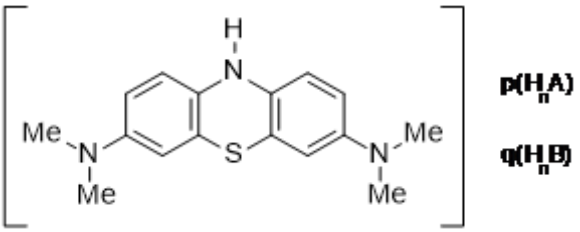
Nevertheless it is well known that there is inter-individual variability between subjects in respect of how a given dosage of a drug will translate into the concentration of the drug in the subject's body fluids. It is advantageous that any dosing regimen which is to be applied to populations of such subjects can as far as possible take such variability into account, in order to ensure maximal therapeutic benefit for all subjects, without the need for personalised regimes, and while nevertheless maintaining a desirable clinical profile.

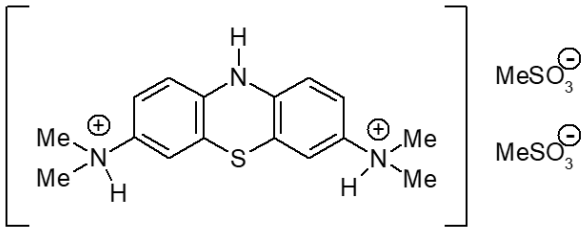
Summary

In one aspect, the present disclosure refers to a use of a methylthioninium ("MT")-containing compound in the manufacture of a medicament for therapeutic or prophylactic treatment of a neurodegenerative disorder in a human subject, wherein the subject is to be orally administered the MT-containing compound, wherein said administration provides a total daily oral dose of between 20.5 and 60 mg of MT to the subject per day, optionally split into 2 or more doses, wherein the MT-containing compound is an LMTX compound of the following formula:



wherein each of H_nA and H_nB (where present) are protic acids which may be the same or different, and wherein p = 1 or 2; q = 0 or 1; n = 1 or 2; (p + q) × n = 2, and wherein the disorder is selected from: (i) a synucleinopathy, which is optionally selected from Parkinson's disease, dementia with Lewy bodies and multiple system atrophy; or (ii) an FTLD syndrome; or (iii) a polyglutamine disorder, which is optionally selected from Huntington's disease, spinal bulbar muscular atrophy, dentatorubropallidoluysian atrophy or spinocerebellar ataxias; or (iv) hereditary cerebral angiopathy, amyotrophic lateral sclerosis, familial encephalopathy with neuronal inclusion bodies or Lafora disease, and wherein the therapeutic treatment is not combined with an acetylcholinesterase inhibitor or an N-methyl-D-aspartate receptor antagonist.

In another aspect, the present disclosure refers to a use of a methylthioninium ("MT")-containing compound in the manufacture of a medicament for therapeutic or prophylactic treatment of a neurodegenerative disorder in a human subject, wherein the subject is to be orally administered the MT-containing compound, wherein said administration provides a total daily oral dose of between 20.5 and 60 mg of MT to the subject per day, optionally split into 2 or more doses, wherein the MT-containing compound is LMTM:



and wherein the disorder is mild cognitive impairment.

Disclosure of the invention

The present inventors have devised a novel pharmacokinetic (PK) model for dosing MT compounds in patient populations. This versatile model was derived from a Phase 1 study in elderly volunteers, and is described in the Examples hereinafter.

The novel population PK model was then used to estimate Cmax of parent MT in patients who received LMTM in the two phase 3 trials of AD studies described in WO2018/019823 (Studies “005” and “015”, for treatment of mild, or mild to moderate, AD patients respectively). Once the Cmax was estimated in each of the subjects, a distribution of Cmax estimates for each of the treated population could be derived.

