07/2019	\$3,400.00	
Refund Option (Select one)			
☒ If approved, issue the refund to the account associated with the original payment.			
☐ If approved, and the original payment was a check, issue the refund to deposit account # _____.			
☐ If approved, and the original payment was a check, issue the refund as a U.S. Treasury check.			
Reason for Refund Request <i>Refund requests must generally be filed within 2 years of payment date (37 CFR 1.26 and 2.209)</i>			
☐ Duplicate Payment		☐ No Fee Due	
☐ Small Entity Later Established* (*must be filed within 3 months of payment date, 37 CFR 1.28)		☐ Office Error	
☒ Other		Number of claims reduced by attached Preliminary Amendment	
Rationale (Supporting documentation may be submitted with this form)			
Number of claims reduced by the filing of attached Preliminary Amendment (previously paid for: 48 excess total claims = \$4,800.00; 1 extra independent claim = \$460.00) TOTAL CLAIMS FEES: \$5,260 After filing of Preliminary Amendment: 14 excess total claims = \$1,400.00; 1 extra independent claim = \$460.00 TOTAL CLAIMS FEES: \$1,860.00			

Requester's Information

Company or Firm Name (if applicable)		
GRUNEBERG AND MYERS PLLC		
Address Line 1	City	State/Region
1775 Tysons Blvd.	Tysons	VA
Address Line 2 (if applicable)	Country	Zip/Postal Code
5th Floor	USA	22102
Email Address (You will receive an acknowledgment of receipt only if you provide a valid email address)		Phone Number
patent@gandmpatent.com		571-458-7790
Requester's Name		Registration Number (if applicable)
Dr. Kirsten Grueneberg		47,297
Signature		Date (mm/dd/yyyy)
/Kirsten Grueneberg/		02/19/2019

Submit online: EFS-Web (registered users only; select "Request for Refund" from the document description menu), or

Fax to: 571-273-6500, or

Mail to: Director of the U.S. Patent and Trademark Office, Attn: Refunds, 2051 Jamieson Avenue, Suite 300, Alexandria, VA 22314

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875						Application or Docket Number 16/199,119			
APPLICATION AS FILED - PART I									
(Column 1)		(Column 2)		SMALL ENTITY		OTHER THAN SMALL ENTITY			
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)		
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	300		
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	660		
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760		
TOTAL CLAIMS (37 CFR 1.16(j))	71	minus 20 = *	51			x 100 =	5100		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4	minus 3 = *	1			x 460 =	460		
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00		
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00		
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL		TOTAL	7280		
APPLICATION AS AMENDED - PART II									
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OTHER THAN SMALL ENTITY	
AMENDMENT A		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)	RATE(\$)	ADDITIONAL FEE(\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=	x	=	x	=
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x	=	x	=
	Application Size Fee (37 CFR 1.16(s))								
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
						TOTAL ADD'L FEE		TOTAL ADD'L FEE	
AMENDMENT B		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)	RATE(\$)	ADDITIONAL FEE(\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=	x	=	x	=
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x	=	x	=
	Application Size Fee (37 CFR 1.16(s))								
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))								
						TOTAL ADD'L FEE		TOTAL ADD'L FEE	
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3. ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.									



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/199,119	11/23/2018	Fernando Dangond	000696US

CONFIRMATION NO. 8647

FORMALITIES LETTER



151167
Gruneberg and Myers PLLC
1775 Tysons Blvd
5th Floor
Tysons, VA 22102

Date Mailed: 01/09/2019

NOTICE OF INCOMPLETE REPLY (NONPROVISIONAL)

Filing Date Granted

The U.S. Patent and Trademark Office has received your reply on 01/03/2019 to the Notice to File Missing Parts (Notice) mailed 12/19/2018 and it has been entered into the nonprovisional application. The reply, however, does not include the following items required in the Notice. A complete reply must be timely filed to prevent ABANDONMENT of the above-identified application. Replies should be mailed to: Mail Stop Missing Parts, Commissioner for Patents, P.O. Box 1450, Alexandria VA 22313-1450.

Applicant is given **TWO MONTHS** from the date of the Notice to File Missing Parts (Notice) mailed 12/19/2018 within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

Items Required to Avoid Abandonment:

The required items noted below SHOULD be filed along with any items required above. The filing date of this nonprovisional application will be the date of receipt of the items required above.

- Additional claim fees of \$ **300** as an undiscounted entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.

SUMMARY OF FEES DUE:

The fee(s) required within **TWO MONTHS** from the date of the Notice to avoid abandonment is/are itemized below. No entity status discount is in effect. If applicant is qualified for small entity status, a written assertion of small entity status must be submitted to establish small entity status. (See 37 CFR 1.27). If applicant is qualified for micro entity status, an acceptable Certification of Micro Entity Status must be submitted to establish micro entity status. (See 37 CFR 1.29 and forms PTO/SB/15A and 15B.)

- \$ **5100** for **51** total claims over 20.
- \$(**4800**) previous unapplied payment amount.
- \$ **300** TOTAL FEE BALANCE DUE.

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice".
<https://portal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html>

For more information about EFS-Web please call the USPTO Electronic Business Center at 1-866-217-9197 or visit our website at <http://www.uspto.gov/ebc>.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at (571) 272-4000 or (571) 272-4200 or 1-888-786-0101.

/fasrat/

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 01/07/2019

MTEKLEMI	SALE	#00000001	Mailroom Dt:	01/03/2019	601920	16199119
		01	FC : 1011	300.00	DA	
		02	FC : 1111	660.00	DA	
		03	FC : 1311	760.00	DA	
		04	FC : 1201	460.00	DA	
		05	FC : 1051	160.00	DA	
		06	FC : 1202	4,800.00	DA	

Application of Fernando Dangond

Serial No.: 16/199,119

Filed on: November 23, 2018

Examiner:

Group Art Unit: 1629

For: Cladribine regimen for treating progressive forms of Multiple Sclerosis

Commissioner for Patents
Alexandria, Virginia 22313

Commissioner:

The following papers are attached herewith:

**Declaration (37 CFR 1.63) for Utility or Design Application Using an Application
Data Sheet (37 CFR 1.76) and Assignment for Single Assignee**

Please charge additional fee(s) or underpayment of fee(s) to Deposit Account No. 601920 under 37 CFR 1.16 and 1.17, and please credit any overpayment of fee(s) to Deposit Account No. 601920. If these papers are not considered timely, then Applicants hereby petition under 37 CFR 1.136 for any necessary extension of time, further authorizing any necessary extension of time fees to be charged to Deposit Account No. 601920.

Respectfully Submitted,
GRÜNEBERG AND MYERS PLLC

/Eric Myers/

Customer Number

151167

Phone: (571) 458-7790

Fax: (571) 458-7789

Dr. Kirsten Grueneberg
Attorney of Record
Registration No. 47,297

Eric Myers
Registration No. 68,546

Declaration (37 CFR 1.63) For Utility Or Design Application Using An Application Data Sheet (37 CFR 1.76) And Assignment For Single Assignee

Title of Invention: Cladribine regimen for treating progressive forms of Multiple Sclerosis

As the below named inventor, I hereby declare that:

This declaration is directed to:

- ☐ The attached application, or
- ☒ United States application or PCT international application number **16/199,119**,
filed on **November 23, 2018**.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

WHEREAS, **Merck Patent GmbH** (hereinafter referred to as "ASSIGNEE"), having a place of business at: **Frankfurterstrasse 250, Darmstadt, 64283 Germany** is desirous of acquiring the entire right, title, and interest in and to said invention and in and to any Letters Patent that may be granted therefore in the United States and its territorial possessions and in any and all foreign countries;

NOW, THEREFORE, in consideration of the sum of FIVE DOLLARS (\$5.00), the receipt whereof is hereby acknowledged, and for other good and valuable consideration, I, by these presents do sell, assign, and transfer unto said ASSIGNEE, the full and exclusive right to the said invention in the United States and its territorial possessions and in all foreign countries (including the right to claim priority under the terms of the International Convention and other relevant International Treaties and Arrangements from the aforesaid application) and the entire right, title, and interest in and to any and all Letters Patent which may be granted therefor in the United States and its territorial possessions and in any and all foreign countries, and in and to any and all divisions, reissues, continuations, substitutions, and renewals thereof.

I hereby authorize and request the Patent Office Officials in the United States and its territorial possessions and any and all foreign countries to issue any and all of said Letters Patent, when granted, to said ASSIGNEE as the assignee of my entire right, title, and interest in and to the same, for the sole

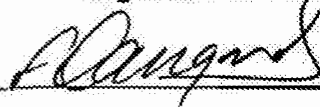
use and behoof of said ASSIGNEE, its (his) successors and assigns, to the full end of the term for which said Letters Patent may be granted, as fully and entirely as the same would have been held by me had this Assignment and sale not been made.

Further, I agree that I will communicate to said ASSIGNEE or its (his) representatives any facts known to me respecting said invention, and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuation, substitute, renewal, and reissue applications, execute all necessary assignment papers to cause any and all of said Letters Patent to be issued to said ASSIGNEE, make all rightful oaths, and, generally do everything possible to aid said ASSIGNEE, its (his) successors and assigns, to obtain and enforce proper protection for said invention in the United States and its territorial possessions and in any and all foreign countries.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

Signature of Inventor

Signature



Fernando DANGOND

Name

Date

12/14/2018

(December 14, 2018)

Attorney Docket No.: 000696US

Declaration (37 CFR 1.63) For Utility Or Design Application Using An Application
Data Sheet (37 CFR 1.76) And Assignment For Single Assignee

Title of Invention: Cladribine regimen for treating progressive forms of Multiple Sclerosis

As the below named inventor, I hereby declare that:

This declaration is directed to:

- ☐ The attached application, or
- ☒ United States application or PCT international application number 16/199,119,
filed on November 23, 2018.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the
application.

WHEREAS, Merck Patent GmbH (hereinafter referred to as "ASSIGNEE"), having a place of
business at: **Frankfurterstrasse 250, Darmstadt, 64293 Germany**
is desirous of acquiring the entire right, title, and interest in and to said invention and in and to any Letters
Patent that may be granted therefore in the United States and its territorial possessions and in any and all
foreign countries;

NOW, THEREFORE, in consideration of the sum of FIVE DOLLARS (\$5.00), the receipt whereof
is hereby acknowledged, and for other good and valuable consideration, I, by these presents do sell,
assign, and transfer unto said ASSIGNEE, the full and exclusive right to the said invention in the United
States and its territorial possessions and in all foreign countries (including the right to claim priority under
the terms of the International Convention and other relevant International Treaties and Arrangements
from the aforesaid application) and the entire right, title, and interest in and to any and all Letters Patent
which may be granted therefor in the United States and its territorial possessions and in any and all
foreign countries, and in and to any and all divisions, reissues, continuations, substitutions, and renewals
thereof.

I hereby authorize and request the Patent Office Officials in the United States and its territorial
possessions and any and all foreign countries to issue any and all of said Letters Patent, when granted,
to said ASSIGNEE as the assignee of my entire right, title, and interest in and to the same, for the sole

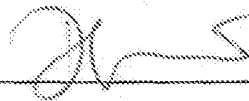
use and behoof of said ASSIGNEE, its (his) successors and assigns, to the full end of the term for which said Letters Patent may be granted, as fully and entirely as the same would have been held by me had this Assignment and sale not been made.

Further, I agree that I will communicate to said ASSIGNEE or its (his) representatives any facts known to me respecting said invention, and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuation, substitute, renewal, and reissue applications, execute all necessary assignment papers to cause any and all of said Letters Patent to be issued to said ASSIGNEE, make all rightful oaths, and, generally do everything possible to aid said ASSIGNEE, its (his) successors and assigns, to obtain and enforce proper protection for said invention in the United States and its territorial possessions and in any and all foreign countries.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

Signature of Inventor

Signature



Name

Matthias DOTZAUER

Date

17. December 2018

Electronic Acknowledgement Receipt

EFS ID:	34747562
Application Number:	16199119
International Application Number:	
Confirmation Number:	8647
Title of Invention:	Cladribine regimen for treating progressive forms of Multiple Sclerosis
First Named Inventor/Applicant Name:	Fernando Dangond
Customer Number:	151167
Filer:	Eric J.I. Myers/Danielle Jones
Filer Authorized By:	Eric J.I. Myers
Attorney Docket Number:	000696US
Receipt Date:	03-JAN-2019
Filing Date:	23-NOV-2018
Time Stamp:	11:49:01
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
------------------------	----

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2019-01-03-Declarations-as-filed.pdf	671672	yes	5
			edfd69809c2fee3c471cc7bdbcbb8a7b182a935c		

Multipart Description/PDF files in .zip description			
Document Description		Start	End
Transmittal Letter		1	1
Oath or Declaration filed		2	5
Warnings:			
Information:			
Total Files Size (in bytes):		671672	
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.			



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/199,119	11/23/2018	Fernando Dangond	000696US

CONFIRMATION NO. 8647

FORMALITIES LETTER



151167
Gruneberg and Myers PLLC
1775 Tysons Blvd
5th Floor
Tysons, VA 22102

Date Mailed: 12/19/2018

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
- The application search fee must be submitted.
- The application examination fee must be submitted.
- Additional claim fees of \$ **5560** as an undiscounted entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.
- Surcharge as set forth in 37 CFR 1.16(f) must be submitted.

The surcharge is due for any one of:

- late submission of the basic filing fee, search fee, or examination fee,
- late submission of inventor's oath or declaration,
- filing an application that does not contain at least one claim on filing, or
- submission of an application filed by reference to a previously filed application.

SUMMARY OF FEES DUE:

The fee(s) required within **TWO MONTHS** from the date of this Notice to avoid abandonment is/are itemized below. No entity status discount is in effect. If applicant is qualified for small entity status, a written assertion of small entity status must be submitted to establish small entity status. (See 37 CFR 1.27). If applicant is qualified for micro entity status, an acceptable Certification of Micro Entity Status must be submitted to establish micro entity status. (See 37 CFR 1.29 and forms PTO/SB/15A and 15B.)

- \$ **300** basic filing fee.
- \$ **160** surcharge.
- \$ **660** search fee.
- \$ **760** examination fee.
- \$ **460** for **1** independent claims over 3.
- \$ **5100** for **51** total claims over 20.

- \$(0) previous unapplied payment amount.
- **\$ 7440** TOTAL FEE BALANCE DUE.

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
Fernando Dangond
Matthias Dotzauer

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice".
<https://portal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html>

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/zretta/

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875						Application or Docket Number 16/199,119	
APPLICATION AS FILED - PART I							
(Column 1)		(Column 2)		SMALL ENTITY		OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	300
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	660
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760
TOTAL CLAIMS (37 CFR 1.16(j))	71	minus 20 = *	51			x 100 =	5100
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4	minus 3 = *	1			x 460 =	460
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL		TOTAL	7280
APPLICATION AS AMENDED - PART II							
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY	
AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)
	Total (37 CFR 1.16(i))	*	Minus **	=	x =		x =
	Independent (37 CFR 1.16(h))	*	Minus ***	=	x =		x =
	Application Size Fee (37 CFR 1.16(s))						
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
				TOTAL ADD'L FEE		TOTAL ADD'L FEE	
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY	
AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)
	Total (37 CFR 1.16(i))	*	Minus **	=	x =		x =
	Independent (37 CFR 1.16(h))	*	Minus ***	=	x =		x =
	Application Size Fee (37 CFR 1.16(s))						
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
				TOTAL ADD'L FEE		TOTAL ADD'L FEE	
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3. ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.							



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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
16/199,119	11/23/2018	1629	0.00	000696US	71	4

CONFIRMATION NO. 8647

FILING RECEIPT



00000000104504861

151167
Gruneberg and Myers PLLC
1775 Tysons Blvd
5th Floor
Tysons, VA 22102

Date Mailed: 12/19/2018

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Fernando Dangond, Weston, MA;
Matthias Dotzauer, Erzhausen, GERMANY;

Applicant(s)

Merck Patent GmbH, Darmstadt, GERMANY;

Assignment For Published Patent Application

Merck Patent GmbH, Darmstadt, GERMANY

Power of Attorney: The patent practitioners associated with Customer Number 151167

Domestic Priority data as claimed by applicant

This appln claims benefit of 62/590,442 11/24/2017

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 12/17/2018

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/199,119**

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No

Title

Cladribine regimen for treating progressive forms of Multiple Sclerosis

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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Application Number: 16199119

Document Date: 11/23/2018

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UTILITY PATENT APPLICATION TRANSMITTAL <i>(Only for new nonprovisional applications under 37 CFR 1.53(b))</i>		Attorney Docket No. 000696US	
		First Named Inventor Fernando DANGOND	
		Title Cladribine regimen for treating progressive forms of Multiple Sclerosis	
APPLICATION ELEMENTS <i>See MPEP chapter 600 concerning utility patent application contents.</i>		ADDRESS TO: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	
1. ☐ Fee Transmittal Form (PTO/SB/17 or equivalent) 2. ☐ Applicant asserts small entity status. See 37 CFR 1.27 3. ☐ Applicant certifies micro entity status. See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent. 4. ☒ Specification [Total Pages <u>131</u>] Both the claims and abstract must start on a new page. (See MPEP § 608.01(a) for information on the preferred arrangement) 5. ☒ Drawing(s) (35 U.S.C. 113) [Total Sheets <u>4</u>] 6. Inventor's Oath or Declaration [Total Pages _____] (including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e)) a. ☐ Newly executed (original or copy) b. ☐ A copy from a prior application (37 CFR 1.63(d)) 7. ☒ Application Data Sheet * See note below. See 37 CFR 1.76 (PTO/AIA/14 or equivalent) 8. CD-ROM or CD-R in duplicate, large table, or Computer Program (Appendix) ☐ Landscape Table on CD 9. Nucleotide and/or Amino Acid Sequence Submission (if applicable, items a. – c. are required) a. ☐ Computer Readable Form (CRF) b. ☐ Specification Sequence Listing on: i. ☐ CD-ROM or CD-R (2 copies); or ii. ☐ Paper c. ☐ Statements verifying identity of above copies		ACCOMPANYING APPLICATION PAPERS 10. ☐ Assignment Papers (cover sheet & document(s)) Name of Assignee _____ 11. ☐ 37 CFR 3.73(c) Statement ☒ Power of Attorney (when there is an assignee) 12. ☐ English Translation Document (if applicable) 13. ☐ Information Disclosure Statement (PTO/SB/08 or PTO-1449) ☐ Copies of citations attached 14. ☐ Preliminary Amendment 15. ☐ Return Receipt Postcard (MPEP § 503) (Should be specifically itemized) 16. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed) 17. ☐ Nonpublication Request Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent. 18. ☐ Other: _____ _____ _____ _____	
*Note: (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 must be included in an Application Data Sheet (ADS). (2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).			
19. CORRESPONDENCE ADDRESS			
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Address _____			
City _____		State _____	Zip Code _____
Country _____		Telephone _____	Email _____
Signature	/Eric Myers/		Date
Name (Print/Type)	Eric Myers		Registration No. (Attorney/Agent)
			68,546

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If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronic Acknowledgement Receipt

EFS ID:	34383903
Application Number:	16199119
International Application Number:	
Confirmation Number:	8647
Title of Invention:	Cladribine regimen for treating progressive forms of Multiple Sclerosis
First Named Inventor/Applicant Name:	Fernando DANGOND
Customer Number:	151167
Filer:	Eric J.I. Myers/Malika Ash Shakur
Filer Authorized By:	Eric J.I. Myers
Attorney Docket Number:	000696US
Receipt Date:	23-NOV-2018
Filing Date:	
Time Stamp:	21:17:51
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2018-11-23-new-app-as-filed.pdf	1564719	yes	141
			7d86da965e32f2e73577fc7415641781ba43122e		

	Multipart Description/PDF files in .zip description		
	Document Description	Start	End
	Power of Attorney	140	141
	Drawings-other than black and white line drawings	136	139
	Abstract	135	135
	Claims	121	134
	Specification	9	120
	Application Data Sheet	2	8
	Transmittal of New Application	1	1
Warnings:			
Information:			
Total Files Size (in bytes):		1564719	
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TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

This form is to be submitted with the Power of Attorney by Applicant Form to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form.

Application Number	New Application
Patent Number	
Filing Date	Herewith
Issue Date	
First Named Inventor	Fernando Dangond
Art Unit	
Examiner Name	
Attorney Docket Number	000696US
Title	Cladribine regimen for treating progressive forms of Multiple Sclerosis

Signature of Applicant or Patent Practitioner

Signature /Eric Myers/

Name Eric Myers

Reg. No. 68,546

Customer No. 151167

Note: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

*Total of 1 form(s) is/are submitted.

POWER OF ATTORNEY BY APPLICANT

Assignee, Legal Representative, or Person Who Otherwise
Shows Sufficient Proprietary Interest

I hereby revoke all previous powers of attorney given in the application identified in the attached Transmittal For Power of Attorney form.

I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached Transmittal For Power of Attorney form:

CUSTOMER NUMBER **151167**

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- ☒ The address associated with the above-mentioned Customer Number.
- Or
- ☐ The address associated with Customer Number: _____

I am the Applicant:

- ☒ Assignee or Person to Whom the Inventor is Under Obligation to Assign (Signer's title provided when Applicant is a juristic entity).
- ☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g. a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (Signer's title provided when Applicant is a juristic entity).

Signature of Applicant for Patent

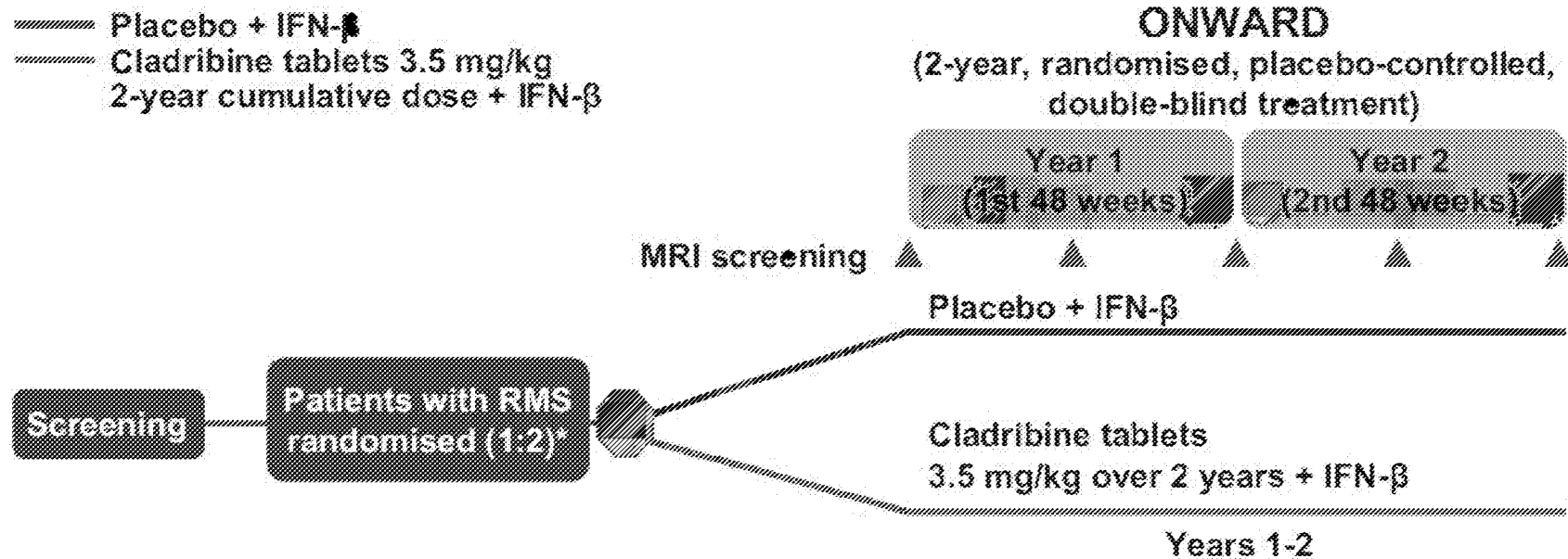
The undersigned (whose title is supplied below) is authorized to act on behalf of the Applicant (e.g. where the applicant is a juristic entity).

