Table 1: Summary of symptomatic treatments commonly used in patients with ALS [adapted from Jenkins 2014]

Drug	Population indicated / Common usage
Baclofen (Lioresal)	Indicated for the relief of spasticity of voluntary muscle resulting from such disorders, for example, multiple sclerosis. In patients 0 to <18 years it is indicated for the symptomatic treatment of spasticity of cerebral origin, including ALS.
Hyoscine	Hypersalivation
Carbocisteine	Difficulty expectorating secretions
Amitriptyline	Neuropathic pain
Gabapentin	Neuropathic pain
Citalopram	Depression and emotional lability
Venlafaxine	Depression
Nortriptyline	Depression

In conclusion, the treatment of ALS remains a challenge to clinicians because of the diversity and complexity of the disease itself and the lack of standard and clinically meaningful effective therapy.

Furthermore, existing treatments do not take into account the progression rate of the disease, i.e. non-aggressive or moderately aggressive ALS versus aggressive ALS.

None of the known approved or investigational drugs appear to represent a cure for ALS. Moreover, the efficacy of known drugs is limited and may decrease over time, with undesirable side effects reported. Thus, there exists a continuing need to identify new targeted drugs that possess greater efficacy to treat ALS, and in particular the non-aggressive or moderately aggressive ALS affecting the majority of ALS patients.

SUMMARY

The present disclosure thus relates to a method for treating non-aggressive or moderately aggressive amyotrophic lateral sclerosis (ALS) comprising administering a tyrosine kinase inhibitor or a pharmaceutically acceptable salt or solvate thereof, optionally in combination with at least one pharmaceutically active ingredient, to a subject in need thereof.

The present disclosure also relates to a method for treating non-aggressive or moderately aggressive ALS comprising administering an inhibitor of at least one tyrosine kinase selected from c-Kit, Lyn, Fyn, PDGFR, and CSF1R, or any combination thereof, optionally in combination with at least one pharmaceutically active ingredient, to a subject in need thereof.

The disclosure aims to solve the technical problem of providing an active ingredient for the treatment of patients afflicted with non-aggressive or moderately aggressive ALS.

In one embodiment, non-aggressive or moderately aggressive ALS is defined as a progression of the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) score before treatment initiation of less than 1.1 points per month.

In another embodiment, non-aggressive or moderately aggressive ALS is defined as a rate of change of ALSFRS-R score from the date of first ALS-related symptom to time of first treatment (baseline) of less than 1.1 points per month.

In one embodiment, non-aggressive ALS is defined as a progression of the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) score before treatment initiation of less than 0.8 points per month. In another embodiment, non-aggressive ALS is defined as a rate of change of ALSFRS-R score from the date of first ALS-related symptom to time of first treatment (baseline) of less than 0.8 points per month.

In one embodiment, moderately aggressive ALS is defined as a progression of the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) score before treatment initiation of less than 1.1 points per month and equal to or greater than 0.8 points per month ($\geq$0.8 to <1.1 points per month). In another embodiment, moderately aggressive ALS is defined as a rate of change of ALSFRS-R score from the date of first ALS-related symptom to time of first treatment (baseline) of less than 1.1 points per month and equal to or greater than 0.8 points per month ($\geq$0.8 to <1.1 points per month).

This disclosure thus also relates to a method for treating patients with non-aggressive or moderately aggressive ALS (i.e. patient whose progression of ALSFRS-R score before treatment initiation is less than 1.1 points per month), comprising administering a tyrosine kinase inhibitor or a pharmaceutically acceptable salt or solvate thereof, preferably masitinib or a pharmaceutically acceptable salt or solvate thereof, optionally in combination with at least one pharmaceutically active ingredient, to subject in need thereof.

The disclosure relates to a method for treating patients suffering from amyotrophic lateral sclerosis (ALS) having a progression of ALSFRS-R score before treatment initiation of less than 1.1 points per month, comprising administering a tyrosine kinase inhibitor or a pharmaceutically acceptable salt or solvate thereof, preferably masitinib or a pharmaceutically acceptable salt or solvate thereof, optionally in combination with at least one pharmaceutically active ingredient, to subject in need thereof.

In one embodiment, patients have a progression of ALSFRS-R score before treatment initiation of less than 0.8 points per month. In another embodiment, patients have a progression of ALSFRS-R score before treatment initiation of less than 1.1 points per month and equal to or greater than 0.8 points per month ($\geq$0.8 to <1.1 points per month).

This disclosure further relates to an inhibitor of at least one tyrosine kinase selected from c-Kit, Lyn, Fyn, PDGFR and CSF1R, or any combination thereof, preferably masitinib or a pharmaceutically acceptable salt or solvate thereof, for use for treating patients with non-aggressive or moderately aggressive ALS (i.e. patient whose progression of ALSFRS-R score before treatment initiation is less than 1.1 points per month).