As expected, there was substantial variability in the MT Cmax values across the population for the given low dosage. Analysis of this distribution confirmed the findings in WO2018/019823 that low dosages (4 mg MT bid) were efficacious (as measured, for example, by reduced decline on the Alzheimer’s Disease Assessment Scale – cognitive subscale (ADAS-cog). It further confirmed that monotherapy gave a substantial benefit by this criterion compared to add-on therapy with AChEIs and\or memantine (with the mean benefit of between monotherapy and add-on being ~ 4 ADAS-cog units over 65 weeks) (see Figure 3a).

However, unexpectedly in view of the published literature which described a lack of recognisable *dose* response, the novel analysis revealed that there exists a *concentration* response within the low dose treated population. This can be shown for patients receiving the 8 mg/day using a sigmoid E_{max} analysis for for ADAS-cog_{11} decline over 65 weeks in patients pooled from Studies 015 and 005 (Figure 12).

Based on a *median* Cmax threshold split of the population, the group of individuals with “high” estimated Cmax showed an improvement of around ~ 2 to 3 ADAS-cog units compared to the group of individuals with “low” estimated Cmax (see Figure 3a).

However based on splitting of patients according to the threshold of 0.373 ng/ml, that encompasses the 35% of patients with the lowest values, the treatment difference in patients receiving the 8 mg/day dose is -3.4 ADAS-cog units (see Figure 14).

These insights suggest that it is advantageous to adopt a dosing regimen which both maximises the proportion of subjects in which the MT concentration will exceed the C_{max} or C_{ave} threshold, and also maximises the expected therapeutic efficacy of LMTM whether it is taken alone or in combination with (or at least preceded by) symptomatic treatments, while

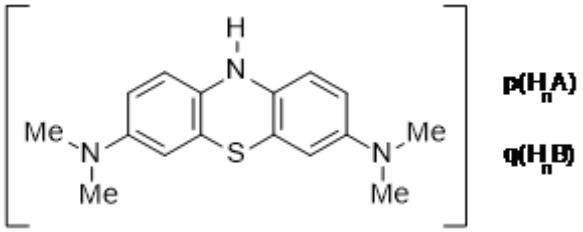
Claims

1 Use of a methylthioninium ("MT")-containing compound in the manufacture of a medicament for therapeutic or prophylactic treatment of a neurodegenerative disorder in a human subject,

wherein the subject is to be orally administered the MT-containing compound,

wherein said administration provides a total daily oral dose of between 20.5 and 60 mg of MT to the subject per day, optionally split into 2 or more doses,

wherein the MT-containing compound is an LMTX compound of the following formula:



wherein each of H_nA and H_nB (where present) are protic acids which may be the same or different,

and wherein p = 1 or 2; q = 0 or 1; n = 1 or 2; (p + q) × n = 2,

and wherein the disorder is selected from:

(i) a synucleinopathy, which is optionally selected from Parkinson's disease, dementia with Lewy bodies and multiple system atrophy; or

(ii) an FTLD syndrome; or

(iii) a polyglutamine disorder, which is optionally selected from Huntington’s disease, spinal bulbar muscular atrophy, dentatorubropallidoluysian atrophy or spinocerebellar ataxias; or

(iv) hereditary cerebral angiopathy, amyotrophic lateral sclerosis, familial encephalopathy with neuronal inclusion bodies or Lafora disease,

and wherein the therapeutic treatment is not combined with an acetylcholinesterase inhibitor or an N-methyl-D-aspartate receptor antagonist.

***

2 The use as claimed in claim 1 wherein the disorder is an FTLD syndrome which is:

(i) a TAR DNA-binding protein 43 (TDP-43) proteinopathy; and/or

(ii) FTLD with tau pathology or FTLD with TDP-43 pathology; and/or

(iii) selected from behavioral-variant frontotemporal dementia (bvFTD), primary progressive aphasia, and semantic dementia.

***

3 The use as claimed in claim 1 wherein the disorder is a polyglutamine disorder, which is optionally selected from Huntington’s disease, spinal bulbar muscular atrophy, dentatorubropallidoluysian atrophy or spinocerebellar ataxias.