Signature Dr. Hartmann Date November 29, 2017
Name Dr. Hartmann Dr. Dotzauer Telephone +49 6151 72 7569 / 4371
Title Authorized Employees
Company Merck Patent GmbH

Note: Signature – This form must be signed by the applicant. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms for more than one signature, see below *

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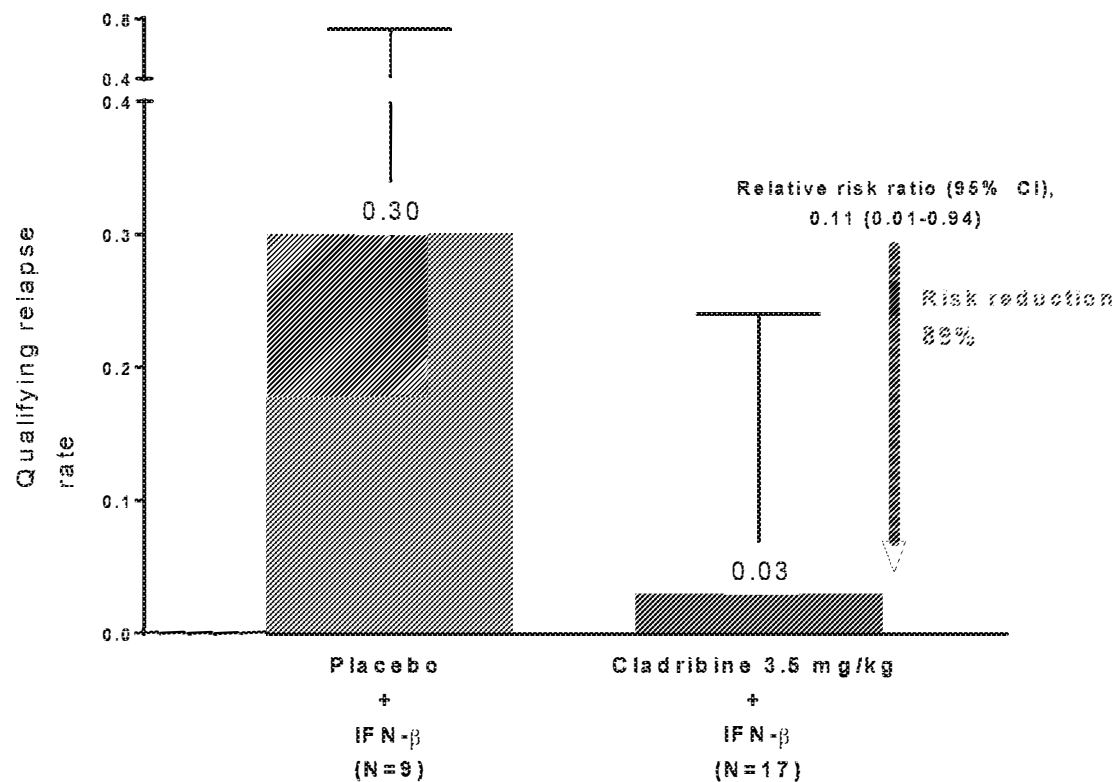
ONWARD study design



*prior to an early protocol amendment, the ONWARD study included randomisation to treatment with cladribine tablets 5.25 mg/kg (cumulative dose over 2 years) + IFN- β

Fig. 1

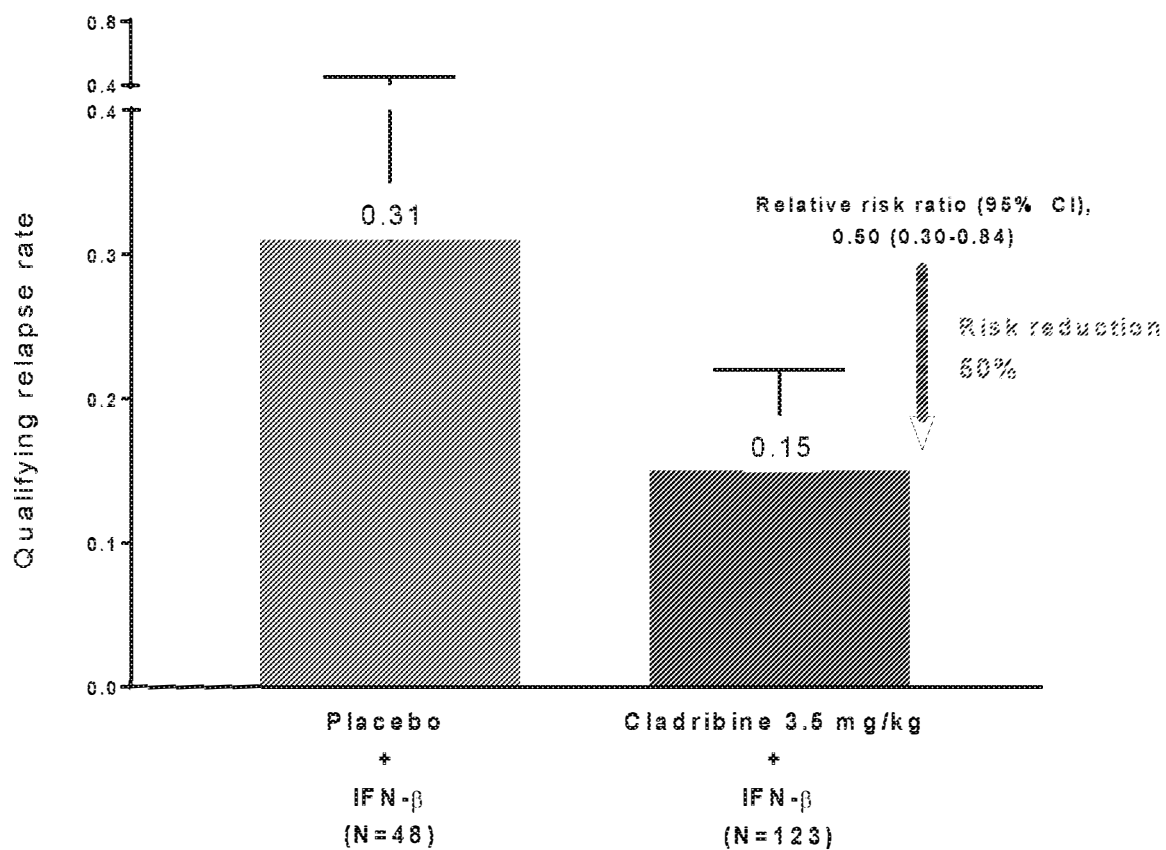
Qualifying relapse rate (annualized, adjusted) in patients with SPMS treated with cladribine tablets 3.5 mg/kg + IFN- β or placebo + IFN- β in ONWARD



CI, confidence interval; IFN- β , interferon- β . SPMS, secondary progressive multiple sclerosis

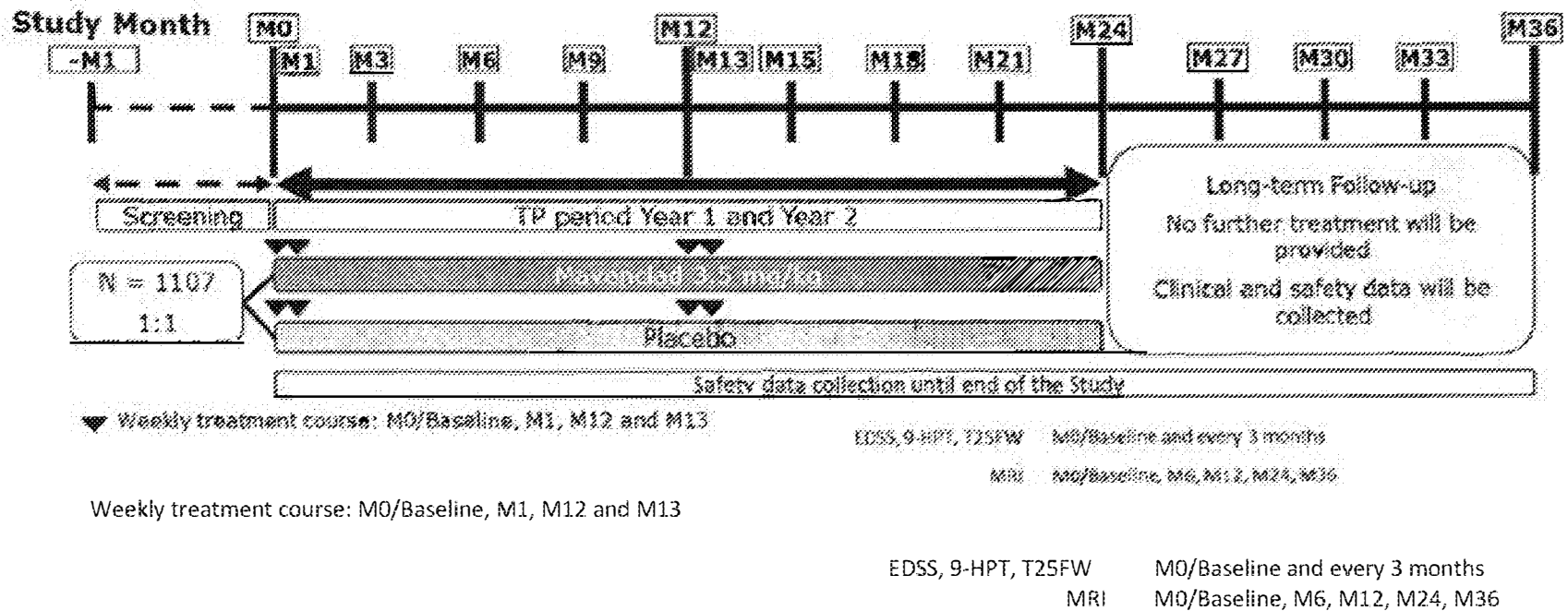
Fig. 2

Qualifying relapse rate (annualized, adjusted) in patients with RRMS treated with cladribine tablets
3.5 mg/kg + IFN- β or placebo + IFN- β in ONWARD



CI, confidence interval; IFN- β , interferon- β . RRMS, relapsing-remitting multiple sclerosis

Fig. 3



9-HPT=9-Hole Peg Test, EDSS= Expanded Disability Status Scale, MRI=magnetic resonance imaging; T25FW=Timed 25-Foot Walk, TP=treatment period.

Fig. 4

Abstract

Specific oral dosings, specific oral dosage forms, and/or specific oral dose regimens including Cladribine can be effective for the treatment of progressive forms of Multiple Sclerosis, especially Primary Progressive Multiple Sclerosis and/or Secondary Progressive Multiple Sclerosis. Methods of treatment can be based on specific oral dosings, specific oral dosage forms, and/or specific oral dose regimens including Cladribine.

Claims:

1. A method of treating a progressive form of Multiple Sclerosis, said method comprising: orally administering Cladribine to a patient in need thereof at fixed dose per patient, per body weight and per treatment year, wherein said fixed dose is in a range of 1.5 mg/kg to 4.0 mg/kg.
2. The method according to claim 1, wherein said fixed dose is in a range of 1.5 mg/kg to 2.0 mg/kg.
3. The method according to claim 1, wherein said fixed dose per patient is 1.75 mg/kg per treatment year with a maximum deviation of ± 0.2 mg/kg.
4. The method according to claim 1, wherein said progressive form of multiple sclerosis comprises Primary Progressive Multiple Sclerosis and/or Secondary Progressive Multiple Sclerosis.
5. The method according to claim 1, wherein said progressive form of Multiple Sclerosis is Primary Progressive Multiple Sclerosis.
6. The method according to claim 1, wherein said progressive form of Multiple Sclerosis is Secondary Progressive Multiple Sclerosis.
7. The method according to claim 1, wherein said patient has an age between 18 and 65 years.
8. The method according to claim 1, wherein said patient has an age between 18 and 51 years.

9. The method according to claim 1, wherein said patient has an age between 12 and 51 years.
10. The method according to claim 1, wherein said Cladribine is orally administered to patients of female gender and/or to patients of male gender.
11. The method according to claim 1, wherein said Patient has High Disease Activity (HDA) and/or has been diagnosed High Disease Activity.
12. The method according to claim 1, wherein the patient is treatment naïve to Cladribine and/or disease modifying drugs other than Cladribine.
13. The method according to claim 1, wherein the patient previously received Cladribine and/or one or more disease modifying drugs other than Cladribine.
14. The method according to claim 1, wherein the patient is also receiving at least one disease modifying drug other than Cladribine.
15. The method according to claim 14, wherein said at least one disease modifying drug other than Cladribine is at least one selected from the group consisting of:
Interferon beta-1a, Beta interferon-1a,
Interferon beta-1b, Beta interferon-1b,
Peginterferon beta 1a,
Alemtuzumab,
Daclizumab,
Dimethyl fumarate,
Fingolimod,
Glatiramer acetate,
Natalizumab, and

Teriflunomide.

16. The method according to claim 1, wherein said fixed dose is orally administered to said patient within two adjacent months within said treatment year.
17. The method according to claim 16, wherein said fixed dose is orally administered to said patient within two adjacent months starting at the beginning of said treatment year.
18. The method according to claim 16, wherein said fixed dose is orally administered to said patient within one week or two weeks of each of said two adjacent months.
19. The method according to claim 16, wherein said fixed dose is orally administered to said patient within one week or two adjacent weeks at the beginning of each one of said two adjacent months.
20. The method according to claim 16, wherein said fixed dose is orally administered to said patient within 2 to 7 days during said week, or within 2 to 7 days of each of said weeks.
21. The method according to claim 16, wherein said fixed dose is orally administered to said patient within 4 to 5 days during said week, or within 4 to 5 days of each of said weeks.
22. The method according to claim 1, wherein said Cladribine is orally administered for at least three treatment years.
23. The method according to claim 1, wherein said Cladribine is orally administered to for at least two treatment years.

24. The method according to claim 23, wherein two of said treatment years are either directly adjacent to each other, or are separated by a gap of from 1 to 10 months.
25. The method according to claim 1, wherein each treatment year comprises:
- (i) a treatment period of 2 months at the beginning of said treatment year, wherein said fixed dose of Cladribine is orally administered on about 1 to about 7 days each month, said fixed dose being divided into daily doses of 5 to 20 mg of Cladribine, and
 - (ii) a Cladribine-free period lasting 10 months, during which no Cladribine is administered.
26. The method according to claim 1, wherein each treatment year comprises:
- (i) a treatment period of 2 months at the beginning of said treatment year, wherein said fixed dose of Cladribine is orally administered on 3 to 5 days each month at the beginning of each month, said fixed dose being divided into daily doses of 10 or 20 mg of Cladribine, and
 - (ii) a Cladribine-free period lasting 10 months, during which no Cladribine is administered.
27. The method according to claim 1, wherein said patient suffers from Primary Progressive Multiple Sclerosis and/or from Secondary Progressive Multiple Sclerosis, wherein said fixed dose per patient is 1.75 mg/kg per treatment year with a maximum deviation of ± 0.2 mg/kg, and wherein orally administering Cladribine comprises at least two treatment years.
28. The method according to claim 1, wherein orally administering Cladribine comprises two treatment years that are substantially adjacent to either each other, or that are separated by a gap of 1 to 10 months.

29. The method according to claim 1, wherein orally administering Cladribine comprises at least three treatment years,
- a) wherein said fixed dose per treatment year is from 0.75 mg/kg to 2.0 mg/kg,
 - b) wherein the third treatment year comprises:
 - (i) a treatment period of 1 month or 2 months at the beginning of said treatment year, wherein said fixed dose of Cladribine is orally administered on 3 to 5 days each month at the beginning of each month, said fixed dose being divided into daily doses of 10 or 20 mg of Cladribine, and
 - (ii) a Cladribine-free period lasting 11 or 10 months respectively, during which no Cladribine is administered.
30. The method according to claim 1, wherein orally administering Cladribine is in one or two treatment years, optionally plus an additional subsequent treatment year, followed by at least one year in which no Cladribine is administered to said patient.
31. The method according to claim 1, wherein said Cladribine is orally administered as a liquid, a tablet, or a capsule.
32. The method according to claim 1, wherein said Cladribine is orally administered as a tablet.
33. The method according to claim 1, wherein said Cladribine is orally administered as a tablet comprising 10 mg of Cladribine in the form of a mixture of Cladribine, 2-hydroxypropyl- β -cyclodextrin and Cladribine-2-hydroxypropyl- β -cyclodextrin-complexes, wherein the weight ratio of Cladribine to 2-hydroxypropyl- β -cyclodextrin is between about 1:10 to about 1:16.
34. A method of treating a patient diagnosed as suffering from a progressive form of Multiple Sclerosis, said method comprising orally administering to said patient a cumulative dose of Cladribine of about 3.5

mg/kg body weight, with a maximum deviation of ± 0.4 mg/kg, over 2 years, administered in each year as 1 treatment course of about 1.75 mg/kg ± 0.2 mg/kg per year, wherein each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year.

35. The method according to claim 34, wherein each treatment week consists of 4 or 5 days on which said patient receives 10 mg or 20 mg of Cladribine for oral administration, depending on the body weight of the patient.
36. The method according to claim 35, wherein said patient receives the 10 mg or 20 mg of Cladribine for oral administration as a tablet or capsule.
37. The method according to claim 36, wherein said patient receives the 10 mg or 20 mg of Cladribine for oral administration as a tablet or capsule comprising 10 mg of Cladribine in the form of a mixture of Cladribine, 2-hydroxypropyl- β -cyclodextrin and Cladribine-2-hydroxypropyl- β -cyclodextrin-complexes, wherein the weight ratio of Cladribine to 2-hydroxypropyl- β -cyclodextrin is between about 1:10 to about 1:16.
38. The method according to claim 34, wherein the progressive form of Multiple Sclerosis is Primary Progressive Multiple Sclerosis.
39. The method according to claim 34, wherein the progressive form of Multiple Sclerosis is Secondary Progressive Multiple Sclerosis.
40. The method according to claim 34, where the progressive form of Multiple Sclerosis is selected from the group consisting of Primary Progressive Multiple Sclerosis and Secondary Progressive Multiple Sclerosis.

41. The method according to claim 40, wherein each treatment week consists of 4 or 5 days on which said patient receives 10 mg or 20 mg of Cladribine for oral administration.
42. The method according to claim 34, wherein said patient is between 18 and 65 years old.
43. The method according to claim 34, wherein said patient is between 18 and 51 years old.
44. The method according to claim 34, wherein said patient is between 12 and 51 years old.
45. The method according to claim 34, wherein patients to be treated are patients of female gender and/or patients of male gender.
46. The method according to claim 34, wherein the patient is treatment naïve to Cladribine and/or disease modifying drugs other than Cladribine.
47. The method according to claim 34, wherein said patient previously received Cladribine and/or one or more disease modifying drugs other than Cladribine.
48. The method according to claim 34, wherein the patient additionally receives at least one disease modifying drug other than Cladribine.
49. The method according to claim 48, wherein said at least one disease modifying drug other than Cladribine is at least one selected from the group consisting of:
Interferon beta-1a, Beta interferon-1a,
Interferon beta-1b, Beta interferon-1b,
Peginterferon beta 1a,

Alemtuzumab,
 Daclizumab,
 Dimethyl fumarate,
 Fingolimod,
 Glatiramer acetate,
 Natalizumab, and
 Teriflunomide.

50. The method according to claim 34, wherein after the completion of said 2 years with said 2 treatment courses, no Cladribine is administered to the patients in the subsequent 1 or 2 years following the completion of said 2 years with said 2 treatment courses.
51. The method according to claim 34, wherein after said 2 treatment courses of one year each, no further Cladribine treatment is administered to said patient in the subsequent years 3 and 4.
52. A method of treating a patient suffering from a progressive form of Multiple Sclerosis, comprising orally administering to said patient tablets or capsules containing about 10 mg of Cladribine each, wherein said tablets or capsules are administered during a treatment year comprising the following regimen:
 - (i) a treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on a treatment week of from 3 to up to 6 days each month;
 - (ii) followed by a Cladribine-free period lasting 10 months wherein no Cladribine is administered to said patient;
 wherein patients having a bodyweight
 -in the range of 40 to less than 50 kg are administered
 1) 4 tablets or capsules (40 mg of Cladribine) in the 1st treatment week of said treatment course,

2) 4 tablets or capsules (40 mg of Cladribine) in the 2nd treatment week of said treatment course;

-in the range of 50 to less than 60 kg are administered

1) 5 tablets or capsules (50 mg of Cladribine) in the 1st treatment week of said treatment course, respectively,

2) 5 tablets or capsules (50 mg of Cladribine) in the 2nd treatment week of said treatment course;

-in the range of 60 to less than 70 kg are administered

1) 6 tablets or capsules (60 mg of Cladribine) in the 1st treatment week of said treatment course,

2) 6 tablets or capsules (60 mg of Cladribine) in the 2nd treatment week of said treatment course;

-in the range of 70 to less than 80 kg are administered

1) 7 tablets or capsules (70 mg of Cladribine) in the 1st treatment week of said treatment course,

2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd treatment week of said treatment course;

-in the range of 80 to less than 90 kg are administered

1) 8 tablets or capsules (80 mg of Cladribine) in the 1st treatment week of said treatment course,

2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd treatment week of said treatment course;

-in the range of 90 to less than 100 kg are administered

1) 9 tablets or capsules (90 mg of Cladribine) in the 1st treatment week of said treatment course,

2) 8 tablets or capsules (80 mg of Cladribine) in the 2nd treatment week of said treatment course;

-in the range of 100 to less than 110 kg are administered

1) 10 tablets or capsules (100 mg of Cladribine) in the 1st treatment week of said treatment course,

2) 9 tablets or capsules (90 mg of Cladribine) in the 2nd treatment week of said treatment course; or

-in the range of 110 kg and above are administered

1) 10 tablets or capsules (100 mg of Cladribine) in the 1st treatment week of said treatment course,

2) 10 tablets or capsules (100 mg of Cladribine) in the 2nd treatment week of said treatment course.

53. The method according to claim 52, wherein the method further comprises at least one subsequent additional treatment year, wherein said additional treatment year is substantially identical to said treatment year.
54. The method according to claim 53, wherein said additional treatment year is directly adjacent to said treatment year, or wherein the method comprises a gap of 1 to 10 months in between the two treatment years.
55. The method according to claim 52, wherein the method further comprises two additional treatment years, wherein all said additional treatment years are substantially identical, and wherein said additional treatment years are directly adjacent to each other, or wherein the method comprises a gap of 1 to 10 months in between at least two of said additional treatment years.
56. A method of treating a patient suffering from a progressive form of Multiple Sclerosis, said method comprising orally administering to said patient tablets or capsules containing about 10 mg of Cladribine each, wherein said tablets or capsules are administered during two treatment years comprising the following regimen:
 - (i) a first treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of

Cladribine on 3 to up to 6 days each month;

(ii) followed by a first Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient;

(iii) followed by a second treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month; and

(iv) followed by a second Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient, and

wherein patients having a bodyweight

-in the range of 40 to less than 50 kg are administered

1) 4 tablets or capsules (40 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 4 tablets or capsules (40 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively:

-in the range of 50 to less than 60 kg are administered

1) 5 tablets or capsules (50 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 5 tablets or capsules (50 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively:

-in the range of 60 to less than 70 kg are administered

1) 6 tablets or capsules (60 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 6 tablets or capsules (60 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively;

-in the range of 70 to less than 80 kg are administered

1) 7 tablets or capsules (70 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively;

-in the range of 80 to less than 90 kg are administered

1) 8 tablets or capsules (80 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively;

-in the range of 90 to less than 100 kg are administered

1) 9 tablets or capsules (90 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 8 tablets or capsules (80 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively;

-in the range of 100 to less than 110 kg are administered

1) 10 tablets or capsules (100 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 9 tablets or capsules (90 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively; or

-in the range of 110 kg and above are administered

1) 10 tablets or capsules (100 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 10 tablets or capsules (100 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively.

57. The method according to claim 56, wherein said 10 mg or 20 mg of Cladribine for oral administration are administered to the patient as a tablet or capsule comprising 10 mg of Cladribine in the form of a mixture of Cladribine, 2-hydroxypropyl- β -cyclodextrin and Cladribine-2-hydroxypropyl- β -cyclodextrin-complexes, wherein the weight ratio of Cladribine to 2-hydroxypropyl- β -cyclodextrin is between about 1:10 to about 1:16.

58. The method according to claim 56, wherein the progressive form of Multiple Sclerosis is Primary Progressive Multiple Sclerosis.

59. The method according to claim 56, wherein the progressive form of Multiple Sclerosis is Secondary Progressive Multiple Sclerosis.
60. The method according to claim 56, wherein the patient is between 12 and 51 years old.
61. The method according to claim 56, wherein patients to be treated are patients of female gender and/or patients of male gender.
62. The method according to claim 56, wherein the patient is treatment naïve to Cladribine and/or disease modifying drugs other than Cladribine.
63. The method according to claim 56, wherein the patient previously received Cladribine and/or disease modifying drugs other than Cladribine.
64. The method according to claim 56, wherein the patient additionally receives at least one disease modifying drug other than Cladribine.
65. The method according to claim 64, wherein said at least one disease modifying drug other than Cladribine is at least one selected from the group consisting of:
Interferon beta-1a, Beta interferon-1a,
Interferon beta-1b, Beta interferon-1b,
Peginterferon beta 1a,
Alemtuzumab,
Daclizumab,
Dimethyl fumarate,
Fingolimod,
Glatiramer acetate,
Natalizumab, and

Teriflunomide.

66. The method according to claim 56, wherein after the completion of said 2 years with said 2 treatment courses, no Cladribine is administered to the patients in the subsequent 1 or 2 years following the completion of said 2 years with said 2 treatment courses.
67. The method according to claim 56, wherein to the patients having completed said 2 treatment courses of one year each, no further Cladribine treatment is administered to said patients in the subsequent years 3 and 4.
68. The method according to claim 56, wherein the progressive form of Multiple Sclerosis is selected from the group consisting of Primary Progressive Multiple Sclerosis and Secondary Progressive Multiple Sclerosis.
69. The method according to claim 56, wherein the progressive form of Multiple Sclerosis is Primary Progressive Multiple Sclerosis.
70. The method according to claim 56, wherein the progressive form of Multiple Sclerosis is Secondary Progressive Multiple Sclerosis.
71. The method according to claim 56, wherein said Patient has High Disease Activity (HDA) and/or has been diagnosed High Disease Activity.

DOCKET NO. 000696US

TITLE OF THE INVENTION

CLADRIBINE REGIMEN FOR TREATING PROGRESSIVE FORMS OF MULTIPLE
SCLEROSIS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 62/590,442, filed on November 24, 2018, the entirety of which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to the use of specific oral dosings, specific oral dosage forms and/or specific oral dose regimens comprising Cladribine for the treatment of progressive forms of Multiple Sclerosis, especially Primary Progressive Multiple Sclerosis and/or Secondary Progressive Multiple Sclerosis.

DESCRIPTION OF THE RELATED ART

Multiple sclerosis (MS) is the most known chronic inflammatory demyelinating disease of the central nervous system in humans. The onset of the disease typically occurs during ages 20 to 40. Women are affected approximately twice as often as men.

Over time, MS may result in the accumulation of various neurological disabilities. Clinical disability in MS is presumed to be a result of repeated inflammatory injury with subsequent loss of myelin and axons, leading to tissue atrophy.

MS is often manifested in physical symptoms (relapses and disability progression), Central Nervous System (CNS) inflammation, brain atrophy and cognitive impairment. Presenting symptoms include focal sensory deficits, focal weakness, visual problems, imbalance and

fatigue. Sexual impairment and sphincter dysfunction may occur. Approximately half of the patients with MS may experience cognitive impairment or depression.

MS is often considered to be a multi-phasic disease and periods of clinical quiescence (remissions) occur between exacerbations. Remissions vary in length and may last several years but are infrequently permanent.

Four courses of the disease are generally differentiated: relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP) and progressive relapsing (PR) multiple sclerosis.

More than 80% of patients with MS will initially display a RR course with clinical exacerbation of neurological symptoms, followed by a recovery that may or may not be complete (*Lublin and Reingold, Neurology, 1996, 46:907-911*).