Thus, the disclosure relates to an inhibitor of at least one tyrosine kinase selected from c-Kit, Lyn, Fyn, PDGFR and CSF1R, or any combination thereof, preferably masitinib or a pharmaceutically acceptable salt or solvate thereof, for use in the treatment of patients suffering from amyotrophic lateral sclerosis (ALS) having a progression of ALSFRS-R score before treatment initiation of less than 1.1 points per month.

In one embodiment, said patients have a progression of ALSFRS-R score before treatment initiation of less than 0.8 points per month. In another embodiment, said

patients have a progression of ALSFRS-R score before treatment initiation of less than 1.1 points per month and equal to or greater than 0.8 points per month (≥0.8 to <1.1 points per month).

The disclosure also aims to solve the technical problem of providing an active ingredient that improves prior art methods for the treatment of non-aggressive or moderately aggressive ALS, more particularly for treating patients with ALS whose progression of ALSFRS-R score before treatment initiation is less than 1.1 points per month.

In one embodiment, said patients have a progression of ALSFRS-R score before treatment initiation of less than 0.8 points per month. In another embodiment, said patients have a progression of ALSFRS-R score before treatment initiation of less than 1.1 points per month and equal to or greater than 0.8 points per month (≥0.8 to <1.1 points per month).

In one embodiment, the tyrosine kinase inhibitor of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, is an inhibitor of at least one tyrosine kinase selected from c-Kit, Lyn, Fyn, PDGFR and CSF1R, or any combination thereof.

In one embodiment, the tyrosine kinase inhibitor of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, is an inhibitor of mast cell activity. In another embodiment, the tyrosine kinase inhibitor of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, is an inhibitor of microglia cell activity. In another embodiment, the tyrosine kinase inhibitor of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, is an inhibitor of mast cell activity and microglia cell activity.

In one embodiment, the tyrosine kinase inhibitor of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, is a mast cell inhibitor chosen from the group comprising: masitinib, imatinib, cromolyn sodium, midostaurin, BLU-285, bosutinib, ibrutinib, LAS189386, DP-2618, fostamatinib, nilotinib, dasatinib, sunitinib, axitinib, pazopanib, and toceranib.

In another embodiment, the tyrosine kinase inhibitor of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, is a microglia cell inhibitor chosen from the group comprising: masitinib, GW2580, pexidartinib, BLZ945, linifanib, OSI-930, imatinib, sunitinib, nilotinib, pazopanib, emactuzumab, FPA008, quizartinib, axitinib, motesanib, cediranib, JNJ-28312141, Ki-20227, MLN-518, sorafenib, and SU-14813.

In one embodiment, the tyrosine kinase inhibitor of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, is a 2-aminoarylthiazole derivative, or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, said tyrosine kinase inhibitor, or a pharmaceutically acceptable salt or solvate thereof, is masitinib or a pharmaceutically acceptable salt or solvate thereof. In one embodiment, said tyrosine kinase inhibitor or a pharmaceutically acceptable salt or solvate thereof is masitinib mesilate.

The present disclosure thus relates to a method for the treatment of non-aggressive or moderately aggressive ALS, especially non-aggressive or moderately aggressive ALS defined as a progression of ALSFRS-R score before treatment initiation of less than 1.1 points per month, wherein said method comprises administering to a human patient in need thereof, masitinib or a pharmaceutically acceptable salt or solvate thereof.

In one embodiment, the method of the disclosure is for the treatment of patients having a progression of ALSFRS-R score before treatment initiation of less than 0.8 points per month. In another embodiment, the method of the disclosure is for the treatment of patients having a progression of ALSFRS-R score before treatment initiation of less than 1.1 points per month and equal to or greater than 0.8 points per month ($\geq$0.8 to <1.1 points per month).

In one embodiment, the tyrosine kinase inhibitor of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, is administered in combination with at least one pharmaceutically active ingredient. Said pharmaceutically active ingredient is preferably active in the treatment of ALS. Said pharmaceutically active ingredient is preferably an antiglutamate compound, especially riluzole (6-

(trifluoromethoxy)benzothiazol-2-amine); topiramate (2,3:4,5-Bis-O-(1-methylethylidene)-beta-D-fructopyranose sulfamate); gabapentin (2-[1-(aminomethyl)cyclohexyl]acetic acid); lamotrigine (6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine); talampanel ((8R)-7-Acetyl-5-(4-aminophenyl)-8,9-dihydro-8-methyl-7H-1,3-dioxolo[4,5-h] [2,3]benzodiazepine); ceftriaxone ((6R,7R)-7-[[(2Z)-2-(2-amino-1,3-thiazol-4-yl)-2-methoxyiminoacetyl]amino]-3-[(2-methyl-5,6-dioxo-1H-1,2,4-triazin-3-yl)sulfanylmethyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid); an inhibitor of glutamate carboxypeptidase II. Preferably said other pharmaceutically active ingredient is riluzole.