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4 The use as claimed in claim 1 wherein the disorder is a synucleinopathy, which is optionally selected from Parkinson's disease, dementia with Lewy bodies and multiple system atrophy.

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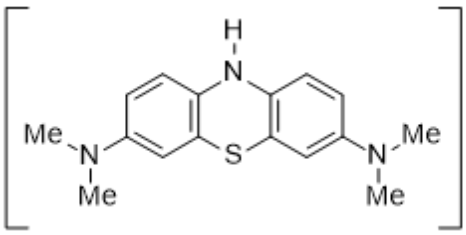
5 The use as claimed in claim 1 wherein the disorder is hereditary cerebral angiopathy, amyotrophic lateral sclerosis, familial encephalopathy with neuronal inclusion bodies or Lafora disease.

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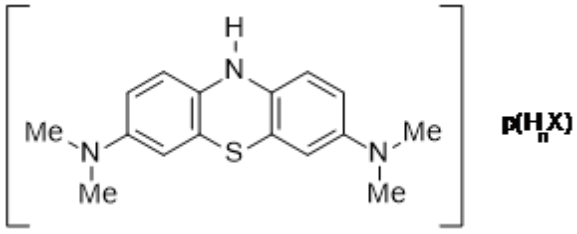
6 The use as claimed in claim 2 wherein the FTLD syndrome is behavioral-variant frontotemporal dementia (bvFTD) optionally where the total daily dose is between 20.5 and 40 mg of MT to the subject per day, optionally split into 2 or more doses.

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7 The use as claimed in any one of claims 1-6 wherein the MT-containing compound has the following formula, where HA and HB are different mono-protic acids:

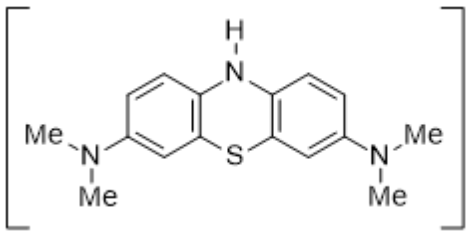


8 The use as claimed in any one of claims 1-6 wherein the MT-containing compound has the following formula:



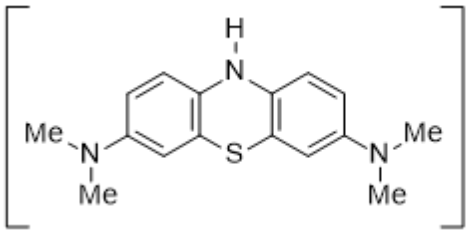
wherein each of H_nX is a protic acid.

9 The use as claimed in any one of claims 1-6 wherein the MT-containing compound has the following formula and H_2A is a di-protic acid:



H_2A

10 The use as claimed in claim 8 wherein the MT-containing compound has the following formula and is a bis-monoprotic acid:



2(HA)

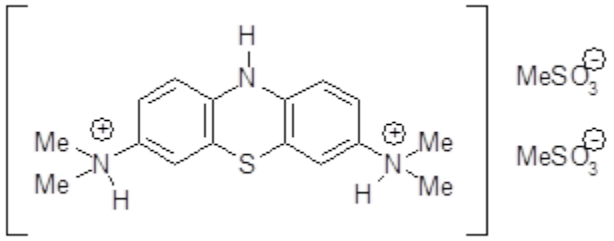
11 The use as claimed in any one of claims 1-10 wherein the or each protic acid is an inorganic acid.

12 The use as claimed in claim 11 wherein each protic acid is a hydrohalide acid.

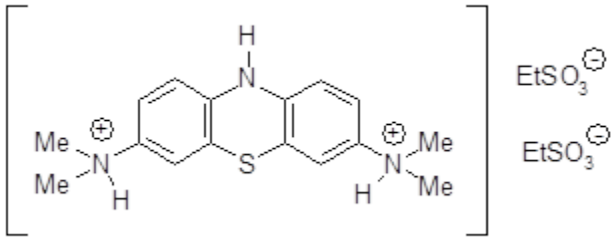
13 The use as claimed in any one of claims 1-10 wherein the or each protic acid is an organic acid.