During RRMS, accumulation of disability results from incomplete recovery from relapses. Approximately, half of the patients with RRMS switch to a progressive course, called SPMS, 10 years after the diseased onset. During the SP phase, worsening of disability results from the accumulation of residual symptoms after exacerbation but also from insidious progression between exacerbations (*Lublin and Reingold above*). 10% of MS patients have PPMS which is characterized by insidious progression of the symptoms from the disease onset. Less than 5 % of patients have PRMS and are often considered to have the same prognosis as PPMS. It is suggested that distinct pathogenic mechanisms may be involved in different patient sub-groups and have wide-ranging implications for disease classification (*Lassmann et al., 2001, Trends Mol. Med., 7, 115-121; Lucchinetti et al., Curr. Opin. Neurol., 2001, 14, 259-269*).

MS onset is defined by the occurrence of the first neurological symptoms of CNS dysfunction. Advances in cerebrospinal fluid (CSF) analysis and magnetic resonance imaging (MRI) have simplified the diagnostic process and facilitated early diagnostic

(Noseworthy et al., *The New England Journal of Medicine*, 2000, 343, 13, 938-952). The International Panel on the Diagnosis of MS issued revised criteria facilitating the diagnosis of MS and including MRI together with clinical and para-clinical diagnostic methods (McDonald et al., 2001, *Ann. Neurol.*, 50:121-127).

5

Current medications for MS which are disease modifying treatments, i.e. modifying the course of MS, modulate or suppress the immune system. There have been several FDA approved immunomodulating agents for RRMS in the past, including the following: three beta interferons (Betaseron®, Berlex; Avonex®, Biogen; Rebif®, Serono) and Glatiramer Acetate (Copaxone®, Amgen). There is also one FDA approved immunosuppressing drug for worsening MS, Mitoxantrone (Novantrone®, Amgen). Several other immunosuppressive agents are used, although not FDA approved. However, meanwhile the arsenal of the so-called Disease Modifying Drugs (DMDs) or Disease Modifying Therapeutics/Therapies (DMTs) comprises the following:

15

Interferon beta-1a, Beta interferon-1a (e.g. Avonex®, Rebif®),
Interferon beta-1b, Beta interferon-1b (e.g. Betaferon®, Extavia®),
Peginterferon beta 1a (e.g. Plegridy®),
Alemtuzumab (e.g. Lemtrada®),
Daclizumab (e.g. Zinbryta®),
Dimethyl fumarate (e.g. Tecfidera®),
Fingolimod (e.g. Gilenya®),
Glatiramer acetate (e.g. Copaxone®),
Natalizumab (e.g. Tysabri®), and
Teriflunomide (e.g. Aubagio®).

25

The newest addition to this class of therapeutics is Cladribine Tablets (Mavenclad®), approved by the EMA in August 2017 for the treatment of Relapsing Remitting Multiple Sclerosis in patients with high disease activity.

30

However, all those therapeutics are only approved by the health authorities (such as FDA, EMA) for the treatment of Relapsing Remitting Multiple Sclerosis (RRMS), however none of them is approved for progressive forms of Multiple Sclerosis, including, but not limited to Primary Progressive Multiple Sclerosis (PPMS) and Secondary Progressive Multiple Sclerosis (SPMS).

In fact, there is to date only one therapeutic approved for the treatment of PPMS, Ocrelizumab (Ocrevus®), but it has gained so far moderate interest and success in this indication, at best. Other Clinical Studies in PPMS, e.g. the PROMISE Study (employing glatiramer acetate as the study drug), the OLYMPUS study (employing rituximab as the study drug), and the INFORMS Study (employing fingolimod as the study drug) did not reach meaningful clinical endpoints. However, minor clinical activity was seen in a subset of patients identified as Early Secondary Progressive Multiple Sclerosis patients.

Interestingly, this so-called Early Secondary Progressive Multiple Sclerosis (ESPMS) is some form of Multiple Sclerosis that marks some kind of transition state between the relapsing remitting forms of MS and the progressive forms of MS. This form combines the very different aspects and also very different mechanisms of both the pure relapsing remitting forms and the progressive forms of MS.

As a result, without wishing to be bound by theory, it is believed that the minor efficacy or minor clinical effects seen in all the above mentioned PPMS trials with DMDs other than Ocrelizumab, i.e. DMDs originally approved for RRMS, is just based on a simple mechanism:

all patients that experienced said minor or moderate efficacy of the DMDs approved for RRMS where actually patients in the transition state between relapsing remitting forms of MS and progressive forms of MS, including ESPMS, in which the RRMS aspects and mechanisms exclusively were (partly) treated, not having any effect or efficacy against the progressive aspects and mechanisms of the SPMS or PPMS and their contribution to the overall state of the patient. Accordingly, the very unsatisfying results of the above

discussed trials employing RRMS approved DMDs clearly show that the mechanism underlying the relapsing remitting forms on one hand and the progressive forms on the other hand are very different and were not accessible by those RRMS approved DMDs.

- 5 Based on the above, there is clearly a high unmet medical need for therapeutics that are effective in the field of progressive forms of MS.

Based on new and surprisingly advantageous clinical results discussed herein in detail, without wishing to be bound by theory, it is believed that specific oral dosings, specific oral
10 dosage forms and/or specific oral dose regimens described herein comprising the active ingredient Cladribine, newly approved for the treatment of RRMS in patients with high disease activity, are also effective in the treatment of progressive forms of MS, clearly beyond the treatment of ESPMS, and especially effective for the treatment of PPMS and/or SPMS, both with Cladribine as a single agent and in combination with other DMDs.

15

To go into more detail, the results from the ONWARD Study, which contained both RRMS and SPMS patients, surprisingly show that Cladribine-treated RRMS patients (i.e. patients that received oral Cladribine according to the now approved RRMS label for Cladribine) were 50% less likely to have a qualifying relapse than those treated with placebo, whereas
20 Cladribine-treated SPMS patients (i.e. SPMS patients that likewise received oral Cladribine according to the now approved RRMS label for Cladribine) were 89% less likely to have a qualifying relapse than those treated with placebo. This significant difference in efficacy as shown by the instant clinical data is a to date unexpected advantage for the SPMS patients treated with Cladribine and clearly shows the clinical efficacy and potential of Cladribine in
25 the treatment of progressive forms of MS, including both SPMS and PPMS, which appears to be clearly independent from the co-medication administered to all patients, including the patients that received placebo instead of Cladribine. Remarkably, oral Cladribine appears to be able to strongly downregulate the targets and mechanisms of the severely different inflammatory processes that are characteristic for progressive forms of MS, preferably
30 including both SPMS and PPMS. Due to oral Cladribine's unique properties, including, but

not limited to, a short half-life combined with a prolonged pharmacodynamic (PD) and a uniquely specific effect on a variety of specific immune cells, most notably a reversible reduction in T-cell and B-cell counts with previously unknown selectivity, oral Cladribine for use according to the instant invention it is believed to become a breakthrough
 5 therapeutic in the treatment of one or more progressive forms of MS, including but not limited PPMS and/or SPMS, preferably PPMS.

Cladribine, a synthetic chlorinated purine analogue 2-chloro-2'-deoxyadenosine (2-CdA) (Beutler, 1992), has been suggested to be useful in the treatment of MS (*EP 626853B1 and*
 10 *US 5,506,214*).

Several clinical studies with Cladribine in patients with multiple sclerosis have investigated the use of i.v. and s.c. Cladribine in MS.

15 Two double-blind, placebo-controlled Phase II studies were conducted respectively in the treatment of Chronic Progressive MS (*Selby et al., 1998, Can. J. Neurol. Sci., 25:295-299*) and Relapsing-Remitting MS respectively (*Romine et al., 1999, Proceedings of the Association of American Physicians, 111, 1, 35-44*).

In the first trial, the Cladribine dose used was 0.1 mg/kg/day for 7 days by continuous i.v.
 20 infusion. The treatment for repeated for 4 consecutive months.

In the second clinical trial, the Cladribine dose used was 0.07mg/kg/day for 5 days by subcutaneous injection. The treatment was repeated for 6 consecutive months.

In addition, placebo-controlled Phase III study was conducted in patients with primary progressive (PP) or secondary progressive (SP) multiple sclerosis (*Rice et al., 2000,*
 25 *Neurology, 54, 5, 1145-1155*). In this study, both patient groups received Cladribine by subcutaneous injection at a dose of 0.07 mg/kg/day. The treatment was repeated for either 2 months or 6 months.

The Phase II clinical studies provided evidence for the positive effects of Cladribine in patients with MS in terms of Kutzke Extended Disability Status Scale (EDSS), Scripps
 30 Neurologic rating Scale (SNRS) scores and Magnetic Resonance Imaging (MRI) findings

(Beutler *et al.*, 1996, *Proc. Nat. Acad. Sci. USA*, 93, 1716-1720; Romine *et al.*, 1999 *above*). Phase III study results were positive on the significant reduction of MRI-measured brain lesions (Rice *et al.*, 2000, *above*).

5 Some adverse effects (AEs), such as increased incidence of infections related to compromised immune function or myelosuppression, were observed with the highest doses (Selby *et al.*, 1998, *above*; Beutler *et al.*, 1994, *Acta hematol.*, 91:10-15). Due to the narrow margin of safety between the efficacy dose and the dose of occurrence of AEs, to date, all clinical trials for Cladribine in multiple sclerosis have been conducted using either i.v. or
10 s.c. administration. As a result, Beutler *et al.* (Beutler *et al.*, 1996, *Seminars in Hematology*, 33, 1(S1), 45-52) excluded the oral route for the treatment of multiple sclerosis with Cladribine.

Grieb *et al.* reported a small trial in 11 patients with relapsing-remitting multiple sclerosis
15 (Grieb *et al.*, 1995, *Archivum Immunologiae et Therapiae Experimentalis*, 43 (5-6), 323-327) wherein Cladribine has been orally administered during 6 monthly courses of 5 days at a total dose of about 4-5.7 mg/kg (patients of about 52 and about 75 kilos, respectively) i.e. a total effective dose of 2-2.85 mg/kg. For some patients, a single re-treatment of 5 days was performed at a cumulative dose of 0.4-0.66 mg/kg after a Cladribine free-period of 3 or
20 6 months. The side effects observed with the regimen above were said to be less severe than the ones observed in the study on patients suffering from chronic progressive multiple sclerosis treated by i.v. infusion of Cladribine (Sipe *et al.*, 1994, *Lancet*, 344, 9-13) but were still present. In addition, the therapeutic efficacy of the oral regimen above versus the i.v. infusion therapy was questioned (Grieb *et al.*, 1995, *above*) and a group of “non-
25 responders” has been identified (Stelmasiak *et al.*, 1998, *Laboratory Investigations*, 4(1), 4-8).

Giovannoni *et al.* (N Engl J Med 2010) report about a placebo-controlled phase III trial of oral Cladribine for relapsing multiple sclerosis (ClinicalTrials.gov number,
30 NCT00213135). According to that, Cladribine provides immunomodulation through

selective targeting of lymphocyte subtypes. Giovannoni et al describe the results of a 96-week phase 3 trial of a short-course oral tablet therapy in patients with relapsing–remitting multiple sclerosis. In that trial, 1326 patients were randomly assigned in an approximate 1:1:1 ratio to receive one of two cumulative doses of Cladribine tablets (either 3.5 mg or 5.25 mg per kilogram of body weight) or matching placebo, given in two or four short courses for the first 48 weeks, then in two short courses starting at week 48 and week 52 (for a total of 8 to 20 days per year). The primary end point was the rate of relapse at 96 weeks. Among patients who received Cladribine tablets (either 3.5 mg or 5.25 mg per kilogram), there was a significantly lower annualized rate of relapse than in the placebo group (0.14 and 0.15, respectively, vs. 0.33; $P < 0.001$ for both comparisons), a higher relapse-free rate (79.7% and 78.9%, respectively, vs. 60.9%; $P < 0.001$ for both comparisons), a lower risk of 3-month sustained progression of disability (hazard ratio for the 3.5-mg group, 0.67; 95% confidence interval [CI], 0.48 to 0.93; $P = 0.02$; and hazard ratio for the 5.25-mg group, 0.69; 95% CI, 0.49 to 0.96; $P = 0.03$), and significant reductions in the brain lesion count on magnetic resonance imaging (MRI) ($P < 0.001$ for all comparisons). Adverse events that were more frequent in the Cladribine groups included lymphocytopenia (21.6% in the 3.5-mg group and 31.5% in the 5.25-mg group, vs. 1.8%) and herpes zoster (8 patients and 12 patients, respectively, vs. no patients). Thus, treatment with Cladribine tablets significantly reduced relapse rates, the risk of disability progression, and MRI measures of disease activity at 96 weeks. However, the benefits are said to be needed to be weighed against the risks.

Therefore, it would be desirable to have a method for treating multiple sclerosis comprising the oral administration of Cladribine that would permit the same or improved effect on MS lesions while decreasing the occurrence adverse events, severity of adverse events and/or the progression of the disease in general also for patients suffering from progressive forms of MS, preferably selected from the group consisting of PPMS and/or SPMS. In addition, as MS is a chronic disease, it would be desirable to decrease the occurrence and/or severity adverse events in such a way that re-treatments are possible. A sustained benefit of

Cladribine treatment between the treatment periods and/or beyond treatment periods is also desirable.

BRIEF SUMMARY OF THE INVENTION

5 The present invention is inter-alia directed towards new uses of Cladribine for the preparation of oral pharmaceutical formulations for the treatment of progressive forms of Multiple Sclerosis, including, but not limited to Primary Progressive Multiple Sclerosis and/or Secondary Progressive Multiple Sclerosis, wherein said pharmaceutical formulations are to be orally administered according a certain regimen. Additionally, the invention is
10 directed towards specific methods of treating patients suffering from progressive forms of Multiple Sclerosis, including, but not limited to Primary Progressive Multiple Sclerosis and/or Secondary Progressive Multiple Sclerosis, comprising orally administering Cladribine according to a certain regimen.

15 Furthermore, the invention provides improved dosing regimen for the oral use of Cladribine in the treatment of progressive form of Multiple Sclerosis.

An additional aspect of the invention relates to a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of progressive forms of Multiple Sclerosis,
20 wherein efficacy to the patient is provided and/or wherein adverse effects are reduced, thus preferably providing new therapeutic options for patients suffering from progressive forms of multiple sclerosis.

Furthermore, the invention preferably provides a use of Cladribine for the preparation of a
25 pharmaceutical formulation wherein the formulation is to be orally administered as described herein.

The efficacy of cladribine in the treatment of progressive forms of MS, including PPMS and/or SPMS, can preferably be shown by improvements with regard to one or more
30 selected from Expanded Disability Status Scale (EDSS), No Evidence of Disease Activity

(NEDA), No Evidence Of Progression Or Active Disease (NEPAD) and/or Quality of Life (QoL), preferably as known and described in the art and/or as described herein. Additionally, or alternatively, MRI measures of lesions can preferably be likewise used in order to track efficacy, preferably as known and described in the art and/or as described
 5 herein.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

Fig. 1 shows the ONWARD study design in Example 1.

Fig. 2 shows the qualifying relapse rate (annualized, adjusted) in patients with
 10 SPMS treated with cladribine tablets 3.5 mg/kg + IFN- β or placebo + IFN- β in ONWARD in Example 1.

Fig. 3 shows the qualifying relapse rate (annualized, adjusted) in patients with RRMS treated with cladribine tablets 3.5 mg/kg + IFN- β or placebo + IFN- β in ONWARD in Example 1.

15 Fig. 4 shows a schematic of the study design for the PPMS Study in Example 2.

DETAILED DESCRIPTION OF THE INVENTION

The instant invention is described in more detail in the Sections given below including the following embodiments:

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1. Cladribine for use in the oral treatment of patients suffering from progressive forms of Multiple Sclerosis, wherein said Cladribine is to be orally administered to each patient at a certain dose that is calculated per patient, per body weight and per treatment year, wherein said dose or said certain dose is selected from the range of
 25 1.5 mg/kg to 4.0 mg/kg. Preferably, a dose that is calculated per patient, per body weight of the patient and per treatment year is referred to as a “fixed dose”. Thus, preferred is Cladribine for use in the oral treatment of patients suffering from progressive forms of Multiple Sclerosis, wherein said Cladribine is to be orally administered to each patient at fixed dose per patient, per body weight and per
 30 treatment year, wherein said fixed dose is selected from the range of 1.5 mg/kg to

4.0 mg/kg. Typically, a treatment year lasts about 12 months. Administration of Cladribine may be to a patient in need thereof or a subject in need thereof.

2. Cladribine for use as described herein, preferably as described in one or more of the
5 numbered Sections above and/or below and more preferably as described in Section
1, wherein said fixed dose is selected from the range of 1.5 mg/kg to 2.0 mg/kg,
preferably selected from the range of 1.5 mg/kg to 2.0 mg/kg per year. Especially
preferred is Cladribine for use as described herein, preferably as described in one or
more of the numbered Sections above and/or below and more preferably as
10 described in Section 1, wherein said fixed dose is selected from the range of 1.5
mg/kg to 2.0 mg/kg, preferably selected from the range of 1.5 mg/kg to 2.0 mg/kg
per year, for two consecutive treatment years. Thus, said fixed dose is preferably
selected from the range of 3.0 mg/kg to 4.0 mg/kg over two consecutive years (or to
be administered over two consecutive years), wherein said fixed dose is selected
15 from the range of 1.5 mg/kg to 2.0 mg/kg per year in each of the two years.
3. Cladribine for use as described herein, preferably as described in one or more of the
numbered Sections above and/or below and more preferably as described in Section
numbered 1 and/or 2, wherein said fixed dose per patient, preferably for each
20 patient, is 1.75 mg/kg per treatment year with a maximum deviation of +/- 0.2
mg/kg. Especially preferred is Cladribine for use as described herein, preferably as
described in one or more of the numbered Sections above and/or below and more
preferably as described in Section numbered 1 and/or 2, wherein said fixed dose per
patient, preferably for each patient, is 1.75 mg/kg per treatment year with a
25 maximum deviation of +/- 0.2 mg/kg, for two consecutive treatment years. Thus,
said fixed dose per patient, preferably for each patient, is preferably 3.5 mg/kg over
two consecutive years with a maximum deviation of +/- 0.4 mg/kg.
4. Cladribine for use as described herein, preferably as described in one or more of the
30 numbered Sections above and/or below and more preferably as described in Section

1, 2 and/or 3, where said progressive forms of multiple sclerosis comprise Primary Progressive Multiple Sclerosis and/or Secondary Progressive Multiple Sclerosis, and especially consist of Primary Progressive Multiple Sclerosis and/or Secondary Progressive Multiple Sclerosis.

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5. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 1, 2, 3 and/or 4, wherein said progressive form of Multiple Sclerosis is Primary Progressive Multiple Sclerosis. Preferably, Cladribine is used according to the invention for patients that are already diagnosed Primary Progressive Multiple Sclerosis before the start of the treatment. More preferably, Cladribine is used as described herein and especially as described above and/or below for patients that are already diagnosed Primary Progressive Multiple Sclerosis before the start of the treatment.

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6. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 1, 2, 3 and/or 4, wherein said progressive form of Multiple Sclerosis is Secondary Progressive Multiple Sclerosis. Preferably, Cladribine is used according to the invention for patients that are already diagnosed Secondary Progressive Multiple Sclerosis before the start of the treatment. Preferably, Secondary Progressive Multiple Sclerosis does not include Early Secondary Progressive Multiple Sclerosis.

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7. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to one or more of the preceding Sections, wherein said Cladribine is to be orally administered to patients having an age between 18 and 65 years, preferably inclusive of patients having the age of 18 years and patients having the age of 65 years.

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8. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to one or more of the preceding Sections, wherein said Cladribine is to be orally administered to patients having an age between 18 and 51 years, preferably inclusive of patients having the age of 18 years and having the age of 51 years.
9. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to one or more of the preceding Sections, wherein said Cladribine is to be orally administered to patients having an age between 12 and 51 years, preferably inclusive of patients having the age of 18 years and having the age of 51 years.
10. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to one or more of the preceding numbered Sections, wherein said Cladribine is to be orally administered to patients of female gender and/or to patients of male gender. Since female patients are more often affected and/or often more severely affected by progressive forms of multiple sclerosis, it is a preferred aspect of the instant invention to treat female patients in this regard.
11. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to one or more of the preceding numbered Sections, wherein said Patient has High Disease Activity (HDA) and/or has been diagnosed High Disease Activity. Preferably, Cladribine is used according to the invention for patients that are already diagnosed High Disease Activity before the start of the treatment. More preferably, Cladribine is used described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to one or more of the preceding numbered Sections, for patients that are already

diagnosed High Disease Activity before the start of the treatment

12. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to one or more of the preceding Sections, wherein said Cladribine is to be orally administered to patients being treatment naïve to Cladribine and/or disease modifying drugs other than Cladribine.
13. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to one or more of Sections 1 to 11, wherein said Cladribine is to be orally administered to patients who previously received Cladribine and/or disease modifying drugs other than Cladribine. Preferably, in this regard the disease modifying drugs other than Cladribine comprise Interferon beta-1a, Beta interferon-1a (e.g. Avonex®, Rebif®).
14. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to one or more of the preceding Sections, wherein said Cladribine is to be orally administered to patients also receiving one or more disease modifying drugs other than Cladribine. Preferably, in this regard the disease modifying drugs other than Cladribine comprise Interferon beta-1a, Beta interferon-1a (e.g. Avonex®, Rebif®).
15. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to one or more of Sections 12-14, wherein said disease modifying drugs other than Cladribine are selected from the group consisting of:
Interferon beta-1a, Beta interferon-1a (e.g. Avonex®, Rebif®),
Interferon beta-1b, Beta interferon-1b (e.g. Betaferon®, Extavia®),
Peginterferon beta 1a (e.g. Plegriidy®),
Alemtuzumab (e.g. Lemtrada®),

Daclizumab (e.g. Zinbryta®),
 Dimethyl fumarate (e.g. Tecfidera®),
 Fingolimod (e.g. Gilenya®),
 Glatiramer acetate (e.g. Copaxone®),
 5 Natalizumab (e.g. Tysabri®), and
 Teriflunomide (e.g. Aubagio®).

- 10 16. Cladribine for use as described herein, preferably as described in one or more of the
 numbered Sections above and/or below and more preferably for use according to
 one or more of the preceding Sections, wherein said Cladribine is to be orally
 administered to each patient at fixed dose per patient, per body weight and per
 treatment year, wherein said fixed dose is selected from the range of 1.5 mg/kg to
 4.0 mg/kg, preferably selected from the range of 1.5 mg/kg to 2.0 mg/kg, and
 especially is, preferably for each patient, 1.75 mg/kg per treatment year with a
 15 maximum deviation of +/- 0.2 mg/kg,
 and wherein the said fixed dose is orally administered to said patient within two
 adjacent months within said treatment year, preferably within two adjacent months
 at the beginning of said treatment year.
- 20 17. Cladribine for use as described herein, preferably as described in one or more of the
 numbered Sections above and/or below and more preferably for use according to
 Section 16, wherein said fixed dose is orally administered to said patient within two
 adjacent months starting at the beginning of said treatment year. More preferred is
 Cladribine for use as described herein, preferably as described in one or more of the
 25 numbered Sections above and/or below and more preferably for use according to
 Section 16, wherein said fixed dose is orally administered to said patient within two
 adjacent months starting at the beginning of each of said treatment years.
- 30 18. Cladribine for use as described herein, preferably as described in one or more of the
 numbered Sections above and/or below and more preferably for use according to

Section 16 and/or 17, wherein said fixed dose is orally administered to said patient within one week or two weeks, preferably two adjacent weeks, in each one of said two adjacent months.

- 5 19. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to Section 16, 17 and/or 18, wherein said fixed dose is orally administered to said patient within one week or two adjacent weeks located at the beginning of each one of said two adjacent months.

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20. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to Section 16, 17, 18 and/or 19, wherein said fixed dose is orally administered to said patient, preferably divided into the respective amounts
15 numbers of daily doses, more preferably about equal doses, to be administered to said patient within 2 to 7 days during said week, or within 2 to 7 days of each of said weeks.

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21. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to Section 16, 17, 18, 19 and/or 20, wherein said fixed dose is orally administered to said patient, preferably divided into the respective amounts
our numbers of daily doses, preferably about equal doses, within 2 to 7 days, preferably within 4 to 5 days during said week, or within 2 to 7 days, preferably
25 within 4 to 5 days, of each of said weeks.

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Accordingly, a treatment year typically consists of 2 months of active treatment, i.e. 2 months wherein Cladribine is administered to the patient, and 10 months without active treatment, i.e. 10 months wherein no Cladribine is administered to said patients. Preferably, the 2 months of active treatment mark the beginning of the

treatment year. Preferably, the Cladribine is administered to the patient during the respective first week of each said two months of active treatment.

22. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to one or more of the preceding Sections, wherein said Cladribine is to be orally administered to each patient at said fixed dose per patient, per body weight and per treatment year, preferably as described in the Sections above and/or below, and wherein the treatment comprises one or more additional treatment years. Preferably, Cladribine for use as described herein is administered during two or more treatment years, more preferably 2 treatment years, which are preferably adjacent treatment years that are preferably basically identical.

However, depending on the hematological state of the patient, it can become necessary or advantageous to separate two treatment years by a gap, i.e. a certain time where the previous treatment year is over and the foreseen next treatment year cannot or should not be started. Preferably and intentionally, Cladribine is not administered during such a gap. Typically, a gap in this regard lasts between 1 and 8 months, preferably between 1 and 6 months, more preferably between 1 and 3 months. Often, during such a gap, the hematological state of the patient is monitored in order to decide when the next treatment year can be started.

23. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to one or more of the preceding Sections, wherein said Cladribine is to be orally administered to each patient at said fixed dose per patient, per body weight and per treatment year, preferably as described in the Sections above and/or below, and wherein the treatment comprises two treatment years, preferably two substantially identical treatment years.

24. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to Section 20 and/or 21, wherein two of said treatment years are either directly adjacent to each other, or are separated by a gap 1 to 10 months. Typically, such a gap, if any, is induced by the hematological state of the patient at the end of the respective treatment year before the start of the new or subsequent treatment year. Sometimes, it can become necessary or advantageous to separate two treatment years by a gap, i.e. a certain time where the previous treatment year is over and the foreseen next treatment year cannot or should not be started. Preferably and intentionally, Cladribine is not administered during such a gap.

25. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to one or more of the preceding Sections, wherein said Cladribine is to be orally administered to each patient at a fixed dose per patient, per body weight and per treatment year,

a) wherein said fixed dose per treatment year is selected from the range of 1.5 mg/kg to 4.0 mg/kg, preferably selected from the range of 1.5 mg/kg to 2.0 mg/kg, and especially is, preferably for each patient, 1.75 mg/kg per treatment year with a maximum deviation of +/- 0.2 mg/kg,

b) wherein said treatment year comprises:

- (i) a treatment period of 2 months at the beginning of said treatment year, wherein said fixed dose of Cladribine is orally administered on about 1 to about 7 days each month, preferably on about 1 to about 7 days each month at the beginning of each month, said fixed dose being divided into daily doses of 5 to 20 mg of Cladribine, and
- (ii) a Cladribine-free period lasting 10 months, during which no Cladribine is administered.

26. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to one or more of the preceding Sections, wherein said Cladribine is to be orally administered to each patient at a fixed dose per patient, per body weight and per treatment year,
- 5 a) wherein said fixed dose per treatment year is selected from the range of 1.5 mg/kg to 4.0 mg/kg, preferably selected from the range of 1.5 mg/kg to 2.0 mg/kg, and especially is, preferably for each patient, 1.75 mg/kg per treatment year with a maximum deviation of +/- 0.2 mg/kg,
- 10 b) wherein said treatment year comprises:
- (i) a treatment period of 2 months at the beginning of said treatment year, wherein said fixed dose of Cladribine is orally administered on 3 to 5 days each month at the beginning of each month, said fixed dose being divided into daily doses of 10 or 20 mg of Cladribine,
- 15 (ii) a Cladribine-free period lasting 10 months, during which no Cladribine is administered.
27. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to one or more of the preceding Sections, wherein said oral treatment of patients suffering from Primary Progressive Multiple Sclerosis and/or patients suffering from Secondary Progressive Multiple Sclerosis, wherein said Cladribine is to be orally administered to each patient at fixed dose per patient, per body weight and per treatment year, wherein said fixed dose per patient is, preferably for each
- 20 patient, 1.75 mg/kg per treatment year with a maximum deviation of +/- 0.2 mg/kg, and wherein said treatment comprises at least two treatment years, preferably two or three treatment years.
28. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to
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one or more of the preceding Sections, wherein the treatment comprises two treatment years that are substantially adjacent to either each other, or that are separated by a gap of 1 to 10 months, preferably 1 to 6 months, and especially 1 to 3 months.

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29. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to one or more of the preceding Sections, wherein the treatment additionally comprises a subsequent treatment year,

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a) wherein said fixed dose per treatment year is selected from the range of 0.75 mg/kg to 2.0 mg/kg, preferably selected from the range of 1.0 mg/kg to 1.5 mg/kg, and especially is, preferably for each patient, 0.8 mg/kg per treatment year with a maximum deviation of ± 0.2 mg/kg,

b) wherein said subsequent treatment year comprises:

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(i) a treatment period of 1 month or 2 months at the beginning of said treatment year, wherein said fixed dose of Cladribine is orally administered on 3 to 5 days each month at the beginning of each month, said fixed dose being divided into daily doses of 10 or 20 mg of Cladribine,

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(ii) a Cladribine-free period lasting 11 or 10 months respectively, during which no Cladribine is administered.

30. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to one or more of the preceding Sections, wherein the treatment comprises one or two treatment years as described in the Sections above and/or below, preferably 2 treatment years as described in the Sections above and/or below, optionally plus an additional subsequent treatment year as described in Section 26 or 29, followed by at least one year, preferably at least 2 years, in which no Cladribine is administered

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to said patients.

31. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to one or more of the preceding Sections, wherein said Cladribine is to be orally administered as a liquid, a tablet or a capsule.
32. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to one or more of the preceding Sections, wherein said Cladribine is to be orally administered as a tablet, preferably a tablet comprising about 10 mg of Cladribine.
33. Cladribine for use as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably for use according to one or more of the preceding Sections, wherein said Cladribine is to be orally administered as a tablet comprising 10 mg of Cladribine in the form of a mixture of Cladribine, 2-hydroxypropyl- β -cyclodextrin and Cladribine-2-hydroxypropyl- β -cyclodextrin-complexes, wherein the weight ratio of Cladribine to 2-hydroxypropyl- β -cyclodextrin is between about 1:10 to about 1:16, preferably between 1:13 to 1:15.
34. A method of treating patients diagnosed to suffer from progressive forms of Multiple Sclerosis, said method comprising orally administering to said patients, preferably to each of said patients, a cumulative dose of Cladribine of about 3.5 mg/kg body weight, with a maximum deviation of ± 0.4 mg/kg, over 2 years (i.e. two treatment years), administered as one treatment course of about 1.75 mg/kg ± 0.2 mg/kg per year (i.e. per treatment year), wherein each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the

respective treatment year.

35. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 34, wherein each treatment week consists of 4 or 5 days on which said patient receives 10 mg or 20 mg of Cladribine for oral administration, preferably as a single daily dose, depending on the body weight of the respective patient.
36. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably according to Section 35, wherein said patient receives the 10 mg or 20 mg of Cladribine for oral administration as a tablet or capsule, preferably a tablet or capsule containing 10 mg of Cladribine.
37. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably according to Section 36, wherein said patient receives the 10 mg or 20 mg of Cladribine for oral administration as a tablet or capsule comprising 10 mg of Cladribine in the form of a mixture of Cladribine, 2-hydroxypropyl- β -cyclodextrin and Cladribine-2-hydroxypropyl- β -cyclodextrin-complexes, wherein the weight ratio of Cladribine to 2-hydroxypropyl- β -cyclodextrin is between about 1:10 to about 1:16, preferably between 1:13 to 1:15.
38. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably according to one or more of Sections 34 to 37, wherein the progressive form of Multiple Sclerosis is Primary Progressive Multiple Sclerosis.
39. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably according to one or

more of Sections 34 to 37, wherein the progressive form of Multiple Sclerosis is Secondary Progressive Multiple Sclerosis.

- 5 40. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably according to one or more of Sections 34 to 37, where the progressive form of Multiple Sclerosis is selected from the group consisting of Primary Progressive Multiple Sclerosis and Secondary Progressive Multiple Sclerosis, said method comprising orally administering to said patients a cumulative dose of Cladribine of about 3.5
10 mg/kg body weight over 2 years, administered as 1 treatment course of about 1.75 mg/kg, wherein each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year.
- 15 41. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably according to Section 40, wherein each treatment week consists of 4 or 5 days on which said patient receives 10 mg or 20 mg of Cladribine for oral administration, preferably as a single daily dose, and preferably depending on the body weight of the respective patient.
- 20 42. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably according to one or more of the preceding Sections, wherein said patients to be treated are between 18 and 65 years old, preferably inclusive.
- 25 43. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably according to one or more of the preceding Sections, wherein said patients to be treated are between 18 and 51 years old, preferably inclusive.
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44. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably according to one or more of the preceding Sections, wherein said patients to be treated are between 12 and 51 years old, preferably inclusive.

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45. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably according to one or more of the preceding Sections, wherein said patients to be treated are patients of female gender and/or patients of male gender. Since female patients are more often affected and/or often more severely affected by progressive forms of multiple sclerosis, it is a preferred aspect of the instant invention to treat female patients in this regard.

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46. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably according to one or more of the preceding Sections, wherein said patients to be treated are treatment naïve to Cladribine and/or disease modifying drugs other than Cladribine.

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47. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably according to one or more of the preceding Sections, wherein said patients are patients who previously received Cladribine and/or disease modifying drugs other than Cladribine. Preferably, in this regard the disease modifying drugs other than Cladribine comprise Interferon beta-1a, Beta interferon-1a (e.g. Avonex®, Rebif®).

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48. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably according to one or more of the preceding Sections, wherein said patients to be treated additionally receive one or more disease modifying drugs other than Cladribine. Preferably, in this regard the disease modifying drugs other than Cladribine comprise Interferon

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beta-1a, Beta interferon-1a (e.g. Avonex®, Rebif®).

49. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably according to one or more of the preceding Sections, wherein said disease modifying drugs other than Cladribine are selected from the group consisting of:
- Interferon beta-1a, Beta interferon-1a (e.g. Avonex®, Rebif®),
 Interferon beta-1b, Beta interferon-1b (e.g. Betaferon®, Extavia®),
 Peginterferon beta 1a (e.g. Plegridy®),
 Alemtuzumab (e.g. Lemtrada®),
 Daclizumab (e.g. Zinbryta®),
 Dimethyl fumarate (e.g. Tecfidera®),
 Fingolimod (e.g. Gilenya®),
 Glatiramer acetate (e.g. Copaxone®),
 Natalizumab (e.g. Tysabri®), and
 Teriflunomide (e.g. Aubagio®).
50. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably according to one or more of the preceding Sections, wherein after the completion of said 2 years with said 2 treatment courses, no Cladribine is administered to the patients in the subsequent 1 or 2 years following the completion of said 2 years with said 2 treatment courses.
51. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably according to one or more of the preceding Sections, wherein to the patients having completed said 2 treatment courses of one year each, no further Cladribine treatment is required and/or administered to said patients in the subsequent years 3 and 4.

52. A method of treating patients suffering from progressive forms of Multiple Sclerosis, comprising orally administering to said patient tablets or capsules containing about 10 mg of Cladribine each, wherein said tablets or capsules are administered during a period called treatment year comprising the following regimen:

(i) a treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered to the patient daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month, preferably on 4 or 5 days of each month, preferably in the 1st week of the respective month (each a treatment week);

(ii) followed by a Cladribine-free period lasting 10 months, preferably until the end of the 1st treatment year, wherein no Cladribine is administered to said patient;

wherein a patient having a bodyweight

- in the range of 40 to less than 50 kg is or is to be administered

1) 4 tablets or capsules (40 mg of Cladribine) in the 1st month or treatment week of said treatment course,

2) 4 tablets or capsules (40 mg of Cladribine) in the 2nd month or treatment week of said treatment course,

- in the range of 50 to less than 60 kg is or is to be administered

1) 5 tablets or capsules (50 mg of Cladribine) in the 1st month or treatment week of said treatment course, respectively,

2) 5 tablets or capsules (50 mg of Cladribine) in the 2nd month or treatment week of said treatment course,

- in the range of 60 to less than 70 kg is or is to be administered

1) 6 tablets or capsules (60 mg of Cladribine) in the 1st month or treatment week of said treatment course,

2) 6 tablets or capsules (60 mg of Cladribine) in the 2nd month or treatment week of said treatment course,

- in the range of 70 to less than 80 kg is or is to be administered

1) 7 tablets or capsules (70 mg of Cladribine) in the 1st month or treatment week of

said treatment course,

2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd month or treatment week of said treatment course,

- in the range of 80 to less than 90 kg is or is to be administered

5 1) 8 tablets or capsules (80 mg of Cladribine) in the 1st month or treatment week of said treatment course,

2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd month or treatment week of said treatment course,

- in the range of 90 to less than 100 kg is or is to be administered

10 1) 9 tablets or capsules (90 mg of Cladribine) in the 1st month or treatment week of said treatment course,

2) 8 tablets or capsules (80 mg of Cladribine) in the 2nd month or treatment week of said treatment course,

- in the range of 100 to less than 110 kg is or is to be administered

15 1) 10 tablets or capsules (100 mg of Cladribine) in the 1st month or treatment week of said treatment course,

2) 9 tablets or capsules (90 mg of Cladribine) in the 2nd month or treatment week of said treatment course,

- in the range of 110 kg and above is or is to be administered

20 1) 10 tablets or capsules (100 mg of Cladribine) in the 1st month or treatment week of said treatment course,

2) 10 tablets or capsules (100 mg of Cladribine) in the 2nd month or treatment week of said treatment course.

25 53. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably according to Section 52, wherein the method further comprises at least one subsequent period called additional treatment year, wherein said additional treatment year is substantially identical, or preferably identical, to said regimen called treatment year. Preferably,

Cladribine is administered during two or more treatment years, more preferably 2 treatment years, which are preferably adjacent treatment years that are preferably basically identical.

However, depending on the hematological state of the patient, it can become
5 necessary or advantageous to separate two treatment years by a gap, i.e. a certain time where the previous treatment year is over and the foreseen next treatment year cannot or should not be started. Preferably and intentionally, Cladribine is not administered during such a gap. Typically, a gap in this regard lasts between 1 and 8 months, preferably between 1 and 6 months, more preferably between 1 and 3
10 months. Often, during such a gap, the hematological state of the patient is monitored in order to decide when the next treatment year can be started.

54. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably according to Section
15 53, wherein said additional treatment year is directly adjacent to said regimen called treatment year, or there is gap of 1 to 10 months in between the two treatment years. Typically, such a gap, if any, is induced by the hematological state of the patient at the end of the respective treatment year before the start of the new or subsequent treatment year. Sometimes, it can become necessary or advantageous to separate
20 two treatment years by a gap, i.e. a certain time where the previous treatment year is over and the foreseen next treatment year cannot or should not be started. Preferably and intentionally, Cladribine is not administered during such a gap.

55. The method as described herein, preferably as described in one or more of the
25 numbered Sections above and/or below and more preferably according to Section 52 or 53, wherein the method further comprises more than one subsequent periods called additional treatment year, preferably two additional treatment years, wherein all said additional treatment years are substantially identical, or preferably identical, and wherein said additional treatment years are directly adjacent to each other, or
30 there is gap of 1 to 10 months in between at least two of said additional treatment

years.

56. A method of treating patients suffering from progressive forms of Multiple Sclerosis, comprising orally administering to said patient tablets or capsules containing about 10 mg of Cladribine each, wherein said tablets or capsules are administered during a period called treatment year according comprising the following regimen:

(i) a first treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month, preferably on 4 or 5 days of each month, preferably in the 1st week of the respective month (treatment week);

(ii) followed by a first Cladribine-free period lasting 10 months, preferably until the end of a first treatment year, wherein no Cladribine is administered to said patient;

(iii) followed by a second treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month, preferably on 4 or 5 days of each month, preferably in the 1st week of the respective month (treatment week); and

(iv) followed by a second Cladribine-free period lasting 10 months, preferably until the end of a second treatment year, wherein no Cladribine is administered to said patient, and

wherein a patient having a bodyweight

- in the range of 40 to less than 50 kg is administered or is to be administered

1) 4 tablets or capsules (40 mg of Cladribine) in the 1st month or treatment week of both the 1st and the 2nd treatment course, respectively,

2) 4 tablets or capsules (40 mg of Cladribine) in the 2nd month or treatment week of both the 1st and the 2nd treatment course, respectively,

- in the range of 50 to less than 60 kg is administered or is to be administered

1) 5 tablets or capsules (50 mg of Cladribine) in the 1st month or treatment week of

both the 1st and the 2nd treatment course, respectively,

2) 5 tablets or capsules (50 mg of Cladribine) in the 2nd month or treatment week of both the 1st and the 2nd treatment course, respectively,

- in the range of 60 to less than 70 kg is administered or is to be administered

5 1) 6 tablets or capsules (60 mg of Cladribine) in the 1st month or treatment week of both the 1st and the 2nd treatment course, respectively,

2) 6 tablets or capsules (60 mg of Cladribine) in the 2nd month or treatment week of both the 1st and the 2nd treatment course, respectively,

- in the range of 70 to less than 80 kg is administered or is to be administered

10 1) 7 tablets or capsules (70 mg of Cladribine) in the 1st month or treatment week of both the 1st and the 2nd treatment course, respectively,

2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd month or treatment week of both the 1st and the 2nd treatment course, respectively,

- in the range of 80 to less than 90 kg is administered or is to be administered

15 1) 8 tablets or capsules (80 mg of Cladribine) in the 1st month or treatment week of both the 1st and the 2nd treatment course, respectively,

2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd month or treatment week of both the 1st and the 2nd treatment course, respectively,

- in the range of 90 to less than 100 kg is administered or is to be administered

20 1) 9 tablets or capsules (90 mg of Cladribine) in the 1st month or treatment week of both the 1st and the 2nd treatment course, respectively,

2) 8 tablets or capsules (80 mg of Cladribine) in the 2nd month or treatment week of both the 1st and the 2nd treatment course, respectively,

- in the range of 100 to less than 110 kg is administered or is to be administered

25 1) 10 tablets or capsules (100 mg of Cladribine) in the 1st month or treatment week of both the 1st and the 2nd treatment course, respectively,

2) 9 tablets or capsules (90 mg of Cladribine) in the 2nd month or treatment week of both the 1st and the 2nd treatment course, respectively,

- in the range of 110 kg and above is administered or is to be administered

30 1) 10 tablets or capsules (100 mg of Cladribine) in the 1st month or treatment week

of both the 1st and the 2nd treatment course, respectively,
2) 10 tablets or capsules (100 mg of Cladribine) in the 2nd month or treatment week
of both the 1st and the 2nd treatment course, respectively.

- 5 57. The method as described herein, preferably as described in one or more of the
numbered Sections above and/or below and more preferably as described in the
preceding Sections, wherein said 10 mg or 20 mg of Cladribine for oral
administration are administered to the patient as a tablet or capsule comprising 10
mg of Cladribine in the form of a mixture of Cladribine, 2-hydroxypropyl- β -
10 cyclodextrin and Cladribine-2-hydroxypropyl- β -cyclodextrin-complexes, wherein
the weight ratio of Cladribine to 2-hydroxypropyl- β -cyclodextrin is between about
1:10 to about 1:16, preferably between 1:13 to 1:15.
- 15 58. The method as described herein, preferably as described in one or more of the
numbered Sections above and/or below and more preferably according to one or
more of the preceding Sections, wherein the progressive form of Multiple Sclerosis
is Primary Progressive Multiple Sclerosis.
- 20 59. The method as described herein, preferably as described in one or more of the
numbered Sections above and/or below and more preferably according to one or
more of the preceding Sections, wherein the progressive form of Multiple Sclerosis
is Secondary Progressive Multiple Sclerosis.
- 25 60. The method as described herein, preferably as described in one or more of the
numbered Sections above and/or below and more preferably according to one or
more of the preceding Sections, wherein said patients to be treated are between 18
and 51 years or 12 and 51 years old.
- 30 61. The method as described herein, preferably as described in one or more of the
numbered Sections above and/or below and more preferably according to one or

more of the preceding Sections, wherein said patients to be treated are patients of female gender and/or patients of male gender. Since female patients are more often affected and/or often more severely affected by progressive forms of multiple sclerosis, it is a preferred aspect of the instant invention to treat female patients in this regard.

62. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably according to one or more of the preceding Sections, wherein said patients to be treated are treatment naïve to Cladribine and/or disease modifying drugs other than Cladribine.

63. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably according to one or more of the preceding Sections, wherein said patients are patients who previously received Cladribine and/or disease modifying drugs other than Cladribine.

64. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably according to one or more of the preceding Sections, wherein said patients to be treated additionally receive one or more disease modifying drugs other than Cladribine.

65. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably according to one or more of the preceding Sections, wherein said disease modifying drugs other than Cladribine are selected from the group consisting of:

Interferon beta-1a, Beta interferon-1a (e.g. Avonex®, Rebif®),
 Interferon beta-1b, Beta interferon-1b (e.g. Betaferon®, Extavia®),
 Peginterferon beta 1a (e.g. Plegridy®),
 Alemtuzumab (e.g. Lemtrada®),
 Daclizumab (e.g. Zinbryta®),

Dimethyl fumarate (e.g. Tecfidera®),
 Fingolimod (e.g. Gilenya®),
 Glatiramer acetate (e.g. Copaxone®),
 Natalizumab (e.g. Tysabri®), and
 5 Teriflunomide (e.g. Aubagio®).

66. The method as described herein, preferably as described in one or more of the
 numbered Sections above and/or below and more preferably according to one or
 more of the preceding Sections, wherein after the completion of said 2 years with
 10 said 2 treatment courses, no Cladribine is administered to the patients in the
 subsequent 1 or 2 years following the completion of said 2 years with said 2
 treatment courses.

67. The method as described herein, preferably as described in one or more of the
 15 numbered Sections above and/or below and more preferably according to one or
 more of the preceding Sections, wherein to the patients having completed said 2
 treatment courses of one year each, no further Cladribine treatment is required
 and/or administered to said patients in the subsequent years 3 and 4.

68. The method as described herein, preferably as described in one or more of the
 20 numbered Sections above and/or below and more preferably according to one or
 more of the preceding Sections, wherein to the patients to be treated have been
 diagnosed to suffer from progressive forms Multiple Sclerosis, preferably selected
 from the group consisting of Primary Progressive Multiple Sclerosis and Secondary
 25 Progressive Multiple Sclerosis, preferably before the start of treatment according to
 the method.

69. The method as described herein, preferably as described in one or more of the
 numbered Sections above and/or below and more preferably according to one or
 30 more of the preceding Sections, wherein to the patients to be treated have been

diagnosed Primary Progressive Multiple Sclerosis, preferably before the start of treatment according to the method.

5 70. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably according to one or more of the preceding Sections, wherein to the patients to be treated have been diagnosed Secondary Progressive Multiple Sclerosis, preferably before the start of treatment according to the method.

10 71. The method as described in one or more of the numbered Sections above and/or below and preferably according to one or more of the preceding Sections, wherein said Patient has High Disease Activity (HDA) and/or has been diagnosed High Disease Activity. Preferably, Cladribine is used according to the invention for patients that are already diagnosed High Disease Activity before the start of the
15 treatment.

In another set of Sections, further embodiments are disclosed. The Sections may be combined with those above and below as long as there is no contradiction:

- 20 1. A method of treating a progressive form of Multiple Sclerosis, said method comprising: orally administering Cladribine to a patient in need thereof at fixed dose per patient, per body weight and per treatment year, wherein said fixed dose is in a range of 1.5 mg/kg to 4.0 mg/kg of body weight.
- 25 2. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 1, wherein said fixed dose is in a range of 1.5 mg/kg to 2.0 mg/kg.
- 30 3. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 1, wherein said fixed dose per patient is 1.75 mg/kg per treatment year with a

maximum deviation of +/- 0.2 mg/kg.

4. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 1, wherein said progressive form of multiple sclerosis comprises Primary Progressive Multiple Sclerosis and/or Secondary Progressive Multiple Sclerosis.
5. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 1, wherein said progressive form of Multiple Sclerosis is Primary Progressive Multiple Sclerosis.
6. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 1, wherein said progressive form of Multiple Sclerosis is Secondary Progressive Multiple Sclerosis.
7. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 1, wherein said patient has an age between 18 and 65 years.
8. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 1, wherein said patient has an age between 18 and 51 years.
9. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 1, wherein said patient has an age between 12 and 51 years.

10. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 1, wherein said Cladribine is orally administered to patients of female gender and/or to patients of male gender.

5

11. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 1, wherein said Patient has High Disease Activity (HDA) and/or has been diagnosed High Disease Activity.

10

12. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 1, wherein the patient is treatment naïve to Cladribine and/or disease modifying drugs other than Cladribine.

15

13. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 1, wherein the patient previously received Cladribine and/or one or more disease modifying drugs other than Cladribine.

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14. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 1, wherein the patient is also receiving at least one disease modifying drug other than Cladribine.

25

15. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 14, wherein said at least one disease modifying drug other than Cladribine is at least one selected from the group consisting of:

30

Interferon beta-1a, Beta interferon-1a,

Interferon beta-1b, Beta interferon-1b,
 Peginterferon beta 1a,
 Alemtuzumab,
 Daclizumab,
 5 Dimethyl fumarate,
 Fingolimod,
 Glatiramer acetate,
 Natalizumab, and
 Teriflunomide.

10

16. The method as described herein, preferably as described in one or more of the
 numbered Sections above and/or below and more preferably as described in Section
 1, wherein said fixed dose is orally administered to said patient within two adjacent
 months within said treatment year.

15

17. The method as described herein, preferably as described in one or more of the
 numbered Sections above and/or below and more preferably as described in Section
 16, wherein said fixed dose is orally administered to said patient within two
 adjacent months starting at the beginning of said treatment year.

20

18. The method as described herein, preferably as described in one or more of the
 numbered Sections above and/or below and more preferably as described in Section
 16, wherein said fixed dose is orally administered to said patient within one week or
 two weeks of each of said two adjacent months.

25

19. The method as described herein, preferably as described in one or more of the
 numbered Sections above and/or below and more preferably as described in Section
 16, wherein said fixed dose is orally administered to said patient within one week or
 two adjacent weeks at the beginning of each one of said two adjacent months.

30

20. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 16, wherein said fixed dose is orally administered to said patient within 2 to 7 days during said week, or within 2 to 7 days of each of said weeks.
- 5
21. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 16, wherein said fixed dose is orally administered to said patient within 4 to 5 days during said week, or within 4 to 5 days of each of said weeks.
- 10
22. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 1, wherein said Cladribine is orally administered for at least three treatment years.
- 15
23. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 1, wherein said Cladribine is orally administered to for at least two treatment years.
- 20
24. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 23, wherein two of said treatment years are either directly adjacent to each other, or are separated by a gap of from 1 to 10 months.
- 25
25. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 1, wherein each treatment year comprises:
- (i) a treatment period of 2 months at the beginning of said treatment year, wherein said fixed dose of Cladribine is orally administered on about 1

to about 7 days each month, said fixed dose being divided into daily doses of 5 to 20 mg of Cladribine, and

- (ii) a Cladribine-free period lasting 10 months, during which no Cladribine is administered.

5

26. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 1, wherein each treatment year comprises:

- 10 (i) a treatment period of 2 months at the beginning of said treatment year, wherein said fixed dose of Cladribine is orally administered on 3 to 5 days each month at the beginning of each month, said fixed dose being divided into daily doses of 10 or 20 mg of Cladribine, and
- (ii) a Cladribine-free period lasting 10 months, during which no Cladribine
15 is administered.

27. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 1, wherein said patient suffers from Primary Progressive Multiple Sclerosis and/or
20 from Secondary Progressive Multiple Sclerosis, wherein said fixed dose per patient is 1.75 mg/kg per treatment year with a maximum deviation of +/- 0.2 mg/kg, and wherein orally administering Cladribine comprises at least two treatment years.

28. The method as described herein, preferably as described in one or more of the
25 numbered Sections above and/or below and more preferably as described in Section 1, wherein orally administering Cladribine comprises two treatment years that are substantially adjacent to either each other, or that are separated by a gap of 1 to 10 months.

29. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 1, wherein orally administering Cladribine comprises at least three treatment years, a) wherein said fixed dose per treatment year is from 0.75 mg/kg to 2.0 mg/kg, 5 b) wherein the third treatment year comprises:
- (i) a treatment period of 1 month or 2 months at the beginning of said treatment year, wherein said fixed dose of Cladribine is orally administered on 3 to 5 days each month at the beginning of each month, said fixed dose being divided into daily doses of 10 or 20 mg of Cladribine, and 10
 - (ii) a Cladribine-free period lasting 11 or 10 months respectively, during which no Cladribine is administered.
30. The method as described herein, preferably as described in one or more of the 15 numbered Sections above and/or below and more preferably as described in Section 1, wherein orally administering Cladribine is in one or two treatment years, optionally plus an additional subsequent treatment year, followed by at least one year in which no Cladribine is administered to said patient.
- 20 31. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 1, wherein said Cladribine is orally administered as a liquid, a tablet, or a capsule.
32. The method as described herein, preferably as described in one or more of the 25 numbered Sections above and/or below and more preferably as described in Section 1, wherein said Cladribine is orally administered as a tablet.
33. The method as described herein, preferably as described in one or more of the 30 numbered Sections above and/or below and more preferably as described in Section 1, wherein said Cladribine is orally administered as a tablet comprising 10 mg of

Cladribine in the form of a mixture of Cladribine, 2-hydroxypropyl- β -cyclodextrin and Cladribine-2-hydroxypropyl- β -cyclodextrin-complexes, wherein the weight ratio of Cladribine to 2-hydroxypropyl- β -cyclodextrin is between about 1:10 to about 1:16.

5

34. A method of treating a patient diagnosed as suffering from a progressive form of Multiple Sclerosis, said method comprising orally administering to said patient a cumulative dose of Cladribine of about 3.5 mg/kg body weight, with a maximum deviation of ± 0.4 mg/kg, over 2 years, administered in each year as 1 treatment course of about 1.75 mg/kg ± 0.2 mg/kg per year, wherein each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year.
- 10
35. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 34, wherein each treatment week consists of 4 or 5 days on which said patient receives 10 mg or 20 mg of Cladribine for oral administration, depending on the body weight of the patient.
- 15
36. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 35, wherein said patient receives the 10 mg or 20 mg of Cladribine for oral administration as a tablet or capsule.
- 20
37. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 36, wherein said patient receives the 10 mg or 20 mg of Cladribine for oral administration as a tablet or capsule comprising 10 mg of Cladribine in the form of a mixture of Cladribine, 2-hydroxypropyl- β -cyclodextrin and Cladribine-2-
- 25
- 30

hydroxypropyl- β -cyclodextrin-complexes, wherein the weight ratio of Cladribine to 2-hydroxypropyl- β -cyclodextrin is between about 1:10 to about 1:16.

- 5 38. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 34, wherein the progressive form of Multiple Sclerosis is Primary Progressive Multiple Sclerosis.
- 10 39. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 34, wherein the progressive form of Multiple Sclerosis is Secondary Progressive Multiple Sclerosis.
- 15 40. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 34, where the progressive form of Multiple Sclerosis is selected from the group consisting of Primary Progressive Multiple Sclerosis and Secondary Progressive Multiple Sclerosis.
- 20 41. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 40, wherein each treatment week consists of 4 or 5 days on which said patient receives 10 mg or 20 mg of Cladribine for oral administration.
- 25 42. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 34, wherein said patient is between 18 and 65 years old.
- 30 43. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section

34, wherein said patient is between 18 and 51 years old.

44. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 34, wherein said patient is between 12 and 51 years old.

45. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 34, wherein patients to be treated are patients of female gender and/or patients of male gender.

46. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 34, wherein the patient is treatment naïve to Cladribine and/or disease modifying drugs other than Cladribine.

47. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 34, wherein said patient previously received Cladribine and/or one or more disease modifying drugs other than Cladribine.

48. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 34, wherein the patient additionally receives at least one disease modifying drug other than Cladribine.

49. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 48, wherein said at least one disease modifying drug other than Cladribine is at least one selected from the group consisting of:

Interferon beta-1a, Beta interferon-1a,
 Interferon beta-1b, Beta interferon-1b,
 Peginterferon beta 1a,
 Alemtuzumab,
 5 Daclizumab,
 Dimethyl fumarate,
 Fingolimod,
 Glatiramer acetate,
 Natalizumab, and
 10 Teriflunomide.

50. The method as described herein, preferably as described in one or more of the
 numbered Sections above and/or below and more preferably as described in Section
 34, wherein after the completion of said 2 years with said 2 treatment courses, no
 15 Cladribine is administered to the patients in the subsequent 1 or 2 years following
 the completion of said 2 years with said 2 treatment courses.

51. The method as described herein, preferably as described in one or more of the
 numbered Sections above and/or below and more preferably as described in Section
 20 34, wherein after said 2 treatment courses of one year each, no further Cladribine
 treatment is administered to said patient in the subsequent years 3 and 4.

52. A method of treating a patient suffering from a progressive form of Multiple
 Sclerosis, comprising orally administering to said patient tablets or capsules
 25 containing about 10 mg of Cladribine each, wherein said tablets or capsules are
 administered during a treatment year comprising the following regimen:

(i) a treatment course lasting 2 months, wherein Cladribine tablets or
 capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine
 on a treatment week of from 3 to up to 6 days each month;

30 (ii) followed by a Cladribine-free period lasting 10 months wherein no

Cladribine is administered to said patient;

wherein patients having a bodyweight

-in the range of 40 to less than 50 kg are administered

1) 4 tablets or capsules (40 mg of Cladribine) in the 1st treatment week of
said treatment course,

2) 4 tablets or capsules (40 mg of Cladribine) in the 2nd treatment week of
said treatment course;

-in the range of 50 to less than 60 kg are administered

1) 5 tablets or capsules (50 mg of Cladribine) in the 1st treatment week of
said treatment course, respectively,

2) 5 tablets or capsules (50 mg of Cladribine) in the 2nd treatment week of
said treatment course;

-in the range of 60 to less than 70 kg are administered

1) 6 tablets or capsules (60 mg of Cladribine) in the 1st treatment week of
said treatment course,

2) 6 tablets or capsules (60 mg of Cladribine) in the 2nd treatment week of
said treatment course;

-in the range of 70 to less than 80 kg are administered

1) 7 tablets or capsules (70 mg of Cladribine) in the 1st treatment week of
said treatment course,

2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd treatment week of
said treatment course;

-in the range of 80 to less than 90 kg are administered

1) 8 tablets or capsules (80 mg of Cladribine) in the 1st treatment week of
said treatment course,

2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd treatment week of
said treatment course;

-in the range of 90 to less than 100 kg are administered

1) 9 tablets or capsules (90 mg of Cladribine) in the 1st treatment week of
said treatment course,

2) 8 tablets or capsules (80 mg of Cladribine) in the 2nd treatment week of said treatment course;

-in the range of 100 to less than 110 kg are administered

1) 10 tablets or capsules (100 mg of Cladribine) in the 1st treatment week of said treatment course,

2) 9 tablets or capsules (90 mg of Cladribine) in the 2nd treatment week of said treatment course; or

-in the range of 110 kg and above are administered

1) 10 tablets or capsules (100 mg of Cladribine) in the 1st treatment week of said treatment course,

2) 10 tablets or capsules (100 mg of Cladribine) in the 2nd treatment week of said treatment course.

53. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 52, wherein the method further comprises at least one subsequent additional treatment year, wherein said additional treatment year is substantially identical to said treatment year.

54. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 53, wherein said additional treatment year is directly adjacent to said treatment year, or wherein the method comprises a gap of 1 to 10 months in between the two treatment years.

55. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 52, wherein the method further comprises two additional treatment years, wherein all said additional treatment years are substantially identical, and wherein said

additional treatment years are directly adjacent to each other, or wherein the method comprises a gap of 1 to 10 months in between at least two of said additional treatment years.

- 5 56. A method of treating a patient suffering from a progressive form of Multiple Sclerosis, said method comprising orally administering to said patient tablets or capsules containing about 10 mg of Cladribine each, wherein said tablets or capsules are administered during two treatment years comprising the following regimen:
- 10 (i) a first treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month;
- (ii) followed by a first Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient;
- 15 (iii) followed by a second treatment course lasting 2 months, wherein Cladribine tablets or capsules are orally administered daily at a daily dose of 10 or 20 mg of Cladribine on 3 to up to 6 days each month; and
- (iv) followed by a second Cladribine-free period lasting 10 months, wherein no Cladribine is administered to said patient, and
- 20 wherein patients having a bodyweight
- in the range of 40 to less than 50 kg are administered
- 1) 4 tablets or capsules (40 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,
- 2) 4 tablets or capsules (40 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively:
- 25 -in the range of 50 to less than 60 kg are administered
- 1) 5 tablets or capsules (50 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,
- 2) 5 tablets or capsules (50 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively:
- 30

-in the range of 60 to less than 70 kg are administered

1) 6 tablets or capsules (60 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 6 tablets or capsules (60 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively;

-in the range of 70 to less than 80 kg are administered

1) 7 tablets or capsules (70 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively;

-in the range of 80 to less than 90 kg are administered

1) 8 tablets or capsules (80 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 7 tablets or capsules (70 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively;

-in the range of 90 to less than 100 kg are administered

1) 9 tablets or capsules (90 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 8 tablets or capsules (80 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively;

-in the range of 100 to less than 110 kg are administered

1) 10 tablets or capsules (100 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 9 tablets or capsules (90 mg of Cladribine) in the 2nd treatment week of both the 1st and the 2nd treatment course, respectively; or

-in the range of 110 kg and above are administered

1) 10 tablets or capsules (100 mg of Cladribine) in the 1st treatment week of both the 1st and the 2nd treatment course, respectively,

2) 10 tablets or capsules (100 mg of Cladribine) in the 2nd treatment week of

both the 1st and the 2nd treatment course, respectively.

57. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 56, wherein said 10 mg or 20 mg of Cladribine for oral administration are administered to the patient as a tablet or capsule comprising 10 mg of Cladribine in the form of a mixture of Cladribine, 2-hydroxypropyl- β -cyclodextrin and Cladribine-2-hydroxypropyl- β -cyclodextrin-complexes, wherein the weight ratio of Cladribine to 2-hydroxypropyl- β -cyclodextrin is between about 1:1 to about 1:16.
58. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 56, wherein the progressive form of Multiple Sclerosis is Primary Progressive Multiple Sclerosis.
59. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 56, wherein the progressive form of Multiple Sclerosis is Secondary Progressive Multiple Sclerosis.
60. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 56, wherein the patient is between 12 and 51 years old.
61. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 56, wherein patients to be treated are patients of female gender and/or patients of male gender.

62. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 56, wherein the patient is treatment naïve to Cladribine and/or disease modifying drugs other than Cladribine.

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63. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 56, wherein the patient previously received Cladribine and/or disease modifying drugs other than Cladribine.

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64. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 56, wherein the patient additionally receives at least one disease modifying drug other than Cladribine.

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65. The method as described herein, preferably as described in one or more of the numbered Sections above and/or below and more preferably as described in Section 64, wherein said at least one disease modifying drug other than Cladribine is at least one selected from the group consisting of:

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Interferon beta-1a, Beta interferon-1a,

Interferon beta-1b, Beta interferon-1b,

Peginterferon beta 1a,

Alemtuzumab,

Daclizumab,

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Dimethyl fumarate,

Fingolimod,

Glatiramer acetate,

Natalizumab, and

Teriflunomide.

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66. The method as described herein, preferably as described in one or more of the
numbered Sections above and/or below and more preferably as described in Section
56, wherein after the completion of said 2 years with said 2 treatment courses, no
Cladribine is administered to the patients in the subsequent 1 or 2 years following
5 the completion of said 2 years with said 2 treatment courses.
67. The method as described herein, preferably as described in one or more of the
numbered Sections above and/or below and more preferably as described in Section
56, wherein to the patients having completed said 2 treatment courses of one year
10 each, no further Cladribine treatment is administered to said patients in the
subsequent years 3 and 4.
68. The method as described herein, preferably as described in one or more of the
numbered Sections above and/or below and more preferably as described in Section
15 56, wherein the progressive form of Multiple Sclerosis is selected from the group
consisting of Primary Progressive Multiple Sclerosis and Secondary Progressive
Multiple Sclerosis.
69. The method as described herein, preferably as described in one or more of the
20 numbered Sections above and/or below and more preferably as described in Section
56, wherein the progressive form of Multiple Sclerosis is Primary Progressive
Multiple Sclerosis.
70. The method as described herein, preferably as described in one or more of the
25 numbered Sections above and/or below and more preferably as described in Section
56, wherein the progressive form of Multiple Sclerosis is Secondary Progressive
Multiple Sclerosis.
71. The method as described herein, preferably as described in one or more of the
30 numbered Sections above and/or below and more preferably as described in Section

56, wherein said Patient has High Disease Activity (HDA) and/or has been diagnosed High Disease Activity.

Alternatively, preferred are methods of treatment as described herein and especially as described in the two sets of sections numbered 1 to 71 above, wherein one or more of the below given preferred features are realized:

- the induction period lasts up to about 2 months;
- the Cladribine free period (ii) lasts about 10 months, about 12 months, about 14 months or about 16 months, preferably about 10 months;
- 10 • the Cladribine free period (iv) lasts at least 10 months, at least 14 months, at least 22 months or at least 32 months, or the Cladribine free period (iv) lasts about 10 months, about 14 months, about 22 months or about 32 months;
- the total dose of Cladribine reached at the end of the induction period is about 1.75 mg/kg, or the total dose of Cladribine reached at the end of the induction period is about 3.5 mg/kg, preferably it is about 1.75 mg/kg;
- 15 • the total dose of Cladribine reached at the end of the maintenance period is about 1.75 mg/kg, or the total dose of Cladribine reached at the end of the maintenance period is about 3.5 mg/kg, preferably it is about 1.75 mg/kg;
- the total dose of Cladribine reached at the end of the induction period is about 1.75 mg/kg, and the total dose of Cladribine reached at the end of the maintenance period is about 1.75 mg/kg;
- 20 • the cumulative total dose of Cladribine reached after the end of both the induction period and the maintenance period is about 3.5 mg/kg;
- the Cladribine-free period (ii) lasts up to about 10 months, or the Cladribine-free as East End does finish Isa period (ii) lasts at least about 10 months;
- 25 • the Cladribine-free period (ii) lasts at least about 10 months, typically 10 to 13 months, and especially about 10 months;

- the Cladribine-free (iv) period lasts at least about 8 months, more preferably at least about 10 months, even more preferably at least 18 months and especially at least 24 months
- the Cladribine-free period (iv) lasts at least about 10 months or at least 10 months;
- 5 • the Cladribine-free (iv) period lasts at least about 8 months, more preferably at least about 10 months, even more preferably at least 18 months and especially at least 24 months.
- the Cladribine-free period (iv) lasts up to about 34 months, up to 20 months, up to 13 months or up to 10 months;
- 10 • the Cladribine-free period (ii) and/or (iv) is free of any administration, more preferably free of any administration regarding MS therapy;
- the maintenance period lasts up to about 4 months, or up to about 3 months, or up to about 2 months, preferably up to about 2 months;
- the maintenance therapy lasts about two months;
- 15 • the steps (iii) to (iv) are repeated at least one or two times.

It is understood that two or more of the above given features are only to be combined if they are not contradicting each other.

Definitions

- 20 The “total dose” or “cumulative dose” preferably refers to the total dose of Cladribine administered during the treatment, i.e. the dose reached at the end of the treatment that is calculated by adding the daily doses. For example, the total dose of Cladribine corresponding to a treatment of 0.7 mg/kg Cladribine per day for 5 days is 3.5 mg/kg or the total dose of Cladribine corresponding to a treatment of 0.35 mg/kg Cladribine per day for
- 25 5 days is 1.7 mg/kg.

“The total effective dose” or “cumulative effective dose” preferably refers to the bioavailable dose of Cladribine after a given administration period, i.e. the bioavailable dose reached at the end of the treatment that is calculated by adding the daily doses reduced by the bioavailability coefficient. For example, the total effective dose of Cladribine corresponding to a treatment of 0.7 mg/kg Cladribine per day for 5 days wherein the bioavailability of Cladribine is of about 40% is 1.4 mg/kg or the total effective dose of Cladribine corresponding to a treatment of 0.35 mg/kg Cladribine per day for 5 days wherein the bioavailability of Cladribine is of about 40% is 0.7 mg/kg.

Typically, the bioavailability of Cladribine or of a Cladribine formulation used in the context of this invention is from about 30% to about 90%, preferably from about 40% to about 60%, such as about 50%.

Cladribine may be orally administered to each patient at a certain dose that is calculated per patient, per body weight and per treatment year, wherein said dose or said certain dose is selected from the range of 1.5 mg/kg to 4.0 mg/kg. Preferably, a dose that is calculated per patient, per body weight of the patient and per treatment year is referred to as a “fixed dose”.

“A week” preferably refers to a period of time of or about 5, about 6 or about 7 days. It may be about 5-8 days.

“A month” preferably refers to a period of time of or about 28, about 29, about 30 or about 31 days. It may be about 26-33 days.

“Treatment” as used herein preferably comprises the sequential succession of an “induction treatment” and at least a “maintenance treatment”. Typically, a treatment according to the invention comprises an “induction treatment” and about one or about two or about three maintenance treatments, preferably one or two maintenance treatments, more preferably one maintenance treatment.

Typically, a treatment according to the invention is of about 2 years (about 24 months) or about 3 years (about 36 months) or about 4 years (about 48 months). Following completion of 2 treatment courses, further Cladribine treatment in Year 3 and/or Year 4 may not be necessary but may be considered as an option in PPMS and/or SPMS.

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An "Induction Treatment" preferably consists in the sequential succession of (i) an induction period wherein the Cladribine or the Cladribine pharmaceutical preparation of the invention is orally administered and (ii) a Cladribine-free period. An induction period preferably lasts up to about 4 months or up to about 3 month or up to about 2 months. For example, an induction period lasts for about 2 to about 4 months. An induction period preferably consists in the oral administration of Cladribine or a pharmaceutical preparation thereof during about 1 to about 7 days each month.

A "Cladribine-free period" preferably is a period wherein no Cladribine is administered to the patient. During a Cladribine-free period, the patient can be free of any administration or be dosed with a placebo-pill, or another drug except Cladribine. A Cladribine-free period preferably lasts up to about 10 months or up to 9 months or up to about 8 months. For example, a Cladribine-free period lasts from about 8 to about 10 months, typically at least of about 8 months. More preferably, a Cladribine-free period lasts at least about 8 months, at least about 9 months or at least about 10 months. Especially preferably, a Cladribine-free period lasts about 10 months. However, if recommended by the physician, the Cladribine-free period can preferably also be extended, preferably by 1-3 months. The durations given for the Cladribine-free period in this section are especially preferred for the Cladribine-free period between the Induction Treatment and the Maintenance Treatment. With regard to the Cladribine-free period after a Maintenance Treatment, duration of at least about 10 months, at least 22 months or at least 34 months is preferred. Typically, a Cladribine-free period after a Maintenance Treatment will be between about 10 months and about 22 months, between.

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A “Maintenance Treatment” preferably consists in the sequential succession of (i) a maintenance period wherein the Cladribine or the Cladribine pharmaceutical preparation of the invention is orally administered at a lower or equal dose than the Cladribine dose orally administered during the induction treatment and (ii) a Cladribine-free period. A maintenance period preferably lasts for up to about 4 months, or up to about 3 months, or up to about 2 months, preferably up to about 2 months. For example, a maintenance period lasts for about 2 to about 4 months, preferably for about 2 months. A maintenance period consists in the oral administration of Cladribine or of a pharmaceutical preparation thereof during about 1 to about 7 days each month.

Within the context of this invention, the beneficial effect, preferably including but not limited to one or more selected from an attenuation, reduction, decrease or diminishing of the pathological development after onset of the disease, may be seen after one or more a “treatments”, after an “induction treatment”, after a “maintenance treatment” or during a Cladribine-free period.

“Daily dose” preferably refers to the total dose of Cladribine orally administered to the patient each day of administration. The daily dose can be reached through a single or several administrations per day, such as for example once a day, twice a day or three times a day. Preferably, it is reached or achieved by single administration per day, preferably consisting of one or more tablets or capsules, preferably tablets or capsules as described herein.

Preferably, the dosage administered, as single or multiple doses, to an individual will vary depending upon a variety of factors, including pharmacokinetic properties, patient conditions and characteristics (sex, age, body weight, health, size), extent of symptoms, concurrent treatments, frequency of treatment and the effect desired. Preferably, the dosage or dose of administered will vary only on one factor, i.e. body weight of the respective individual, patient or human. A dose of about 1.75 mg per kg of body weight of the respective individual, patient, or human is preferred for each Induction Period and each

Maintenance Period. Preferably, said dose of about 1.75 mg per kg of body weight of the includes a deviation of plus or minus 10%, preferably a deviation of plus or minus 5%. Typically, this deviation is caused by the dosage strength of the respective Cladribine-containing dosage form, e.g. 10 mg tablets or capsules, to be administered to the respective individual, patient or human, and/or the weight ranges the respective individuals, patients or humans are preferably divided in, e.g. weight ranges of about 5 kg or about 10 kg, in order to provide sufficient guidance and practicability for administering such a fixed dosing per body weight of that respective individual, patient or human.

Patients suffering from MS can be defined for example as having clinically definite or laboratory-definite MS according to Schumacher or Poser criteria (*Schumacher et al., 1965, Ann. NY Acad. Sci. 1965; 122:552-568; Poser et al., 1983, Ann. Neurol. 13(3): 227-31*).

“Relapses” preferably involve neurologic problems that occur over a short period, typically days but sometimes as short as hours or even minutes. These attacks most often involve motor, sensory, visual or coordination problems early in the disease. Later, bladder, bowel, sexual and cognitive problems may be shown. Sometimes the attack onset occurs over several weeks. Typical MS relapse involves a period of worsening, with development of neurological deficits, then a plateau, in which the patient is not getting any better but also not getting any worse followed by a recovery period. Recovery usually begins within a few weeks.

“Efficacy” of a treatment according to the invention can be preferably measured based on changes in the course of disease in response to a use according to the invention. For example, treatment of MS efficacy can be measured by the frequency of relapses in RRMS and the presence or absence of new lesions in the CNS as detected using methods such as MRI technique (*Miller et al., 1996, Neurology, 47(Suppl 4): S217; Evans et al., 1997, Ann. Neurology, 41:125-132*).

Preferably, the observation of the reduction and/or suppression of MRI T₁ gadolinium-enhanced lesions (thought to represent areas of active inflammation) gives a primary efficacy variable.

Secondary efficacy variables preferably include MRI T₁ enhanced brain lesion volume, MRI T₁ enhanced lesion number, MRI T₂ lesion volume (thought to represent total disease burden, i.e. demyelination, gliosis, inflammation and axon loss), MRI T₁ enhanced hypointense lesion volume (thought to represent primarily demyelination and axon loss), time-to-progression of MS, frequency and severity of exacerbations and time-to-exacerbation, Expanded Disability Status Scale score and Scripps Neurologic Rating Scale (SNRS) score (*Sipe et al., 1984, Neurology, 34, 1368-1372*). Methods of early and accurate diagnosis of multiple sclerosis and of following the disease progression are described in *Mattson, 2002, Expert Rev. Neurotherapeutics, 319-328*.

Degree of disability of MS patients can be for example measured by Kurtzke Expanded Disability Status Scale (EDSS) score (*Kurtzke, 1983, Neurology, 33, 1444-1452*). Typically, a decrease in EDSS score corresponds to an improvement in the disease and conversely, an increase in EDSS score corresponds to a worsening of the disease.

Patients with “high disease activity” (HDA) include

- patients with 1 relapse in the previous year and at least 1 T₁ Gd⁺ lesion or 9 or more T₂ lesions, while on therapy with other DMDs (Disease Modifying Drugs),
- patients with 2 or more relapses in the previous year, whether on DMD treatment or not.

Cladribine (2-CdA)

2-CdA and its pharmacologically acceptable salts may be used in the practice of this invention.

Cladribine can be formulated in any pharmaceutical preparation suitable for oral administration. Representative oral formulations of 2-CdA are described in (*WO 96/19230; WO 96/19229; US 6,194,395; US 5,506,214; WO 2004/087100; WO 2004/087101*), the contents of which are incorporated herein by reference. Examples of ingredients for oral formulations are given below.

Processes for preparing 2-CdA are well known in the art. For example, the preparation of 2-CdA is described in (*EP 173,059; WO 04/028462; WO 04/028462; US 5,208,327; WO 00/64918*) and *Robins et al., J. Am. Chem. Soc., 1984, 106: 6379*. Alternatively, pharmaceutical preparations of 2-CdA may be purchased from Bedford Laboratories, Bedford, Ohio.

Oral administration of Cladribine may be in capsule, tablet, oral suspension, or syrup form. The tablet or capsules may contain from about 3 to 500 mg of Cladribine. Preferably they may contain about 3 to about 10 mg of Cladribine, more preferably about 3, about 5 or about 10 mg of Cladribine. The capsules may be gelatin capsules and may contain, in addition to Cladribine in the quantity indicated above, a small quantity, for example less than 5% by weight, magnesium stearate or another excipient. Tablets may contain the foregoing amount of the compound (Cladribine) and a binder, which may be a gelatin solution, a starch paste in water, polyvinyl alcohol in water, etc. with a typical sugar coating. Alternatively, tablets may contain the foregoing amount of the compound (Cladribine) and a binder, comprising one or more cyclodextrines, or consisting of one or more cyclodextrines. Preferably, said binder is contained in said tablet in an amount of 50% or more, in an amount of 60% or more, in an amount of 70% or more, in an amount of 80% or more or in an amount of 90% or more, e.g. in an amount of about 60%, in an amount of about 70%, in an amount of about 80%, in an amount of about 90% or in an amount of about 95%, based on the total weight of the tablet. Additionally, tablets may contain one or more other excipients in an amount of less than 50% and preferably less than 40%, e.g. in an amount of about 40%, in an amount of about 30%, in an amount of about 20%, or in an amount of about 10%, based on the total weight of the tablet. Preferably, said one or more

cyclodextrines comprise 2-hydroxypropyl- β -cyclodextrin, or essentially consist of 2-hydroxypropyl- β -cyclodextrin.