The disclosure aims to provide an efficient treatment non-aggressive or moderately aggressive ALS at an appropriate dose, route of administration and daily intake.

In one embodiment said tyrosine kinase inhibitor or a pharmaceutically salt or solvate thereof, preferably masitinib or a pharmaceutically acceptable salt or solvate thereof, and more preferably masitinib mesilate, is administered orally.

In one embodiment said tyrosine kinase inhibitor or a pharmaceutically salt or solvate thereof, preferably masitinib or a pharmaceutically acceptable salt or solvate thereof, and more preferably masitinib mesilate, is administered twice a day (i.e. in two daily intakes).

In one embodiment, the tyrosine kinase inhibitor of the disclosure, or a pharmaceutically salt or solvate thereof, preferably masitinib or a pharmaceutically acceptable salt or solvate thereof, and more preferably masitinib mesilate, is administered at a daily dose ranging from about 1.0 to about 9.0 mg/kg (mg per kilo body weight). In another embodiment, the tyrosine kinase inhibitor of the disclosure or a pharmaceutically salt or solvate thereof, preferably masitinib or a pharmaceutically acceptable salt or solvate thereof, and more preferably masitinib mesilate, is administered at a dose of 1.5, 3.0, 4.5, 6.0, or 7.5 mg/kg, more preferably at a dose of 3.0, 4.5 or 6 mg/kg/day (mg per kg bodyweight per day).

In one embodiment, the tyrosine kinase inhibitor of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, is administered at an initial dose of 3.0 mg/kg/day

during at least 4 weeks, then 4.5 mg/kg/day during at least 4 weeks, and at 6.0 mg/kg/day thereafter, with each dose escalation being subjected to toxicity controls.

The present disclosure also relates to a tyrosine kinase inhibitor or a pharmaceutically acceptable salt or solvate thereof for use in the treatment of non-aggressive or moderately aggressive ALS human patients whose progression of ALSFRS-R score before treatment initiation is less than 1.1 points per month as described hereinabove, wherein said tyrosine kinase inhibitor or a pharmaceutically acceptable salt or solvate thereof is masitinib mesilate.

In one embodiment, said patients have a progression of ALSFRS-R score before treatment initiation of less than 0.8 points per month. In another embodiment, said patients have a progression of ALSFRS-R score before treatment initiation of less than 1.1 points per month and equal to or greater than 0.8 points per month ($\geq$0.8 to <1.1 points per month).

In one embodiment, said tyrosine kinase inhibitor is administered in combination with said at least one pharmaceutically active ingredient in a combined preparation for simultaneous, separate, or sequential use.

The disclosure also relates to a tyrosine kinase inhibitor, preferably masitinib, or a pharmaceutically acceptable salt or solvate thereof, as defined according to the present disclosure, for use in a treatment of non-aggressive or moderately aggressive ALS.

The disclosure also relates to a tyrosine kinase tyrosine, preferably masitinib, or a pharmaceutically acceptable salt or solvate thereof, as defined according to the present disclosure, for use in a treatment of non-aggressive or moderately aggressive ALS, in combination with at least pharmaceutically active ingredient, preferably an antiglutamate compound, especially riluzole; topiramate; gabapentin; lamotrigine; talampanel; ceftriaxone; an inhibitor of glutamate carboxypeptidase II, preferably said other pharmaceutically active ingredient is riluzole.

The disclosure also relates to a pharmaceutical composition or a medicament or a kit comprising an inhibitor of at least one tyrosine kinase selected from c-Kit, Lyn, Fyn,

PDGFR and CSF1R, or any combination thereof, preferably masitinib or a pharmaceutically salt or solvate thereof, for use in a method for the treatment of non-aggressive or moderately aggressive ALS as defined according to the present disclosure.

In one embodiment, the pharmaceutical composition or the medicament or the kit of the disclosure also comprises at least one other pharmaceutically active ingredient, preferably an antiglutamate compound, especially riluzole; topiramate; gabapentin; lamotrigine; talampanel; ceftriaxone; an inhibitor of glutamate carboxypeptidase II, preferably said other pharmaceutically active ingredient is riluzole.

The disclosure also relates to the use of a tyrosine kinase inhibitor, preferably masitinib or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament, or a pharmaceutical composition, for the treatment of non-aggressive or moderately aggressive ALS, optionally in combination with at least one other pharmaceutically active ingredient, preferably an antiglutamate compound, especially riluzole; topiramate; gabapentin; lamotrigine; talampanel; ceftriaxone; an inhibitor of glutamate carboxypeptidase II, preferably said other pharmaceutically active ingredient is riluzole, as defined according to the disclosure.