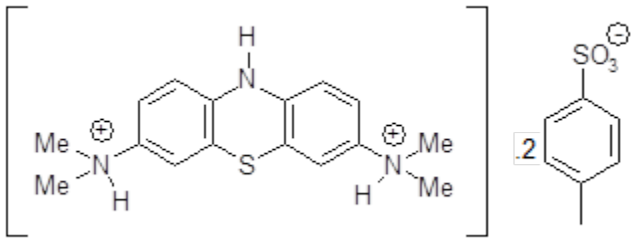
14 The use as claimed in claim 11 or claim 13 wherein the or each protic acid is selected from H_2CO_3; CH_3COOH; methanesulfonic acid, 1,2-ethanedisulfonic acid, ethansulfonic acid, naphthalenedisulfonic acid, p-toluenesulfonic acid.

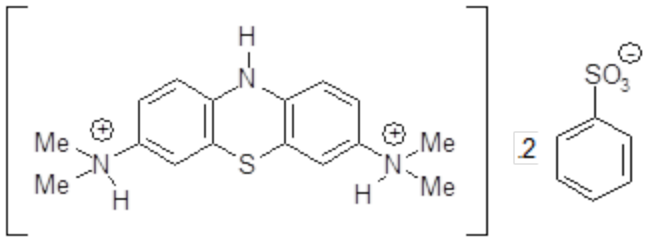
15 The use as claimed in any one of claims 1-6 wherein the MT-containing compound is LMTM:

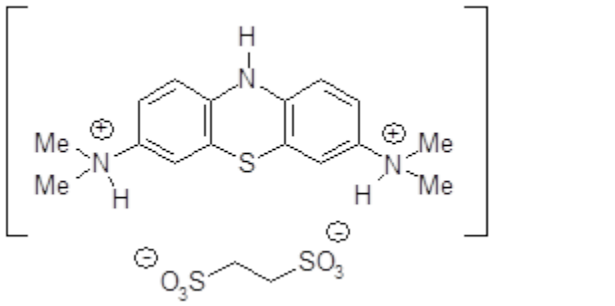


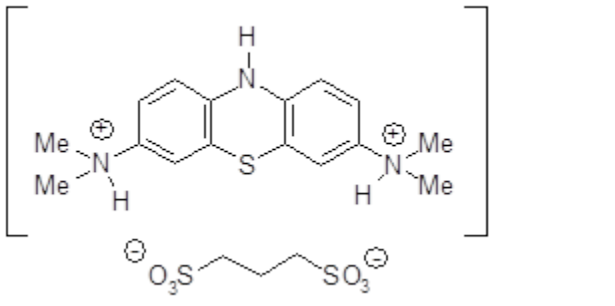
16 The use as claimed in any one of claims 1-6 wherein the MT-containing compound is selected from the list consisting of:

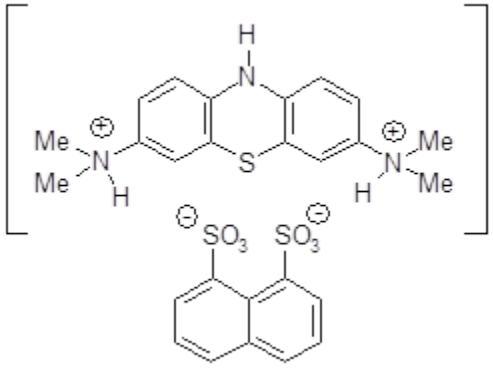












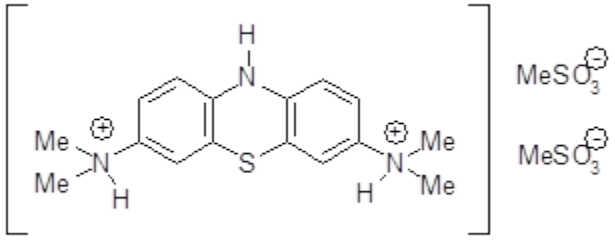
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17 Use of a methylthioninium ("MT")-containing compound in the manufacture of a medicament for therapeutic or prophylactic treatment of a neurodegenerative disorder in a human subject,