Compositions

- 5 Compositions 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.

10 Compositions may be in the form of 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, accacia, gelatin, sorbitol, tragacanth, mucilage of starch and polyvinylpyrrolidone. Fillers include, but are not limited to, lactose, sugar, microcrystalline cellulose, maizestarch, calcium phosphate, and sorbitol. Lubricants include, but are not limited to, magnesium stearate, stearic acid, talc, polyethylene glycol, and silica. Disintegrants include, but are not limited to, potato starch and sodium starch glycollate. Wetting agents include, but are not limited to, sodium lauryl sulfate). Tablets may be coated according to methods well known in the art.

- 20 Compositions may also 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 constitution 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 agent include, but are not limited to, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminum 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
- 25

alcohol. Preservatives include, but are not limited to, methyl or propyl p-hydroxybenzoate and sorbic acid.

Combination

5 Preferably, Cladribine can be administered alone or in combination with IFN-beta, prophylactically or therapeutically to an individual prior to, simultaneously or sequentially with other therapeutic regimens or agents (e.g. multiple drug regimens), in a therapeutically effective amount, especially therapeutic agents for the treatment of multiple sclerosis. Active agents that are administered simultaneously with other therapeutic agents can be
10 administered in the same or different compositions and in the same or different routes of administration.

For example, when Cladribine is administered in combination with IFN-beta, IFN-beta is preferably administered during the Cladribine-free period.

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Alternatively, when Cladribine is administered in combination with IFN-beta, IFN-beta is preferably administered after the “treatment” according to the invention.

The term “interferon-beta (IFN- β)”, as used herein, is preferably intended to include fibroblast
20 interferon in particular of human origin, as obtained by isolation from biological fluids or as obtained by DNA recombinant techniques from prokaryotic or eukaryotic host cells, as well as its salts, functional derivatives, variants, analogues and active fragments.

IFN- β preferably suitable for use accordance with the present invention is commercially available e.g. as Rebif® (Serono), Avonex® (Biogen) or Betaferon® (Schering). The use of
25 interferons of human origin is also preferred in accordance with the present invention. The term interferon, as used herein, is intended to encompass salts, functional derivatives, variants, analogues and active fragments thereof.

Rebif® (recombinant human interferon- β) is one of the latest developments in interferon therapy for multiple sclerosis (MS) and is believed to represent a significant advance in MS
30 therapy. Rebif® is interferon (IFN)-beta 1a, produced from mammalian cell lines. It was

established that interferon beta-1a given subcutaneously three times per week is efficacious in the treatment of Relapsing-Remitting Multiple Sclerosis (RRMS). Interferon beta-1a can have a positive effect on the long-term course of MS by reducing number and severity of relapses and reducing the burden of the disease and disease activity as measured by MRI.

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If applicable, the dosing of IFN- β in the treatment of progressive Forms of MS according to the invention preferably depends on the type of IFN- β used.

If applicable in accordance with the present invention, in case where IFN is recombinant IFN- β 1b produced in E. Coli, commercially available under the trademark Betaseron®, it may preferably be administered sub-cutaneously every second day at a dosage of about of 250 to 300 μ g or 8 MIU to 9.6 MIU per person.

If applicable in accordance with the present invention, in case where IFN is recombinant IFN- β 1a, produced in Chinese Hamster Ovary cells (CHO cells), commercially available under the trademark Avonex®, it may preferably be administered intra-muscularly once a week at a dosage of about of 30 μ g to 33 μ g or 6 MIU to 6.6 MIU per person.

In accordance with the present invention, when IFN is recombinant IFN- β 1a, produced in Chinese Hamster Ovary cells (CHO cells), commercially available under the trademark Rebif®, it may preferably be administered sub-cutaneously three times a week (TIW) at a dosage of 22 to 44 μ g or 6 MIU to 12 MIU per person.

Patients

Preferably, patients according to the invention are patients suffering from Primary Progressive Multiple Sclerosis (PPMS), Secondary Progressive Multiple Sclerosis (SPMS) and Early Secondary Progressive Multiple Sclerosis (ESPMS), preferably Primary Progressive Multiple Sclerosis (PPMS) and Secondary Progressive Multiple Sclerosis (SPMS).

Especially preferably, patients according to the invention are patients diagnosed Primary Progressive Multiple Sclerosis (PPMS), Secondary Progressive Multiple Sclerosis (SPMS) and Early Secondary Progressive Multiple Sclerosis (ESPMS), preferably Primary Progressive Multiple Sclerosis (PPMS) and Secondary Progressive Multiple Sclerosis (SPMS). The criteria for the diagnosis are known to the one skilled in the art, and furthermore described at various sections herein.

Thus, preferably patients according to the invention do not suffer from RRMS and/or or ESPMS, or are not diagnosed RRMS and/or ESPMS. More preferably, patients to be treated according to the invention are diagnosed a form of MS that is different from RRMS and/or ESPMS, or are diagnosed to suffer from a form of MS that is different from relapsing forms of MS.

Preferably, according to this invention, patients are selected from human males or females between 10 and 70 of age, more preferably between 18 and 65 years of age, even more preferably 18 and 55 years of age, and especially 18 and 51 years of age. Since female patients are in the vast majority and often have a higher disease burden, the treatment of female patients is preferred.

Alternative uses and/or methods of treatment according to the invention

In one embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of progressive forms of Multiple Sclerosis, preferably PPMS and/or SPMS, wherein the formulation is to be orally administered following the sequential steps below:

- (i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;
- (ii) A Cladribine-free period wherein no Cladribine is administered;
- (iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the

maintenance period is lower than or an equal to the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

5 In a further embodiment, the invention provides a use according to the invention wherein the induction period lasts up to about 4 months or up to about 3 months or up to about 2 months.

In a further embodiment, the invention provides a use according to the invention wherein
10 the induction period lasts up to about 2 months.

In a further embodiment, the invention provides a use according to the invention wherein the induction period lasts up to about 4 months.

15 In a further embodiment, the invention provides a use according to the invention wherein the Cladribine free period (ii) lasts about 10 months, about 12 months, about 14 months or about 16 months.

In a further embodiment, the invention provides a use according to the invention wherein
20 the Cladribine free period (iv) lasts about 10 months, about 14 months, about 22 months or about 32 months.

In a further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the induction period is about 1.75 mg/kg.

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In a further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the induction period is about 3.5 mg/kg.

In a further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the maintenance period is about 1.75 mg/kg.

- 5 In a further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the maintenance period is about 3.5 mg/kg, more preferably about 1.75 mg/kg.

In another further embodiment, the invention provides a use according to the invention
10 wherein the Cladribine-free period lasts up to about 34 months, or up to 20 months, or up to 10 months. This is especially preferred regarding the Cladribine free period (iv).

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free (ii) period lasts up to about 8 months.

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In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free (ii) period lasts at least about 8 months.

In another further embodiment, the invention provides a use according to the invention
20 wherein the Cladribine-free period (ii) lasts at least about 10 months, typically 10 to 18 months, and especially about 10 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free (iv) period lasts at least about 10 months.

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In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free (iv) period lasts at least about 8 months, more preferably at least about 10 months, even more preferably at least 18 months and especially at least 24 months.

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In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free periods (ii) and/or (iv) last at least about 8, more preferably at least 10 months, and typically either about 10 months or about 10 to 18 months.

- 5 In another further embodiment, the invention provides a use according to the invention wherein a placebo-pill is administered during the Cladribine-free period.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free period is free of any administration.

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In another further embodiment, the invention provides a use according to the invention wherein the maintenance period lasts up to about 4 months, or up to about 3 months, or up to about 2 months, preferably up to about 2 months.

- 15 In another further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the maintenance period (iii) is about 1.75 mg/kg.

- In another further embodiment, the invention provides a use according to the invention
20 wherein the steps (iii) to (iv) are repeated at least one or two times.

In this regard, the Cladribine-free period (iv) preferably lasts at least about 24 months, or least about 18 months, or at least 12 months, or at least about 10 months, or at least about 9 months, or at least about 8 months.

25

In a preferred embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of progressive forms of Multiple Sclerosis, preferably PPMS and/or SPMS, wherein the formulation is to be orally administered following the sequential steps below:

- (i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;
- (ii) A Cladribine-free period wherein no Cladribine is administered;
- 5 (iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than or about equal, preferably about equal, to the total dose of Cladribine reached at the end of the induction period (i)
- (iv) A Cladribine-free period wherein no Cladribine is administered;
- 10 wherein the induction period last up to about 4 months, or up to about 3 months, or up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months, or up to about 9 months, or up to about 8 months; the maintenance period (iii) lasts up to about 2 months; the Cladribine-free period (iv) lasts up to about 10 months; the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg and steps (iii) to (iv) are
- 15 repeated performed one, two or three times.

In another embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of progressive Forms of Multiple Sclerosis, preferably PPMS and/or SPMS, wherein the formulation is to be orally administered

20 following the sequential steps below:

- (i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the induction period is from about 0.7 mg/kg to about 1.4 mg/kg;
- (ii) A Cladribine-free period wherein no Cladribine is administered;
- 25 (iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the maintenance period (iii) is lower than or about equal, preferably about equal, to the total effective dose of Cladribine reached at the end of the induction period (i);
- 30 (iv) A Cladribine-free period wherein no Cladribine is administered.

In a further embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of progressive forms of Multiple Sclerosis, preferably PPMS and/or SPMS, wherein the formulation is to be orally administered following the sequential steps below:

- (i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the induction period is from about 0.7 mg/kg to about 1.4 mg/kg;
 - (ii) A Cladribine-free period wherein no Cladribine is administered;
 - (iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the maintenance period is lower than or equal, preferably equal, to the total effective dose of Cladribine reached at the end of the induction period (i);
 - (iv) A Cladribine-free period wherein no Cladribine is administered;
- wherein the induction period lasts up to about 4 months, or up to about 3 months, or up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months, or up to about 9 months, or up to about 8 months; the maintenance period (iii) lasts up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months; the total effective dose of Cladribine reached at the end of the maintenance period is about 0.7 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

In a preferred embodiment, the invention provides Cladribine for use as a medicament for the treatment of progressive forms of Multiple Sclerosis, preferably PPMS and/or SPMS, wherein the medicament is to be orally administered following the sequential steps below:

- (i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg, preferably either about 1.75 mg/kg are about 3.5 mg/kg, more preferably about 1.75 mg/kg;
- (ii) A Cladribine-free period wherein no Cladribine is administered;

- (iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than or equal to the total dose of Cladribine reached at the end of the induction period (i);
- 5 (iv) A Cladribine-free period wherein no Cladribine is administered;
- wherein the induction period last up to about 4 months, or up to about 3 months, or up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months, or up to about 9 months, or up to about 8 months; the maintenance period (iii) lasts up to about 2 months; the Cladribine-free period (iv) lasts up to about 10 months; the total dose of Cladribine
- 10 reached at the end of the maintenance period is about 1.75 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily

15 dose of Cladribine about 3 to 30 mg Cladribine, preferably 5 to 20 mg Cladribine, most preferably 10 mg Cladribine.

In another further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the induction period is about 3.5

20 mg/kg and the total dose of Cladribine reached at the end of the maintenance period is about 1.75 mg/kg.

In a further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the induction period is about 1.75 mg/kg,

25 and the total dose of Cladribine reached at the end of the maintenance period is about 1.75 mg/kg

In another further embodiment, the invention provides a use according to the invention wherein the total effective dose of Cladribine reached at the end of the induction period is

about 1.4 mg/kg and the total effective dose of Cladribine reached at the end of the maintenance period is about 0.7 mg/kg.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered once a day during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered several times a day administered once a day during the induction period, preferably twice or three times a day, more preferably twice a day.

In another embodiment, the invention provides a use of Cladribine according to the invention whereby the pharmaceutical formulation is orally administered about 1 to about 7 days per month, preferably from about 5 to about 7 days per month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention whereby the pharmaceutical formulation is orally administered about 0.02 days/kg to about 0.08 days/kg per month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention whereby the pharmaceutical formulation is orally administered about 0.02 days/kg to about 0.08 days/kg per month during the maintenance period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 2 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 3 each month during the induction period.

5

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 4 each month during the induction period.

10

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 5 each month during the induction period.

15

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 6 each month during the induction period.

20

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 4 each month during the induction period and wherein the pharmaceutical formulation is a pharmaceutical formulation described in WO 2004/087101 or in WO 2004/087100.

25

In another embodiment, the invention provides a use of Cladribine according to any of the preceding sections wherein the pharmaceutical formulation is to be administered in combination with interferon-beta.

30

In a preferred embodiment, the invention provides a method for the treatment of progressive forms of Multiple Sclerosis, preferably PPMS and/or SPMS, comprising the oral administration of Cladribine or of a pharmaceutical formulation thereof in a patient in need thereof comprising the following steps:

- 5 (i) An induction period, preferably an induction period of about 2 months, wherein Cladribine or a pharmaceutical formulation thereof is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.5 mg/kg to about 3.5 mg/kg, preferably either about 1.75 mg/kg or about 3.5 mg/kg, more preferably about 1.75 mg/kg;
- 10 (ii) A Cladribine-free period, preferably a Cladribine free period of at least 10 months, wherein no Cladribine is administered;
- (iii) A maintenance period, preferably a maintenance period of about 2 months, wherein Cladribine or a pharmaceutical formulation thereof is administered and wherein the total dose of Cladribine reached at the end of the maintenance
15 period is lower than or equal to the total dose of Cladribine reached at the end of the induction period (i), preferably either about 1.75 mg/kg or about 3.5 mg/kg, more preferably about 1.75 mg/kg;
- (iv) A Cladribine-free period, preferably a Cladribine free period of at least 10 months, wherein no Cladribine is administered.

20

In a preferred embodiment, the invention provides a method for the treatment of progressive forms of Multiple Sclerosis, preferably PPMS and/or SPMS, comprising the oral administration of Cladribine or of a pharmaceutical formulation thereof in a patient in need thereof comprising the following steps:

- 25 (i) An induction period wherein Cladribine or a pharmaceutical formulation thereof is administered and wherein the total effective dose of Cladribine reached at the end of the induction period is from about 0.7 mg/kg to about 1.4 mg/kg;
- (ii) A Cladribine-free period wherein no Cladribine is administered;
- (iii) A maintenance period wherein Cladribine pharmaceutical formulation is
30 administered and wherein the total effective dose of Cladribine reached at the

end of the maintenance period is lower than or equal to the total effective dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

5 In another further embodiment, the invention provides a method according to the invention wherein the steps (iii) to (iv) are repeated at least one or two times.

In this regard, the Cladribine-free period (iv) preferably lasts at least about 24 months, or least about 18 months, or at least 12 months, or at least about 10 months, or at least about 9
10 months, or at least about 8 months.

In a preferred embodiment, the invention provides a method of treating progressive forms of Multiple Sclerosis, preferably PPMS and/or SPMS, with Cladribine, wherein Cladribine is orally administered following the sequential steps below:

- 15 (i) Administering Cladribine, such that the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg, preferably about 1.75 mg/kg or about 3.5 mg/kg, more preferably 1.75 mg/kg;
- (ii) Administering no Cladribine during a Cladribine free period;
- 20 (iii) Administering Cladribine such that the total dose of Cladribine reached at the end of a maintenance period is lower than or equal to the total dose of Cladribine reached at the end of the induction period (i), preferably about 1.75 mg/kg or about 3.5 mg/kg, more preferably about 1.75 mg/kg);
- (iv) And optionally, a Cladribine-free period wherein no Cladribine is
25 administered.

In a further preferred embodiment, the invention provides a method wherein the induction period lasts up to about 4 months, or up to about 3 months, or up to about 2 months.

In a further preferred embodiment, the invention provides a method wherein the total dose of Cladribine reached at the end of the induction period is about 1.75 mg/kg.

In a further preferred embodiment, the invention provides a method wherein the total dose
5 of Cladribine reached at the end of the induction period is about 3.5 mg/kg.

In a further preferred embodiment, the invention provides a method wherein the total effective dose of Cladribine reached at the end of the induction period is about 1.4 mg/kg.

10 In a further preferred embodiment, the invention provides a method wherein the Cladribine-free period lasts up to about 18 months, or up to 12 months, or up to 10 months, or up to about 9 months, or up to about 8 months.

In a further preferred embodiment, the invention provides a method wherein the Cladribine-free period (ii) lasts up to about 18 months, or up to 12 months, or up to 10 months, or up to
15 about 9 months, or up to about 8 months.

In a further preferred embodiment, the invention provides a method wherein the maintenance period lasts up to about 4 months, or up to about 3 months or up to about 2
20 months.

In a further preferred embodiment, the invention provides a method wherein the total dose of Cladribine reached at the end of the maintenance period is about 1.75 mg/kg.

25 In a further preferred embodiment, the invention provides a method wherein the total effective dose of Cladribine reached at the end of the maintenance period is about 0.7 mg/kg.

In a further preferred embodiment, the invention provides a method wherein the
30 maintenance period is followed by a Cladribine-free period.

In another further embodiment, the invention provides a method according to the invention wherein the total dose of Cladribine reached at the end of the induction period is about 3.5 mg/kg and the total dose of Cladribine reached at the end of the maintenance period is
5 about 1.75 mg/kg.

In another further embodiment, the invention provides a method according to the invention wherein the total effective dose of Cladribine reached at the end of the induction period is about 1.4 mg/kg and the total effective dose of Cladribine reached at the end of the
10 maintenance period is about 0.7 mg/kg.

In another further embodiment, the invention provides a method according to the invention wherein Cladribine is to be orally administered at a daily dose of about 3 to about 30 mg.

15 In another further embodiment, the invention provides a method according to the invention wherein Cladribine is to be orally administered at a daily dose of about 10 mg.

In another further embodiment, the invention provides a method according to the invention wherein Cladribine is orally administered about 1 to about 7 days per month during the
20 induction period.

In another further embodiment, the invention provides a method according to the invention wherein the steps (iii) are repeated at least one or two times.

25 In another further embodiment, the invention provides a method according to the invention wherein Cladribine is to be administered in combination with interferon-beta.

Further especially preferred aspects of Cladribine for use as described herein, preferably Cladribine tablets for use as described herein, its properties and/or its use are described
30 below.

Preferred Medicinal Product

Cladribine 10 mg tablets (Mavenclad®)

Qualitative and Quantitative Composition: Each tablet contains 10 mg of Cladribine,

5 Excipients with known effect: Each tablet contains 64 mg sorbitol.

Preferred Pharmaceutical Form: Tablet; white, round, biconvex tablets of 8.5 mm diameter

Preferred Clinical Particulars:

Posology and method of administration

Posology

10 In preferred embodiments, a recommended cumulative dose of Cladribine tablets is 3.5 mg/kg body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year. Following completion of 2 treatment courses, further Cladribine treatment in Year 3 and/or Year 4 may not be necessary, but may be considered as an option in PPMS and/or SPMS. In these embodiments, each treatment course consists of 2 treatment weeks, one at
15 the beginning of the first month and one at the beginning of the second month of the respective treatment year. Each treatment week consists of 4 or 5 days on which a patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight. For details, see Tables 1 and 2 below.

The gradual recovery of the lymphocyte counts occurs without the triggering of a
20 homeostatic expansion of residual lymphocyte subtypes potentially associated with rebound activity or autoimmunity seen with some other disease modifying drugs (DMDs) used in MS (Jones, 2013; Zwang, 2014; Willis, 2015). This pharmacokinetic (PK)/PD profile results in a unique posology for an oral drug in the field of MS, with short courses of

treatment administered at the beginning of Year 1 and Year 2 (a total of up to 20 days of treatment).

Criteria for initiating and continuing therapy

Lymphocyte counts are recommended to be:

- normal before initiating MAVENCLAD in year 1,
- at least 800 cells/mm³ before initiating MAVENCLAD in year 2.

If necessary, the treatment course in year 2 can be delayed, preferably for up to 6 months, to allow for recovery of lymphocytes.

Distribution of dose

- In certain embodiments, the preferred distribution of the total dose over the 2 years of treatment is provided in Table 1 below. For some weight ranges the number of tablets may vary from one treatment week to the next.

Table 1: Dose of MAVENCLAD per treatment week by patient weight in each treatment year

Weight range	Dose in mg (number of 10 mg tablets) per treatment week	
kg	Treatment week 1	Treatment week 2
40 to <50	40 mg (4 tablets)	40 mg (4 tablets)
50 to <60	50 mg (5 tablets)	50 mg (5 tablets)
60 to <70	60 mg (6 tablets)	60 mg (6 tablets)
70 to <80	70 mg (7 tablets)	70 mg (7 tablets)
80 to <90	80 mg (8 tablets)	70 mg (7 tablets)
90 to <100	90 mg (9 tablets)	80 mg (8 tablets)
100 to <110	100 mg (10 tablets)	90 mg (9 tablets)
110 and above	100 mg (10 tablets)	100 mg (10 tablets)

Table 2 below shows how the total number of tablets per treatment week is distributed over the individual days. It is recommended that the daily Cladribine doses in each treatment

week be taken at intervals of 24 hours at approximately the same time each day. If a daily dose consists of two tablets, both tablets are taken together as a single dose.

Table 2: MAVENCLAD 10 mg tablets per weekday

Total number of tablets per week	Day 1	Day 2	Day 3	Day 4	Day 5
4	1	1	1	1	●
5	1	1	1	1	1
6	2	1	1	1	1
7	2	2	1	1	1
8	2	2	2	1	1
9	2	2	2	2	1
10	2	2	2	2	2

- 5 In certain preferred embodiments, a missed dose must be taken as soon as remembered on the same day according to the treatment schedule.

In certain preferred embodiments, a missed dose must not be taken together with the next scheduled dose on the following day. In the case of a missed dose, the patient must take the missed dose on the following day, and extend the number of days in that treatment week. If
10 two consecutive doses are missed, the same rule applies, and the number of days in the treatment week is extended by two days.

Method of administration

MAVENCLAD is for oral use. In this embodiment, tablets must be taken with water, and swallowed without chewing. The tablets can be taken independent of food intake.

15 Hematological monitoring

Cladribine's mode of action is closely linked to a reduction in lymphocyte count. The effect on lymphocyte count is dose-dependent. Decreases in neutrophil count, red blood cell count, hematocrit, hemoglobin or platelet count compared to baseline values have also been observed in clinical studies, although these parameters usually remain within normal limits.

Additive hematological adverse reactions may be expected if Cladribine is administered prior to or concomitantly with other substances that affect the hematological profile (see section 4.5).

In certain embodiments, lymphocyte counts must be determined

- 5 • before initiating MAVENCLAD in year 1,
- before initiating MAVENCLAD in year 2,
- 2 and 6 months after start of treatment in each treatment year. If the lymphocyte count is below 500 cells/mm³, it should be actively monitored until values increase again.

Mechanism of action

- 10 Cladribine is a nucleoside analogue of deoxyadenosine. A chlorine substitution in the purine ring protects Cladribine from degradation by adenosine deaminase, increasing the intracellular residence time of the Cladribine prodrug. Subsequent phosphorylation of Cladribine to its active triphosphate form, 2-chlorodeoxyadenosine triphosphate (Cd-ATP), is particularly efficiently achieved in lymphocytes, due to their constitutively high
- 15 deoxycytidine kinase (DCK) and relatively low 5'-nucleotidase (5'-NTase) levels. A high DCK to 5'-NTase ratio favors the accumulation of Cd-ATP, making lymphocytes particularly susceptible to cell death. As a result of a lower DCK/5'-NTase ratio other bone marrow derived cells are less affected than lymphocytes. DCK is the rate limiting enzyme for conversion of the Cladribine prodrug into its active triphosphate form, leading to
- 20 selective depletion of dividing and non-dividing T and B cells.

- The primary apoptosis-inducing mechanism of action of Cd-ATP has direct and indirect actions on DNA synthesis and mitochondrial function. In dividing cells, Cd-ATP interferes with DNA synthesis via inhibition of ribonucleotide reductase and competes with deoxyadenosine triphosphate for incorporation into DNA by DNA polymerases. In resting
- 25 cells Cladribine causes DNA single-strand breaks, rapid nicotinamide adenine dinucleotide consumption, ATP depletion and cell death. There is evidence that Cladribine can also

cause direct caspase-dependent and -independent apoptosis via the release of cytochrome c and apoptosis-inducing factor into the cytosol of non-dividing cells.

Pharmacodynamic effects

Cladribine has been shown to exert long-lasting effects by preferentially targeting lymphocytes and the autoimmune processes involved in the pathophysiology of MS.

Across studies, the largest proportion of patients with grade 3 or 4 lymphopenia (<500 to 200 cells/mm³ or <200 cells/mm³) was seen 2 months after the first Cladribine dose in each year, indicating a time gap between Cladribine plasma concentrations and the maximum hematological effect.

Across clinical studies, data with the proposed cumulative dose of 3.5 mg/kg body weight show a gradual improvement in the median lymphocyte counts back to the normal range at week 84 from the first dose of Cladribine (approximately 30 weeks after the last dose of Cladribine). The lymphocyte counts of more than 75% of patients returned to the normal range by week 144 from the first dose of Cladribine (approximately 90 weeks after the last dose of Cladribine).

Treatment with oral Cladribine leads to rapid reductions in circulating CD4⁺ and CD8⁺ T cells. CD8⁺ T cells have a less pronounced decrease and a faster recovery than CD4⁺ T cells, resulting in a temporarily decreased CD4 to CD8 ratio. Cladribine reduces CD19⁺ B cells and CD16⁺/CD56⁺ natural killer cells, which also recover faster than CD4⁺ T cells.

Clinical efficacy and safety

Relapsing-remitting MS

Efficacy and safety of oral Cladribine were evaluated in a randomized, double-blind, placebo-controlled clinical study (CLARITY) in 1,326 patients with relapsing-remitting MS. Study objectives were to evaluate the efficacy of Cladribine versus placebo in reducing

the annualized relapse rate (ARR) (primary endpoint), slowing disability progression and decreasing active lesions as measured by MRI.

Patients received either placebo (n = 437), or a cumulative dose of Cladribine of 3.5 mg/kg (n = 433) or 5.25 mg/kg body weight (n = 456) over the 96-week (2-year) study period in 2 treatment courses. Patients randomized to the 3.5 mg/kg cumulative dose received a first treatment course at weeks 1 and 5 of the first year and a second treatment course at weeks 1 and 5 of the second year. Patients randomized to the 5.25 mg/kg cumulative dose received additional treatment at weeks 9 and 13 of the first year. The majority of patients in the placebo (87.0%) and the Cladribine 3.5 mg/kg (91.9%) and 5.25 mg/kg (89.0%) treatment groups completed the full 96 weeks of the study.