According to an aspect there is provided use of an inhibitor of at least one tyrosine kinase selected from c-Kit, Lyn, Fyn, PDGFR, and CSF1R, or any combination thereof, in the manufacture of a medicament for the treatment of patients suffering from amyotrophic lateral sclerosis (ALS) having a progression of ALSFRS-R score before treatment initiation of less than 1.1 points per month.

The tyrosine kinase inhibitor and the optional at least one pharmaceutically active ingredient, are administered in a dosage regimen that comprises a therapeutically effective amount.

DEFINITIONS

In the present invention, the following terms have the following meanings:

As disclosed above, the expression "**ALS patients whose rate of progression in ALSFRS-R score prior to treatment initiation is <1.1 points per month**" as used in the present application, encompasses a subpopulation of patients from the overall ALS patient population.

The term "**ALSFRS-R score**" means the revised Amyotrophic Lateral Sclerosis Functional Rating Scale. ALSFRS-R is a score from 0-48 assessing disability. The

CLAIMS

1. Use of an inhibitor of at least one tyrosine kinase selected from c-Kit, Lyn, Fyn, PDGFR, and CSF1R, or any combination thereof, in the manufacture of a medicament for the treatment of patients suffering from amyotrophic lateral sclerosis (ALS) having a progression of ALSFRS-R score before treatment initiation of less than 1.1 points per month.

2. The use according to claim **1**, wherein said patients have a progression of ALSFRS-R score before treatment initiation of less than 0.8 points per month.

3. The use according to claim **1**, wherein said patients have a progression of ALSFRS-R score before treatment initiation of less than 1.1 points per month and equal to or greater than 0.8 points per month (≥0.8 to <1.1 points per month).

4. The use according to any one of claims **1** to **3**, wherein said inhibitor is an inhibitor of mast cell activity.

5. The use according to claim **4**, wherein said mast cell inhibitor is chosen from the group consisting of: masitinib, imatinib, cromolyn sodium, midostaurin, BLU-285, bosutinib, ibrutinib, LAS189386, DP-2618, fostamatinib, nilotinib, dasatinib, sunitinib, axitinib, pazopanib, and toceranib.

6. The use according to any one of claims **1** to **4**, wherein said inhibitor is an inhibitor of microglia cell activity.

7. The use according to claim **6**, wherein said microglia cell inhibitor is chosen from the group consisting of: masitinib, GW2580, pexidartinib, BLZ945, linifanib, OSI-930, imatinib, sunitinib, nilotinib, pazopanib, emactuzumab, FPA008, quizartinib, axitinib, motesanib, cediranib, JNJ-28312141, Ki-20227, MLN-518, sorafenib, and SU-14813.

8. The use according to any one of claims **1** to **7**, wherein said inhibitor is a 2-aminoarylthiazole derivative.

9. The use according to any one of claims **1** to **8**, wherein said inhibitor is masitinib or a pharmaceutically acceptable salt or solvate thereof, preferably masitinib mesilate.

10. The use according to any one of claims **1** to **9,** wherein said inhibitor, preferably masitinib or a pharmaceutically acceptable salt or solvate thereof, and more preferably masitinib mesilate, is to be administered at a dose ranging from about 1.0 to about 9.0 mg/kg/day (mg per kilo body weight per day); preferably at an initial dose of 3.0 mg/kg/day during at least 4 weeks, then 4.5 mg/kg/day during at least 4 weeks, and at 6.0 mg/kg/day thereafter, with each dose escalation being subjected to toxicity controls.

11. The use according to any one of claims **1** to **10**, wherein said inhibitor, preferably masitinib or a pharmaceutically acceptable salt or solvate thereof, and more preferably masitinib mesilate, is to be administered at a dose of 4.5 mg/kg/day.

12. The use according to any one of claims **1** to **10**, wherein said inhibitor, preferably masitinib or a pharmaceutically acceptable salt or solvate thereof, and more preferably masitinib mesilate, is to be administered at a dose of 6 mg/kg/day.

13. The use according to any one of claims **1** to **12**, wherein said inhibitor, preferably masitinib mesilate, is to be administered in two daily intakes.

14. The use according to any one of claims **1** to **13**, wherein said inhibitor, preferably masitinib mesilate, is to be administered orally.

15. The use according to any one of claims **1** to **14**, wherein said inhibitor is to be administered in combination with at least one other pharmaceutically active ingredient.

16. The use according to claim **15**, wherein said other pharmaceutically active ingredient is an antiglutamate compound, especially riluzole, topiramate, gabapentin, lamotrigine, talampanel, ceftriaxone, an inhibitor of glutamate carboxypeptidase II, preferably said other pharmaceutically active ingredient is riluzole.