wherein the subject is to be orally administered the MT-containing compound,

wherein said administration provides a total daily oral dose of between 20.5 and 60 mg of MT to the subject per day, optionally split into 2 or more doses,

wherein the MT-containing compound is LMTM:



and wherein the disorder is mild cognitive impairment.

18 The use as claimed in claim 17 wherein the therapeutic treatment is not combined with an acetylcholinesterase inhibitor or an N-methyl-D-aspartate receptor antagonist.

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19 The use as claimed in claim 17 wherein the therapeutic treatment is combined with an acetylcholinesterase inhibitor or an N-methyl-D-aspartate receptor antagonist.

20 The use as claimed in claim 19, wherein the acetylcholinesterase inhibitor is selected from the list consisting of donepezil; rivastigmine; and galantamine and/or the N-methyl-D-aspartate receptor (NMDA) receptor antagonist memantine.

21 The use as claimed in any one of claims 17-20 wherein the treatment is a combination treatment of a first agent which is the MT-containing compound at the specified dosage in combination with a second agent which is an inhibitor of the processing of amyloid precursor protein to beta-amyloid.

22 The use as claimed in any one of claims 17-21 wherein the treatment achieves or is for achieving a reduction in cognitive decline in the subject, which is optionally an at least 1, 2, 2.5, 3, 4, 5 or 6-point reduction in decline on the 11-item Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) over a 65-week period.

23 The use as claimed in any one of claims 17-22 wherein the treatment is part of a treatment regimen which comprises:
(i) treatment of said subject with the MT-containing compound for a first period of time, wherein said administration provides a total daily dose of between 1 and 10 mg of MT to the subject per day, optionally 8 mg per day, optionally split into 2 or more doses;
(ii) treatment of said subject with the MT-containing compound for a further period of time, wherein said administration provides a total daily dose of between 20.5 and 40, 20.5 and 60, 20.5 and 80 or 20.5 and 100 mg of MT to the subject per day, optionally split into 2 or more doses.

24 The use as claimed in any one of claims 1-23 wherein the subject is a human who has been diagnosed as having said neurodegenerative disorder, or wherein said method comprises making said diagnosis.

25 The use as claimed in any one of claims 1-23 wherein the subject is a human who has been assessed as being susceptible to, or at risk of, the disorder, optionally based on familial or genetic or other data.

26 The use as claimed in any one of claims 1-25 wherein the total daily dosage of MT is 21 to 40mg; 21 to 32 mg; or 24 to 32 mg.

27 The use as claimed in any one of claims 1-26 wherein the total daily dose is about 20.5, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40 mg.

28 The use as claimed in any one of claims 1-27 wherein the total daily dose of the MT-containing compound is to be administered once a day, or as a split dose twice a day or three times a day.

29 The use as claimed in any one of claims 1-28 wherein the subject:
(a) has not historically received treatment with an acetylcholinesterase inhibitor or an N-methyl-D-aspartate receptor antagonist; or
(b) has historically received treatment with an acetylcholinesterase inhibitor or an N-methyl-D-aspartate receptor antagonist, but ceased that treatment at least 1, 2, 3, 4, 5, 6, 7 days, or 2, 3, 4, 5, 6, 7, 8, weeks prior to treatment with the MT-containing compound; or
(c) is selected as one who is receiving treatment with an acetylcholinesterase inhibitor or an N-methyl-D-aspartate receptor antagonist, wherein said treatment is discontinued prior to treatment with the MT-containing compound.