Patients were required to have at least 1 relapse in the previous 12 months. In the overall study population, the median age was 39 years (range 18 to 65), and the female to male ratio was approximately 2:1. The mean duration of MS prior to study enrolment was 8.7 years, and the median baseline neurological disability based on Kurtzke Expanded Disability Status Scale (EDSS) score across all treatment groups was 3.0 (range 0 to 6.0). Over two thirds of the study patients were treatment-naïve for MS disease-modifying drugs (DMDs). The remaining patients were pre-treated with either interferon beta-1a, interferon beta-1b, glatiramer acetate or natalizumab.

Patients with relapsing-remitting MS receiving Cladribine 3.5 mg/kg showed statistically significantly improvements in the annualized relapse rate, proportion of patients relapse-free over 96 weeks, proportion of patients free of sustained disability over 96 weeks and time to 3-month EDSS progression compared to patients on placebo (see Table 3 below).

Table 3 Clinical outcomes in the CLARITY study (96 weeks)

Parameter	Placebo (n = 437)	Cladribine cumulative dose	
		3.5 mg/kg (n = 456)	5.25 mg/kg (n = 456)
Annualised relapse rate (95% CI)	0.33 (0.29, 0.38)	0.14* (0.12, 0.17)	0.15* (0.12, 0.17)
Relative reduction (cladribine vs. placebo)		57.6%	54.5%
Proportion of patients relapse-free over 96 weeks	60.9%	79.7%	78.9%
Time to 3-month EDSS progression, 10 th percentile (months)	10.8	13.6	13.6
Hazard ratio (95% CI)		0.67* (0.48, 0.93)	0.69* (0.49, 0.96)

* p < 0.001 compared to placebo

In addition, the Cladribine 3.5 mg/kg treatment group was statistically significantly superior to placebo with regard to number and relative reduction of T1 Gd+ lesions, active
 5 T2 lesions and combined unique lesions as demonstrated in brain MRI over the entire 96 weeks of the study. Patients taking Cladribine compared to the placebo treatment group had 86% relative reduction in the mean number of T1 Gd+ lesions (adjusted mean number for Cladribine 3.5 mg/kg, and placebo groups were 0.12 and 0.91, respectively), 73% relative reduction in the mean number of active T2 lesions (adjusted mean number for Cladribine
 10 3.5 mg/kg, and placebo groups were 0.38 and 1.43, respectively) and 74% relative reduction in the mean number of combined unique lesions per patient per scan (adjusted mean number for Cladribine 3.5 mg/kg, and placebo groups were 0.43 and 1.72, respectively) (p < 0.001 across all 3 MRI outcomes).

Post-hoc analysis of time to 6-month confirmed EDSS progression resulted in a 47%
 15 reduction of the risk of disability progression in the Cladribine 3.5 mg/kg compared to placebo (hazard ratio = 0.53, 95% CI [0.36, 0.79], p < 0.05); in the placebo group the 10th percentile was reached at 245 days, and not reached at all during the study period in the Cladribine 3.5 mg/kg group.

As shown in Table 3 above, higher cumulative doses did not add any clinically meaningful
 20 benefit, but were associated with a higher incidence in ≥grade 3 lymphopenia (44.9% in the 5.25 mg/kg group vs. 25.6 % in the 3.5 mg/kg group).

Patients who had completed the CLARITY study could be enrolled in CLARITY Extension. In this extension study, 806 patients received either placebo or a cumulative dose of Cladribine 3.5 mg/kg (in a regimen similar to that used in CLARITY) over the 96-week study period. The primary objective of this study was safety, while efficacy endpoints were exploratory.

The magnitude of the effect in reducing the frequency of relapses and slowing disability progression in patients receiving the 3.5 mg/kg dose over 2 years was maintained in years 3 and 4 (see section 4.2).

Efficacy in patients with high disease activity

Post-hoc subgroup efficacy analyses have been conducted in patients with high disease activity treated with oral Cladribine at the recommended 3.5 mg/kg cumulative dose. These included

- patients with 1 relapse in the previous year and at least 1 T1 Gd+ lesion or 9 or more T2 lesions, while on therapy with other DMDs,
- patients with 2 or more relapses in the previous year, whether on DMD treatment or not.

In the analyses of the CLARITY data, a consistent treatment effect on relapses was observed with the annualized relapse rate ranging from 0.16 to 0.18 in the Cladribine groups and 0.47 to 0.50 in the

placebo group ($p < 0.0001$). Compared to the overall population, a greater effect was observed in time to 6-month sustained disability where Cladribine reduced the risk of disability progression by 82% (hazard ratio = 0.18, 95% CI [0.07, 0.47]). For placebo the 10th percentile for disability progression was reached between 16 and 23 weeks, while for the Cladribine groups it was not reached during the entire study.

Secondary progressive MS with relapses

A supportive study in patients treated with Cladribine as an add-on to interferon-beta vs. placebo + interferon-beta also included a limited number of patients with secondary progressive MS (26 patients). In these patients, treatment with Cladribine 3.5 mg/kg
 5 resulted in a reduction of the annualized relapse rate compared to placebo (0.03 versus 0.30, risk ratio: 0.11, $p < 0.05$). There was no difference in annualized relapse rate between patients with relapsing-remitting MS and patients with secondary progressive MS with relapses. An effect on disability progression could not be shown in either subgroup.

Patients with secondary progressive MS were excluded in the CLARITY study. However, a
 10 post-hoc analysis of a mixed cohort including CLARITY and ONWARD patients, defined by a baseline EDSS score of ≥ 3.5 as a proxy for secondary progressive MS, showed a similar reduction in annualized relapse rate compared to patients with an EDSS score below 3.

Pharmacokinetic properties

15 Cladribine is a prodrug that has to be phosphorylated intracellularly to become biologically active. Cladribine pharmacokinetics were studied following oral and intravenous administration in MS patients and patients with malignancies, and in in vitro systems.

Absorption

Following oral administration, Cladribine is rapidly absorbed. Administration of 10 mg
 20 Cladribine resulted in a Cladribine mean C_{max} in the range of 22 to 29 ng/mL and corresponding mean AUC in the range of 80 to 101 ng•h/mL (arithmetic means from various studies).

When oral Cladribine was given in fasted state, median T_{max} was 0.5 h (range 0.5 to 1.5 h). When administered with a high-fat meal, Cladribine absorption was delayed (median
 25 T_{max} 1.5 h, range 1 to 3 h) and C_{max} was reduced by 29% (based on geometric mean),

while AUC was unchanged. The bioavailability of 10 mg oral Cladribine was approximately 40%.

Distribution

The volume of distribution is large, indicating extensive tissue distribution and intracellular uptake. Studies revealed a mean volume of distribution of Cladribine in the range of 480 to 490 L. The plasma protein binding of Cladribine is 20%, and independent of plasma concentration.

The distribution of Cladribine across biological membranes is facilitated by various transport proteins, including ENT1, CNT3 and BCRP.

In vitro studies indicate that Cladribine efflux is only minimally P-gp related. Clinically relevant interactions with inhibitors of P-gp are not expected. The potential consequences of P-gp induction on the bioavailability of Cladribine have not been formally studied.

In vitro studies showed negligible transporter-mediated uptake of Cladribine into human hepatocytes.

Cladribine is almost equally distributed between plasma and whole blood cells and has the potential to penetrate the blood brain barrier by 25% (Liliemark, 1992; Kearns, 1994). A small study in cancer patients has shown a cerebrospinal fluid/plasma concentration ratio of approximately 0.25.

Cladribine and/or its phosphorylated metabolites are substantially accumulated and retained in human lymphocytes. In vitro, intra- versus extracellular accumulation ratios were found to be around 30 to 40 already 1 hour after Cladribine exposure.

Biotransformation

The metabolism of Cladribine was studied in MS patients following the administration of a single 10-mg tablet and a single 3-mg intravenous dose. Following both oral and intravenous administration, the parent compound Cladribine was the main component

present in plasma and urine. The metabolite 2-chloroadenine was a minor metabolite both in plasma and in urine, e.g. accounting only for $\leq 3\%$ of plasma parent drug exposure after oral administration. Only traces of other metabolites could be found in plasma and in urine.

In hepatic in vitro systems, negligible metabolism of Cladribine was observed (at least 90% was unchanged Cladribine).

Cladribine is not a relevant substrate to cytochrome P450 enzymes and does not show significant potential to act as inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. Inhibition of these enzymes or genetic polymorphisms (e.g. CYP2D6, CYP2C9 or CYP2C19) are not expected to result in clinically significant effects on Cladribine pharmacokinetics or exposure. Cladribine has no clinically meaningful inductive effect on CYP1A2, CYP2B6 and CYP3A4 enzymes.

After entering the target cells, Cladribine is phosphorylated to Cladribine monophosphate (Cd-AMP) by DCK (and also by deoxyguanosine kinase in the mitochondria). Cd-AMP is further phosphorylated to Cladribine diphosphate (Cd-ADP) and Cladribine triphosphate (Cd-ATP). The dephosphorylation and deactivation of Cd-AMP is catalyzed by cytoplasmic 5'-NTase. In a study of the intracellular pharmacokinetics of Cd-AMP and Cd-ATP in patients with chronic myelogenous leukemia, the levels of Cd-ATP were approximately half of the Cd-AMP levels.

Intracellular half-life of Cd-AMP was 15 h. Intracellular half-life of Cd-ATP was 10 h.

Elimination

Based on pooled population pharmacokinetic data from various studies, the median values for elimination were 22.2 L/h for renal clearance and 23.4 L/h for non-renal clearance. Renal clearance exceeded the glomerular filtration rate, indicating active renal tubular secretion of Cladribine.

The non-renal part of the elimination of Cladribine (approximately 50%) consists of negligible hepatic metabolism and of extensive intracellular distribution and trapping of the

active Cladribine principle (Cd-ATP) within the targeted intracellular compartment (i.e. the lymphocytes) and subsequent elimination of intracellular Cd-ATP according to the life-cycle and elimination pathways of these cells. The intracellular metabolism of Cladribine plays an important role in the overall efficacy and safety of Cladribine, and is probably the most important non-renal elimination pathway of Cladribine.

The estimated terminal half-life for a typical patient from the population pharmacokinetic analysis is approximately 1 day. This however does not result in any drug accumulation after once daily dosing as this half-life only accounts for a small portion of the AUC.

Dose and time dependence

After oral administration of Cladribine across a dose range from 3 to 20 mg, C_{max} and AUC increased in a dose-proportional fashion, suggesting that absorption is not affected by rate- or capacity-limited processes up to a 20 mg oral dose.

No significant accumulation of Cladribine concentration in plasma has been observed after repeated dosing. There is no indication that Cladribine pharmacokinetics might change in a time-dependent fashion after repeated administration.

Special populations

No studies have been conducted to evaluate the pharmacokinetics of Cladribine in elderly or in pediatric MS patients, or in subjects with renal or hepatic impairment.

A population kinetic analysis did not show any effect of age (range 18 to 65 years) or gender on Cladribine pharmacokinetics.

Renal impairment

Renal clearance of Cladribine was shown to be dependent on creatinine clearance. Based on a population pharmacokinetic analysis including patients with normal renal function and with mild renal impairment, total clearance in patients with mild renal impairment (CLCR

= 60 mL/min) is expected to decrease moderately, leading to an increase in exposure of 25%.

Hepatic impairment

The role of hepatic function for the elimination of Cladribine is considered negligible.

5 Pharmacokinetic interactions

A drug interaction study in MS patients showed that the bioavailability of 10 mg oral Cladribine was not altered when co-administered with pantoprazole.

Preclinical safety data

Non-clinical safety pharmacological and toxicological assessment of Cladribine in animal
 10 models relevant for the safety assessment of Cladribine did not yield significant findings other than those predicted by the pharmacologic mechanism of Cladribine. The primary target organs identified in the repeat-dose toxicology studies by parenteral routes (intravenous or subcutaneous) up to 1-year duration in mice and monkeys were the lymphoid and hematopoietic system. Other target organs after longer administration (14
 15 cycles) of Cladribine to monkeys by subcutaneous route were the kidneys (karyomegaly of renal tubular epithelium), adrenals (cortex atrophy and decreased vacuolation), gastrointestinal tract (mucosa atrophy) and testes. Effects on the kidneys were also seen in mice.

Mutagenicity

20 Cladribine is incorporated into DNA strands and inhibits DNA synthesis and repair. Cladribine did not induce gene mutation in bacteria or mammalian cells, but it was clastogenic causing chromosomal damage in mammalian cells in vitro at a concentration which was 17-fold above the expected clinical C_{max}. In vivo clastogenicity in mice was detected at 10 mg/kg, which was the lowest dose tested.

25

Carcinogenicity

The carcinogenic potential of Cladribine was assessed in a long-term 22-month study with subcutaneous administration in mice and in a short-term 26-week study by oral route in transgenic mice.

- 5 • In the long-term carcinogenicity study in mice, the highest dose used was 10 mg/kg, which was seen to be genotoxic in the mouse micronucleus study (equivalent to approximately 16-fold the expected human exposure in AUC in patients taking the maximum daily dose of 20 mg Cladribine). No increased incidence of lymphoproliferative disorders or other tumor types (apart from Harderian gland tumors, predominantly
10 adenomas) was seen in mice. Harderian gland tumors are not considered to be of clinical relevance, as humans do not have comparable anatomical structures.
- In the short-term carcinogenicity study in Tg rasH2 mice, no Cladribine-related increase in incidence of lymphoproliferative disorders or other tumor types was seen at any dose tested up to 30 mg/kg per day (equivalent to approximately 25-fold the expected human
15 exposure in AUC in patients taking the maximum daily dose of 20 mg Cladribine).

Cladribine was also assessed in a 1-year monkey study by the subcutaneous route. No increased incidence in lymphoproliferative disorders and no tumors were seen in this study.

Although Cladribine may have a potential for genotoxicity, long-term data in mice and monkeys did not provide any evidence of a relevant increased carcinogenicity risk in
20 humans.

Reproduction toxicity

While there were no effects on female fertility, reproductive function or general performance of offspring, Cladribine was shown to be embryo lethal when administered to pregnant mice, and the compound was teratogenic in mice (also following treatment of the
25 males only) and rabbits. The observed embryo lethal and teratogenic effects are consistent

with the pharmacologic mechanisms of Cladribine. In a male mouse fertility study, malformed fetuses with agenesis of portions of appendage(s) distal the humerus and/or femur were seen. The incidence of affected mouse fetuses in this study was in the same range of spontaneous incidence of amelia and phocomelia in this strain of mice. However, considering Cladribine genotoxicity, male-mediated effects related to potential genetic alteration of differentiating sperm cells cannot be excluded.

Cladribine did not affect the fertility of male mice, but observed testicular effects were reduced testicular weights and increased numbers of non-motile sperm. Testicular degeneration and reversible decrease in spermatozoa with rapid progressive motility were also seen in the monkey. Histologically, testicular degeneration was only seen in one male monkey in a 1-year subcutaneous toxicity study.

Pharmaceutical particulars:

List of excipients

Hydroxypropylbetadex (2-hydroxypropyl- β -cyclodextrin)

Sorbitol

Magnesium stearate

How to take MAVENCLAD

This medicine is preferably taken exactly as recommended by the doctor. If in doubt, checking with a doctor or pharmacist it is recommended.

Treatment courses

Patients will be given MAVENCLAD as two treatment courses over 2 years.

Each treatment course consists of 2 treatment weeks, which are one month apart at the beginning of each treatment year.

A treatment week consists of 4 or 5 days on which a patient receives 1 or 2 tablets daily (see Table 4, below).

Example: if a patient starts treatment in mid-April, the tablets are administered as shown in Table 4, below.

5 **Table 4**

Year 1		Year 2	
1st treatment week	1 or 2 tablets daily for 4 or 5 days, mid April	1st treatment week	1 or 2 tablets daily for 4 or 5 days, mid April
2nd treatment week	1 or 2 tablets daily for 4 or 5 days, mid May	2nd treatment week	1 or 2 tablets daily for 4 or 5 days, mid May

Before the start of a treatment course, the doctor will do a blood test to check that the levels of lymphocytes (a type of white blood cells) are in an acceptable range. If this is not the case, treatment can be delayed.

- 10 Once patients have completed the 2 treatment courses over 2 years, the doctor will preferably continue to monitor the health status of the respective patient for another 2 years, in which the respective subject preferably does not need to take the medicine.

Dose

- 15 1. Each patient will be prescribed the correct number of tablets for each treatment week, based on patient body weight as shown in Table 5, below.
2. Each patient will receive one or more packs of Cladribine tablets to provide the correct number of tablets.
3. After receipt of the respective supply of medicine by the respective patient, every patient is recommended to check that he or she has received the correct number of tablets.

4. In the left column of Table 5 below, each patient can preferably find the row that fits his or her body weight (in kg), and then the number of tablets that should be in the pack(s) for the treatment week that he or she will be starting should be again checked.

5. If the number of tablets in the respective pack(s) is different from the number shown for the respective patient for the respective weight in the Table 5 below, the doctor should be contacted.

6. It is highlighted that for some weight ranges the number of tablets may vary from one treatment week to the next.

Example: if the respective patient weighs 85 kg and is about to start treatment week 1, he or she will be given 8 tablets.

Table 5

Your weight	Number of tablets to take			
	Year 1 treatment course		Year 2 treatment course	
	Treatment week 1	Treatment week 2	Treatment week 1	Treatment week 2
less than 40 kg	Your doctor will tell you the number of tablets to take			
40 to less than 50 kg	4	4	4	4
50 to less than 60 kg	5	5	5	5
60 to less than 70 kg	6	6	6	6
70 to less than 80 kg	7	7	7	7
80 to less than 90 kg	8	7	8	7
90 to less than 100 kg	9	8	9	8
100 to less than 110 kg	10	9	10	9
110 kg and above	10	10	10	10

How to take the medicine

The tablet(s) are to be taken at about the same time each day and swallowed without chewing. It is not required to take the tablets at meal times, they can be taken with meals or between meals.

Duration of a treatment week

Depending on the total number of tablets prescribed, they have to be taken over 4 or 5 days, in each treatment week.

Table 6, below, shows how many tablets (1 or 2 tablets) have to be taken on each day. If the daily dose is 2 tablets, they preferably are to be taken at the same time.

Example: if 8 tablets have to be taken, take 2 tablets on Day 1, Day 2, Day 3, then 1 tablet on Day 4 and Day 5.

Table 6

Total number of tablets per treatment week	Day 1	Day 2	Day 3	Day 4	Day 5
4	1	1	1	1	0
5	1	1	1	1	1
6	2	1	1	1	1
7	2	2	1	1	1
8	2	2	2	1	1
9	2	2	2	2	1
10	2	2	2	2	2

10

Further Information

The following abbreviations preferably refer respectively to the definitions below:

kg (kilogram), **µg** (microgram), **mg** (milligram), **AEs** (Adverse effects), **CNS** (Central nervous system), **CSF** (Cerebrospinal fluid), **EDSS** (Expanded Disability Status Scale), **SNRS** (Scripps Neurologic Rating Scale), **IFN** (interferon), **i.v.** (intra-venous), **MIU** (Million International units), **MS** (multiple sclerosis), **MRI** (Magnetic resonance imaging), **p.o.** (per os), **PPMS** (Primary progressive multiple sclerosis), **PRMS** (Progressive relapsing multiple sclerosis), **RRMS** (Relapsing-remitting multiple sclerosis), **SPMS** (Secondary progressive multiple sclerosis), **s.c.** (subcutaneous), **TIW** (Three times a week), **2-ClA** (2-chloro-2'deoxyadenosine or Cladribine), **UI** (International unit).

20

The term "about" as used herein with respect to numbers, figures, ranges and/or amounts is preferably meant to mean "circa" and/or "approximately". The meaning of those terms is well known in the art and preferably includes a variance, deviation and/or variability of the
5 respective number, figure, range and/or amount of plus/minus 15% and especially of plus/minus 10%.

In any case, the term "about" as used herein with respect to numbers, figures, ranges and/or amounts is preferably meant to mean "circa" and/or "approximately". The meaning of those
10 terms is well known in the art and preferably includes a variance, deviation and/or variability of the respective number, figure, range and/or amount of at least plus/minus 5%.

The terms "disorder(s)" and "disease(s)" as used herein are well-known and understood in the art. In the context of the present invention they are preferably used as synonyms and
15 thus are preferably interchangeable, if the context they are used herein does not strongly implicate otherwise.

In the medical context, including, but not limited to treatment regimens, dosing schedules and clinical trial designs, for convenience and/or ease of use by patients, medical staff
20 and/or physicians, as well as reliability and/or reproducibility of results etc., the terms "week"/"a week", "month"/"a month" and/or "year"/"a year" can used with slight deviations from the definitions of the Gregorian calendar. For example, in said medical context, a month is often referred to as 28 days, and a year is often referred to 48 weeks.

25 Thus, in the context of the instant invention, the term "week" or "a week" preferably refers to a period of time of about 5, about 6 or about 7 days, more preferably about 7 days.

In the medical context, the term "month" or "a month" preferably refers to a period of time of about 28, about 29, about 30 or about 31 days, more preferably about 28, about 30 or
30 about 31 days.

In the medical context, the term “year” or “a year” preferably refers to a period of time of about 12 months or to a period of time of about 48, about 50, or about 52 weeks, more preferably 12 months, or about 48 or about 52 weeks.

5

Especially preferred according to the invention are subjects as described herein, wherein the characteristics of two or more preferred, more preferred and/or especially preferred embodiments, aspects and/or subjects are combined into one embodiment, aspect and/or subject. Preferably, according to this invention, preferred subjects or embodiments can be
10 combined with other preferred subjects or embodiments; more preferred subjects or embodiments can be combined with other less preferred or even more preferred subjects or embodiments; especially preferred subjects or embodiments can be combined with other just preferred or just even more preferred subjects or embodiments, and the like.

15 The invention is explained in greater detail below by means of examples. The invention preferably can be carried out throughout the range described and is not restricted to the examples given here.

Moreover, the following examples are given in order to assist the skilled artisan to better
20 understand the present invention by way of exemplification. The examples are not intended to limit the scope of protection conferred by the claims. The features, properties and advantages exemplified for the processes, compounds, compositions and/or uses defined in the examples may be assigned to other processes, compounds, compositions and/or uses not specifically described and/or defined in the examples, but falling under the scope of what is
25 defined in the claims.

Thus, the following examples describe the invention in more detail but do not limit the invention and its scope.

30

EXAMPLES

Example 1: ONWARD Study

Patients aged 18–65 years were eligible to enter the ONWARD study if they fulfilled the following criteria:

- a diagnosis of RRMS or SPMS with relapses (2005 McDonald criteria)⁴
- treatment with IFN- β for ≥ 48 consecutive weeks before screening, with ≥ 1 MS relapse during that period
- clinical stability (other than relapses) during the 28 days before screening
- an Expanded Disability Status Scale (EDSS) score of 1.0–5.5
- normal hematological parameters within 28 days of baseline (Day 1 of randomization), defined as: platelets, 140–450 $\times 10^3/\mu\text{L}$; absolute neutrophil count, 2.03–8.36 $\times 10^3/\mu\text{L}$; absolute lymphocyte count, 1.02–3.36 $\times 10^3/\mu\text{L}$; white blood cell count, 4.1–12.3 $\times 10^3/\mu\text{L}$; haemoglobin, 11.6–16.2 g/dL

- Switching from one IFN- β therapy to another was permitted in the 48 weeks before screening if the patient had been on a stable regimen of the current IFN- β ≥ 3 months prior to screening.

- Patients were excluded if they had an infectious or immune-compromising disease, had been previously treated with an immunosuppressive or cytotoxic therapy, or if they were pregnant, breastfeeding or refused to use contraception during the study.

- In the study, a dose of Cladribine tablets of 3.5 mg/kg, added to existing IFN- β therapy, were applied.

- All analyses were post-hoc and not pre-specified, no multiplicity adjustments were done to the resulting p values. All comparisons where the p value was less than 0.05 by statistical testing should be regarded as nominally significant.

In the CLARITY study, Cladribine tablets given in short-duration treatment courses annually for 2 years to patients with relapsing-remitting multiple sclerosis (RRMS) significantly improved clinical and MRI outcomes. In the 2-year CLARITY Extension study, the clinical benefits of the initial 2-years of Cladribine treatment (3.5 mg/kg of

bodyweight) given in CLARITY were shown to be durable, in patients re-randomised to receive placebo without further active treatment. The ONWARD study confirmed the safety and tolerability of Cladribine tablets (3.5 mg/kg) administered as an add-on to interferon- β (IFN- β) therapy as a primary endpoint in patients who experienced at least one
5 relapse on IFN- β . The ONWARD study also confirmed efficacy as a secondary objective, and showed similar benefits for Cladribine tablets 3.5 mg/kg added on to IFN- β in patients with relapsing MS (RMS). The ONWARD study recruited patients with RMS, (Fig. 1), with patients being eligible for study entry if they had RRMS or secondary progressive MS (SPMS) with relapses. The inclusion of patients with SPMS in ONWARD provided an
10 opportunity to confirm the efficacy of treatment with Cladribine tablets 3.5 mg/kg vs placebo added on to IFN- β in these patients. The objective was to confirm the effect of Cladribine tablets 3.5 mg/kg in patients with SPMS or RRMS in the ONWARD study.

Table 7: Patient demographics and disease characteristics for patients classified as SPMS or RRMS (overall ITT population)

	SPMS patients N=26 ^a		RRMS patients N=171 ^a	
	Placebo + IFN- β N = 9	Cladribine tablets 3.5 mg/kg + IFN- β N = 17	Placebo + IFN- β N = 48	Cladribine tablets 3.5 mg/kg + IFN- β N = 123
Age, years; mean (SD)	39.9 (10.1)	41.1 (11.3)	40.2 (10.0)	38.1 (10.0)
Female, n (%)	5 (55.6)	10 (58.8)	37 (77.1)	84 (68.3)
Disease duration, years; mean (SD)	8.63 (5.15)	8.22 (5.85)	8.18 (6.50)	6.50 (4.85)
Prior use of DMDs, n (%)	9 (100.0)	17 (100.0)	48 (100.0)	123 (100.0)
Relapses in the 12 months prior to study entry, n (%)				
0	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)
1	8 (88.9)	10 (58.8)	28 (58.3)	96 (78.0)
2	1 (11.1)	6 (35.3)	16 (33.3)	24 (19.5)
≥ 3	0 (0.0)	1 (5.9)	3 (6.3)	3 (2.4)
EDSS score at baseline				
Mean (SD)	4.39 (0.42)	4.18 (1.33)	2.80 (1.11)	2.69 (1.09)
Number of T1 Gd+ lesions at baseline				
Mean (SD)	0.1 (0.3)	1.5 (4.8)	1.0 (3.1)	0.9 (3.6)
Number of T2 lesions at baseline				
Mean (SD)	37.8 (26.7)	38.3 (28.8)	32.5 (19.2)	32.7 (21.6)
T2 lesion volume (cm ³)				
Mean (SD)	10.15 (8.60)	12.46 (14.33)	13.58 (16.54)	10.33 (10.73)

EDSS, Expanded Disability Status Scale; Gd+, Gadolinium-enhancing; RRMS, relapsing-remitting multiple sclerosis; SD, Standard Deviation; SPMS, secondary progressive multiple sclerosis.

^a Overall N of placebo and 3.5 mg/kg cladribine groups, excluding 5.25 mg/kg cladribine group in the ITT population (patients randomized under both the original and amended protocols).

5

Clinical efficacy

In patients with SPMS and in patients with RRMS, patients who received treatment with Cladribine tablets 3.5 mg/kg showed nominally statistically significant reductions in annualized relapse rate compared with placebo. In SPMS patients, the annualized relapse rate was 0.03 (95% CI: 0.00–0.24) for patients treated with Cladribine 3.5 mg/kg + IFN-β and 0.30 (95% CI 0.13–0.73) for those who received placebo + IFN-β. Cladribine-treated SPMS patients were 89% less likely to have a qualifying relapse than those treated with placebo (Fig. 2).

15 In contrast thereto, in RRMS patients, the annualized relapse rate was 0.15 (95% CI: 0.11–0.22) for patients treated with Cladribine 3.5 mg/kg + IFN-β and 0.31 (95% CI 0.21–0.45) for those who received placebo + IFN-β. Thus, Cladribine-treated RRMS patients were only 50% less likely to have a qualifying relapse than those treated with placebo (Fig. 3).

Disability progression

No treatment effect was observed for the SPMS or RRMS subgroups on either time to 3-month or 6-month confirmed EDSS progression (not shown). These findings are similar to those the overall ONWARD study population and may reflect the low number of patients in the study.

25

Magnetic resonance imaging (MRI) outcomes

In patients with both SPMS and RRMS, treatment with Cladribine tablets 3.5 mg/kg was associated with reduction in the mean number of T1 Gd+ lesions and in the mean number of active T2 lesions (Table 8, below).

30

Table 8: MRI outcomes for patients classified as SPMS or RRMS

	SPMS patients N=26 ^a		RRMS patients N=171 ^a	
	Placebo + IFN- β N = 9	Cladribine tablets 3.5 mg/kg + IFN- β N = 17	Placebo + IFN- β N = 48	Cladribine tablets 3.5 mg/kg + IFN- β N = 123
Mean number of new T1 Gd+ lesions per patient per scan				
Mean (SD)	0.67 (2.00)	0.13 (0.55)	0.29 (0.64)	0.05 (0.31)
Mean number of T2 lesions per patient per scan				
Mean (SD)	0.59 (1.66)	0.29 (0.52)	1.31 (2.36)	0.58 (1.40)

Gd+, Gadolinium-enhancing; RRMS, relapsing-remitting multiple sclerosis; SD, Standard Deviation; SPMS, secondary progressive multiple sclerosis.

^a Overall N of placebo and 3.5 mg/kg cladribine groups, excluding 5.25 mg/kg cladribine group in the ITT population (patients randomised under both the original and amended protocols)

Example 2: PPMS Study

To confirm the efficacy of Cladribine compared with placebo in delaying 6-month confirmed disability progression in subjects with primary progressive multiple sclerosis (PPMS), a second Example is described. This example also describes the efficacy of

Cladribine compared with placebo on further measures of disability progression in subjects with PPMS and the efficacy of Cladribine compared with placebo on magnetic resonance imaging (MRI) measures of disease progression in subjects with PPMS.

- 5 It also describes the safety and tolerability of treatment with oral Cladribine compared with placebo in subjects with PPMS.

A randomized, double-blind, 2-arm, parallel-group, placebo-controlled, multi-center study, is described for the efficacy and safety of oral Cladribine versus placebo in subjects with
10 PPMS.

This study includes a screening period followed by a 2-year double-blind treatment period with visits occurring at months 0, 1, 3, 6, 9, 11, 12, 13, 15, 18, 21, and 24 followed by a 12-month period of safety follow up.

15 Subjects are randomized to treatment in a 1:1 ratio. Subjects receiving Cladribine are given up to the recommended cumulative dose of 3.5 mg/kg body weight over 2 years (contingent upon meeting re-treatment criteria: at the time of the second yearly treatment course subjects should have a lymphocyte count of Common Terminology Criteria for Adverse
20 Events [CTCAE] Grade ● or 1), administered as 1 treatment course of 1.75 mg/kg per year. Subjects receiving matching placebo are given tablets in a similar schedule as the Cladribine-treated subjects.

Assessments of disability, including assessments of Expanded Disability Status Scale,
25 Timed 25-Foot Walk and 9-hole Peg Test, are performed throughout the treatment period. Magnetic resonance imaging will also be performed. Safety is assessed with monitoring of adverse events. In addition, patient-reported outcomes and clinician-reported outcomes are frequently assessed.

30 **Primary endpoint:** Time to 6-month confirmed disability progression based on EDSS.

Key Secondary endpoints:

The key secondary endpoints of the study include:

- Time to 3-month confirmed disability progression based on a composite score defined by:
 - o A 3-month confirmed EDSS progression and/or;
 - 5 o A 3-month confirmed worsening ($>20\%$) in Timed 25-Foot Walk (T25FW) versus baseline and/or;
 - o A 3-month confirmed worsening ($>20\%$) in 9-Hole Peg Test (9-HPT) versus baseline;
- Percent change in total volume of lesions on T2 weighted images from baseline to Month 24;
- 10 • Percent change in brain volume from Month 6 to Month 24.

Safety endpoints:

- Occurrence of treatment-emergent adverse events (non-serious adverse events [AEs], serious adverse events [SAEs] and adverse events of special interest [AESIs]) in subjects receiving Cladribine compared with placebo;
- 15 • Evaluation of laboratory parameters (hematology and clinical chemistry) in subjects receiving Cladribine compared with placebo.

Diagnosis and key inclusion and exclusion criteria:**Inclusion criteria**

- 20 • Male and female subjects aged 18 to 51 years (inclusive);
- Diagnosis of PPMS as per the revised McDonald criteria, preferably the McDonald 2010 criteria (Polman, 2011), and confirmed by PPMS Adjudication Committee (PPMS AC);
- EDSS score from 2.5 to 5.5, inclusive; subjects with an EDSS score of 2.0 are eligible if the documented deficit affects either the pyramidal or cerebellar functional systems;
- 25 • Time from onset of symptoms of PPMS of < 15 years for subjects with an EDSS score of 5.5 at screening, or < 10 years for subjects with an EDSS score of 5.0 or less at screening.

Medicinal Product: dose/mode of administration/ dosing schedule:

- Cladribine tablets (10 mg) or matching placebo: 3.5 mg/kg body weight to be administered
- 30 over 2 years (i.e., 1 treatment course of 1.75 mg/kg per year), followed by observation for

another 12 months for safety. Each treatment course consists of 2 treatment weeks, 1 week at the beginning of the first month and 1 week at the beginning of the second month of the respective year. Each treatment week consists of 4 or 5 days, in which a subject receives either 10 mg or 20 mg (either 1 or 2 tablets) as a single daily dose, depending on body weight.

Study and treatment duration per subject:

Subjects will undergo screening assessments followed by a 2-year treatment period. Safety will then be followed for an additional 12 months.

Background Information

The preferred cumulative dose of Cladribine is 3.5 mg/kg body weight over 2 years (as approved for the indication of relapsing-remitting MS (RMS)), preferably administered as 2 treatment courses (i.e., 1.75 mg/kg per year).

Cladribine has shown proven efficacy in relapsing MS (RMS). This clinical study is part of the overall development strategy of oral Cladribine to expand the labeling indication to include not only subjects with relapsing MS, but also PPMS, because of the high unmet medical need in this indication. Although PPMS accounts only for 10% to 15% of MS cases (Miller, 2007), the absence of a widely available proven effective oral treatment underscores the unmet medical need.

The results from the Phase II/III oral Cladribine studies provided clinical efficacy data, both individually and in integrated analyses, showing that oral Cladribine is highly efficacious in subjects with active disease across the clinical spectrum of RMS. The CLARITY study demonstrated robust clinical and MRI efficacy in a population comprising both treatment-naïve and treatment-experienced RRMS. Analysis of CLARITY and CLARITY EXT showed that the efficacy of Cladribine in reducing relapses and slowing EDSS progression is maintained for at least 2 additional years off therapy after 2 short treatment courses with the recommended dose of 3.5 mg/kg. The ORACLE MS study showed consistent clinical

and MRI efficacy, with Cladribine reducing the conversion of clinically isolated syndrome (CIS) subjects into clinically definite MS and McDonald 2005 MS. ONWARD was not fully designed for a formal proof of efficacy, but for an evaluation of the safety and efficacy profile of Cladribine as add-on therapy to interferon (IFN)- β ; however, the efficacy data do support the findings of the CLARITY study in a RMS patient population. For all of the above studies, the 5.25 mg/kg Cladribine dose (and in the case of some additional studies, 2 higher doses: 7.0 mg/kg and 8.75 mg/kg) did not add any clinically meaningful benefit, compared with the 3.5 mg/kg dose. The significant efficacy of Cladribine on MRI endpoints highlights the anti-inflammatory characteristics of Cladribine.

Selective depletion of lymphocytes, including B-cells, is thought to play an important role in early PPMS. Ocrelizumab, a humanized monoclonal antibody that targets the CD20 surface molecule on B-cells triggering their depletion, has recently been approved by the Food and Drug Administration (FDA) for the treatment of patients with RRMS and early PPMS; approval has been denied in Europe. No other agents are currently available for clinical use in early PPMS.

Several lines of evidence suggest that B-cells and B-cell-derived products could be instrumental in chronic progression of MS (Fereidan-Esfahani, 2015). In RRMS and secondary progressive MS (SPMS), and in the majority of patients with PPMS, clonally-expanded B-cells sequestered within the central nervous system (CNS) compartment produce oligoclonal bands and further clonally expand within the lesions. Recent findings suggest that meningeal B-cell infiltrates, possibly organized in B-cell follicle-like structures, could be the niche maintaining pathogenic CNS B-cell function (Magliozzi, 2007). In progressive forms of MS, meningeal and perivascular B-cell accumulation often co-localizes with activated T-cells and macrophages and experimental evidence suggests that these meningeal immune cell conglomerates are associated with cortical lesion formation, demyelination and microglia activation. Cladribine is a good candidate drug for PPMS due to its high efficacy, demonstrated in subjects with RMS and CIS, and its ability to target selectively B-cells and T-cells, both in the periphery and potentially in the CNS, since Cladribine is found to be blood-brain barrier penetrant and enters the brain

independent of vascular leakage. Moreover, previous data with parenteral Cladribine in chronic MS showed trends in MRI efficacy (T1-weighted gadolinium-enhanced [T1 Gd+]) (Rice, 2000; see Section 5.2 for details). Therefore, the Sponsor has designed this clinical study to confirm Cladribine's effects in subjects with PPMS. Data from this study is used to achieve indication expansion for Cladribine to patients with PPMS.

Table 9: Large PPMS studies: Comparison of key entry criteria, baseline characteristics, and outcomes

Study/ Study Drug	n	Entry age EDSS	Actual mean age Mean EDSS	Baseline % T1 Gd+ scans	CSF+ at baseline	Endpoint	% with CDP placebo	% with CDP study drug	EDSS progression overall HR (95% CI)
PROMISE glatiramer acetate	943	30-65 3.0-6.5	50.4 4.9	14%	78.4% (not a requirement)	CDP (3) Month 12 Month 24	22% 40%	22% 41%	0.87 (0.71-1.07) p=0.1753
OLYMPUS rituximab	439	18-65 2.0-6.5	49.9 4.8	25%	Required	CDP (3) Week 48 Week 96 CDP (8) Week 96	19.3% 38.5% 30.4%	20.2% 30.2% 27.3%	0.77 (0.55-1.09) p=0.14 p=0.59
INFORMS fingolimod	654	25-65 3.5-6.0	48.5 4.67	13%	Required	CDP (3) EDSS Composite	58.7% 80.3%	54.3% 77.2%	0.88 (0.80-1.12) p=0.21 0.95 (0.80-1.12) p=0.544
ORATORIO ocrelizumab	725	18-65 3.0-6.5	44.7 4.7	~25%	Required	CDP (3) Month 12 Week 120 CDP (8) Month 12 Week 120	~18.9% 39.3% ~21.4% 35.7%	~13.2% 32.9% ~15.2% 29.7%	0.76 (0.59-0.98) p=0.0321 0.75 (0.58-0.98) p=0.0365

CDP=confirm EDSS progression, CSF=cerebrospinal fluid, EDSS=Expanded Disability Status Scale, HR=hazard ratio, PPMS= primary progressive multiple sclerosis, T1 Gd+=T1-weighted gadolinium-enhanced. For ORATORIO: Proportion of subjects with CDP at Month 12 derived from the KM, (Montalban, 2017). Source: (PROMISE) Wolinsky, 2007, (OLYMPUS) Hawker, 2009, (INFORMS) Lublin, 2016, (ORATORIO) Montalban, 2017.

Based on our experience, we believe that a younger PPMS population with greater MRI activity may be more suitable to treatment, especially one with a high inflammatory burden and thus high otherwise unmet medical need.

In summary, based on our assessment, by including a study population with PPMS of < 55
5 years of age and with lower EDSS, the chance of including subjects with inflammatory disease is increased. There is an unmet need for drugs that target PPMS early, prior to the development of irreversible disability. The penetration of Cladribine into the CNS (Liliemark, 1997) and its presumed action beyond the blood-brain barrier provides a strong further rationale for this study, as the pathophysiology of progressive MS is deemed to
10 involve inflammation within the CNS.

Dosage and Administration

Randomized subjects are administered oral Cladribine or matching placebo in a blinded manner, in 2 once yearly treatment courses during the treatment period.

15

The first dose is administered at the site and treatment for the following 3-4 days is taken by the patient at home. See appendix below for details.

The recommended cumulative dose of Cladribine is 3.5 mg/kg body weight over 2 years,
20 administered as 1 treatment course of 1.75 mg/kg per year. Each treatment course consists of 2 treatment weeks, 1 week at the beginning of the first month (Baseline) and 1 week at the beginning of the second month (Month 1) and subsequently in the second year at the beginning of Months 12 and 13. Depending on body weight, each treatment week consists of 4 or 5 days on which a subject receives 10 mg or 20 mg (1 or 2 tablets) as a single daily
25 dose.

Following completion of the 2 treatment courses, no further Cladribine treatment is currently deemed required in years 3 and/or 4. However, re-initiation of therapy in year 3 may be an options to further improve the situation of the patients, especially the PPMS
30 patients.

Preferred criteria for initiating and continuing therapy

5 Lymphocyte counts must be

- normal before initiating Cladribine in year 1,
- at least Grade 0 or 1 ALC before initiating Cladribine in year 2.

If necessary, the treatment course in year 2 can be delayed for up to 6 months to allow for recovery of lymphocytes. If this recovery takes more than 6 months the patient should not
10 receive Cladribine anymore.

Table 10: Dosages by patient weight

Dose of cladribine per treatment week by patient weight in each treatment year		
Weight range	Dose in mg (number of 10 mg tablets) per treatment week	
kg*	Treatment week 1	Treatment week 2
40 to < 50	40 mg (4 tablets)	40 mg (4 tablets)
50 to < 60	50 mg (5 tablets)	50 mg (5 tablets)
60 to < 70	60 mg (6 tablets)	60 mg (6 tablets)
70 to < 80	70 mg (7 tablets)	70 mg (7 tablets)
80 to < 90	80 mg (8 tablets)	70 mg (7 tablets)
90 to < 100	90 mg (9 tablets)	80 mg (8 tablets)
100 to < 110	100 mg (10 tablets)	90 mg (9 tablets)
110 and above	100 mg (10	100 mg (10 tablets)

15 Subjects are instructed to take the medication at the same time each day with water; tablets must be swallowed whole. As tablets are uncoated, they must be taken immediately after being removed from the blister pack. There are no fasting restrictions; tablets may be taken independent of food intake.

A missed dose must be taken as soon as remembered on the same day according to the treatment schedule.

A missed dose must not be taken together with the next scheduled dose on the following day. In the case of a missed dose, the patient must take the missed dose on the following day, and extend the number of days in that treatment week. If two consecutive doses are missed, the same rule applies, and the number of days in the treatment week is extended by two days.

Example 3

The efficacy and safety of oral Cladribine administration, eventually multi-dose administration, as described herein, can alternatively also be assessed for example following the protocol for the treatment of relapsing forms of MS as given below:

Oral Cladribine in the treatment of relapsing forms of MS

A study of sixty patients with relapsing forms of clinically definite multiple sclerosis is undertaken. Each patient is first examined for normal hepatic, renal, and bone marrow functioning to establish baseline values.

Patients are selected from Male or Female, between 18 and 55 years of age who had one or more relapses within the prior 12 months. Female patients are non-pregnant female.

Patients are randomly assigned to one of the treatment groups listed in Table 11 below.

Table 11:

Group	2-CdA
1	-
2	1.75 mg/kg
3	3.5 mg/kg

Each of the patients in Groups 2 and 3 receives 3 mg or 10 mg 2-CdA (1, 2 or 3 administration(s) a day depending on the patient's weight) combined in cyclodextrin

formulation as described in WO 2004/087101, Example 3. The Compositions of the Cladribine formulations in 3 mg or 10 mg 2-CdA tablets containing hydroxypropyl-beta-cyclodextrin are listed in Table 12, below.

5

Table 12:

Name of ingredients	Formula mg/tablet	Formula mg/tablet
Cladribine-2-hydroxypropyl- β -cyclodextrin- complex*	153.75 equivalent to 10 mg 2-CdA	30.60 equivalent to 3 mg 2-CdA
Sorbitol powder	44.25	68.4
Magnesium Stearate (vegetable grade)	2.0	1.00
Total	200.0	100

* Cladribine is complexed and lyophilised with 2-hydroxypropyl- β -cyclodextrin as a separate process as described in WO 2004/087101.

Administration schemes for the induction period depending on the patient's weight are given below in Tables 3 and 4 for the target doses of 1.75 mg/kg and 3.5 mg/kg respectively. For the maintenance period, the example of administration scheme of Table 13 is applicable.

10

Table 13:

Patient weight ranges (kg)			Total target dose (kg) equivalent to 1.75 mg/kg		Number of pills (10 mg)/induction period		
Min	Mid-range	Max	Min	Max	Month 1	Month 2	Total
40	42.5	44.9	28	31.4	4	3	7
45	47.5	49.9	31.5	34.9	4	4	8
50	52.5	54.9	35	38.4	5	4	9
55	57.5	59.9	38.5	41.9	5	5	10
60	62.5	64.9	42	45.4	5	5	10
65	67.5	69.9	45.5	48.9	6	5	11
70	72.5	74.9	49	52.4	6	6	12
75	77.5	79.9	52.5	55.9	7	6	13
80	82.5	84.9	56	59.4	7	6	13
85	87.5	89.9	59.5	62.9	7	7	14
90	92.5	94.9	63	66.4	8	7	15
95	97.5	99.9	66.5	69.9	8	8	16
100	102.5	104.9	70	73.4	9	8	17
105	107.5	109.9	73.5	76.9	9	9	18
110	112.5	114.9	77	80.4	9	9	18
115	117.5	119.9	80.5	83.9	10	9	19

Table 14:

Patient weight ranges (kg)			Total target dose (kg) equivalent to 3.5 mg/kg		Number of pills (10 mg)/induction period				
Min	Mid-range	Max	Min	Max	Month 1	Month 2	Month 3	Month 4	Total
40	42.5	44.9	56	62.9	4	4	3	3	14
45	47.5	49.9	63	69.9	4	4	4	4	16
50	52.5	54.9	70	76.9	5	4	4	4	17
55	57.5	59.9	77	83.9	5	5	5	4	19
60	62.5	64.9	84	90.9	6	5	5	5	21
65	67.5	69.9	91	97.9	6	6	5	5	22
70	72.5	74.9	98	104.9	6	6	6	6	24
75	77.5	79.9	105	111.9	7	7	6	6	26
80	82.5	84.9	112	118.9	7	7	7	6	27
85	87.5	89.9	119	125.9	7	7	7	7	28
90	92.5	94.9	126	132.9	8	8	7	7	30
95	97.5	99.9	133	139.9	8	8	8	8	32
100	102.5	104.9	140	146.9	9	8	8	8	33
105	107.5	109.9	147	153.9	9	9	9	8	35
110	112.5	114.9	154	160.9	10	9	9	9	37
115	117.5	119.9	161	167.9	10	10	9	9	38

In Group 1, patients receive a placebo (saline) for 4 months followed by 8 months of no treatment.

5

In Group 2 patients receive a daily oral administration of Cladribine for about 5 days a month during 2 months (induction period) of 2-CdA cyclodextrin formulation such that the total effective dose administered at the end of the first 2 months approximates about 0.7 mg/kg (total dose of about 1.75 mg/kg for a bioavailability of about 40%); followed by administration of placebo for 2 months; followed by 8 months of no treatment.

10

In Group 3, patients receive a daily oral administration of Cladribine for about 5 days a month for 4 months (induction period) of 2-CdA cyclodextrin formulation such that the

total effective dose administered at the end of the first 4 months approximates about 1.4 mg/kg (total dose of about 3.5 mg/kg for a bioavailability of about 40%); followed by 8 months of no treatment.

- 5 Beginning at month 13, all 3 patient groups receive re-treatment with Cladribine cyclodextrin formulation for about 5 days a month for 2 months (maintenance period) with the lower dose (such that the total effective dose administered at the end of the first 2 months approximates about 0.7 mg/kg) followed by 10 months of no treatment.
- 10 Finally, beginning at month 25, all patient groups receive re-treatment with Cladribine cyclodextrin formulation for about 5 days a month for 2 months (maintenance period) with the lower dose (such that the total effective dose administered at the end of the first 2 months approximates about 0.7 mg/kg) followed by 10 more months of no treatment.
- 15 Patients are monitored to determine whether there is any progression or improvement of brain lesions associated with progression of MS through MRI scans and neurological examination as described in *Miller et al., 1996, above; Evans et al., 1997, above; Sipe et al., 1984, above; and Mattson, 2002, above*. All patients have a baseline and MRI study (brain or spinal cord, according to localization of the lesions) at month 12.
- 20 The patient's disability progression and the time for having a first relapse are monitored as well as the proportion of relapse-free patients at 24 months.

Lymphocyte markers and monocyte counts are monitored in the patients.

- 25 Patients in Groups 2 and 3 have a decrease in brain lesions.

The data show that the 2-CdA regimen consisting in the succession of an induction treatment and maintenance treatments is efficient in decreasing brain lesions and no severe adverse effect is observed.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	000696US
		Application Number	
Title of Invention	Cladribine regimen for treating progressive forms of Multiple Sclerosis		
The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76. This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.			

Secrecy Order 37 CFR 5.2:

☐	Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)
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Inventor Information:

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All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button. Add				

Correspondence Information:

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	000696US
		Application Number	
Title of Invention	Cladribine regimen for treating progressive forms of Multiple Sclerosis		

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ An Address is being provided for the correspondence information of this application.

Customer Number	151167		
Email Address	patent@gandmpatent.com	Add Email	Remove Email

Application Information:

Title of the Invention	Cladribine regimen for treating progressive forms of Multiple Sclerosis		
Attorney Docket Number	000696US	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	4	Suggested Figure for Publication (if any)	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative information during processing.

Please Select One:	☒ Customer Number	☐ US Patent Practitioner	☐ Limited Recognition (37 CFR 11.9)
Customer Number	151167		

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	00696US
		Application Number	
Title of Invention	Cladribine regimen for treating progressive forms of Multiple Sclerosis		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Claims benefit of provisional	62/590442	2017-11-24

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)ⁱ the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Application Number	Country ⁱ	Filing Date (YYYY-MM-DD)	Remove
			Access Code ⁱ (if applicable)

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Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

☐ NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	00696US
		Application Number	
Title of Invention	Cladribine regimen for treating progressive forms of Multiple Sclerosis		

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

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B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	00696US
		Application Number	
Title of Invention	Cladribine regimen for treating progressive forms of Multiple Sclerosis		

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

[Clear](#)

☒ Assignee
 ☐ Legal Representative under 35 U.S.C. 117
 ☐ Joint Inventor

☐ Person to whom the inventor is obligated to assign.
 ☐ Person who shows sufficient proprietary interest

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

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Additional Applicant Data may be generated within this form by selecting the Add button.

Assignee Information including Non-Applicant Assignee Information:

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	00696US
		Application Number	
Title of Invention	Cladribine regimen for treating progressive forms of Multiple Sclerosis		

Assignee 1

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If the Assignee or Non-Applicant Assignee is an Organization check here. ☒

Organization Name	Merck Patent GmbH
-------------------	-------------------

Mailing Address Information For Assignee including Non-Applicant Assignee:

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Country ⁱ	DE	Postal Code	64293
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). However, if this Application Data Sheet is submitted with the **INITIAL** filing of the application **and** either box A or B is **not** checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Eric Myers/		Date (YYYY-MM-DD)	2018-11-23	
First Name	Eric	Last Name	Myers	Registration Number	68,546

Additional Signature may be generated within this form by selecting the Add button.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	00696US
		Application Number	
Title of Invention	Cladribine regimen for treating progressive forms of Multiple Sclerosis		

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