(19) DANMARK

(10) DK/EP 3731815 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *A 61 K 9/14 (2006.01)* *A 61 K 31/135 (2006.01)* *A 61 P 25/24 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2022-02-28**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2021-12-08**

(86) Europæisk ansøgning nr.: **18773471.0**

(86) Europæisk indleveringsdag: **2018-09-28**

(87) Den europæiske ansøgnings publiceringsdag: **2020-11-04**

(86) International ansøgning nr.: **EP2018076394**

(87) Internationalt publikationsnr.: **WO2019129397**

(30) Prioritet: **2017-12-29 EP 17461651**

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

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(54) Benævnelse: **TØRPULVER-KETAMINSAMMENSÆTNING TIL ANVENDELSE I BEHANDLINGEN AF DEPRESSION VIA PULMONAL INDGIVELSE**

(56) Fremdragne publikationer:
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US-A1- 2013 236 573
KELLY JONKMAN ET AL: "Pharmacokinetics and Bioavailability of Inhaled Esketamine in Healthy Volunteers :", ANESTHESIOLOGY., vol. 127, no. 4, 1 October 2017 (2017-10-01), pages 675-683, XP055460101, PHILADELPHIA, PA, US ISSN: 0003-3022, DOI: 10.1097/ALN.0000000000001798

DESCRIPTION

Technical field

[0001] The present invention relates to a composition comprising ketamine, in particular dry powder formulation for use in a method of treatment of depression by pulmonary administration.

Prior art

[0002] Depression, especially major depressive disorder, bipolar disorder and treatment-resistant depression (TRD) is a serious problem in a modern society. Many treatment options have been developed for treating depression, including monotherapy or combination therapy in a convenient for patients oral administration regimen. However, there is a relatively high percentage of patients that are treatment-refractory or partially or totally treatment-resistant to existing antidepressants. In practice, at present the only real choice in such severe cases can be electroshocks.

[0003] Ketamine is a known anesthetic and analgetic, used for anesthesia and in the treatment of chronic pain. Ketamine is a chiral compound and can exist as a racemate and as S-enantiomer (known as esketamine) or R-enantiomer (known as arketamine). Ketamine can form a pharmaceutically acceptable salts and in pharmaceutical applications is generally used as preferred hydrochloride salt. The optical rotation of an enantiomer varies between ketamine and its salts. For example, while esketamine free base is dextrarotatory S-(+), esketamine hydrochloride is levorotatory S-(-).

[0004] Since about one decade antidepressant activity of ketamine and its S-isomer (esketamine) is explored, especially in the treatment of treatment-resistant or treatment refractory depression (G. Serafini et al., The Role of Ketamine in Treatment-Resistant Depression: A Systematic Review., Current Neuropharmacology, 2014, 12, 444-461). Treatment-resistant depression is a term used in clinical psychiatry to describe cases of major depressive disorder that do not respond adequately to appropriate courses of at least two antidepressants in a suitable dose for a suitable time.

[0005] Data collected up to now show exceptional properties of ketamine and esketamine. The effect is very quick (after 2-3 hours from administration) and relatively long-lasting - a few days after single dose of a medicament. The rapidity of the clinical effect is surprisingly high and unexpected, since the effect of antidepressants present on the market appears after at least two weeks, even three to four weeks of day-to-day administration. Therefore, ketamine or esketamine could be used as a drug of first choice in patients with major depression with enhanced suicide risk that are resistant to existing oral antidepressants. The scale of the effect

is also very high; about 2/3 of the patients with treatment-resistant depression is responsive to ketamine treatment.

[0006] The knowledge of the pharmacology of ketamine is still poor. As a dissociative anesthetic, the drug may exert dissociative and psychomimetic effects (DP). Available data show that this effects are correlated with systemic concentration of the drug. Dissociative and psychomimetic effects are among most often observed side-effects and significantly lower the comfort of patients. However, there are still groups of patients that respond to the treatment with ketamine without experiencing DP effects. Hence, still exists a therapeutic window, although narrow, for effective and safe use of ketamine in the treatment of depression without DP.

[0007] Ketamine undergoes extensive first-pass metabolism effect in the liver. Primarily, norketamine is produced as the initial metabolite. Norketamine is then metabolized to further metabolites. The knowledge about norketamine and further metabolites is still not full. On the level of action on NMDA receptor norketamine is many times less active than ketamine. Other metabolites are also mostly less active than ketamine. Furthermore, little is known about toxicity of norketamine and other metabolites. This, in combination with high individual variations of their concentrations dependent on the status of hepatic enzymes, as a rule makes them undesired compounds. There are also reports on correlation of some hydroxylated metabolites of ketamine with psychotic and dissociative symptoms.

[0008] In previous studies ketamine and esketamine were administered in the treatment of depression intravenously or intranasally. Attempts of oral administration were generally unsuccessful or the effects were observed only after several weeks of administration.

[0009] Literature describes many examples of ketamine pharmacokinetics depending on the administration route.

[0010] Administration route with currently expected minimum level of metabolites is an intravenous one. After intravenous infusion of racemic ketamine at 0.5 mg/kg for 40 minutes, the parent drug maintains its systemic concentration about 200 ng/ml for about 40 minutes, afterwards the concentration falls down quickly with a half-period below 2 hours. Simultaneously, norketamine reaches its maximum concentration at the level of 10-20% of ketamine concentration. The percentage of area-under-curve (AUC) norketamine to ketamine is about 20-40%.

[0011] Oral administration is the administration route, after which maximum concentration of metabolites is expected. However, after oral administration the drug rapidly undergoes metabolism to norketamine. Norketamine level is equal to 500-1000% of ketamine level. Area-under-curve (AUC) for norketamine is even higher, exceeding 1000%.

[0012] The bioavailability of orally administered ketamine is very low (ca. 16-20%); while intravenous administration results in marked increase in ketamine bioavailability, it has also

many disadvantages (e.g. long-time of infusion, patient discomfort, need for surveillance).

[0013] US2007/0287753A1 discloses the use of ketamine for treating treatment-resistant or refractory depression. The only formulation tested is the intravenous infusion, and transdermal administration is contemplated as well. Intranasal administration is only generally described, including intranasal administration of a dry powder aerosol formulation comprising finely divided powder of ketamine, a dispersant and bulking agent. However, with intranasal administration ketamine to oropharyngeal area significant amounts of ketamine will be swallowed by a patient by oral route and can undergo systemic metabolism to norketamine to cause undesired side effects.

[0014] DE102007009888 discloses the use of S-ketamine in the treatment of depression, in the dosage of 0.3 to 1.0 mg/kg. Although all possible administration routes are generally mentioned, the only formulation tested is intravenous infusion, mentioned as the preferred one.

[0015] WO2013/138322 discloses the use of esketamine in the treatment of treatment-refractory or treatment-resistant depression. Test for efficacy of esketamine was described in prophetic example with esketamine intravenous infusion.

[0016] WO2014/143646 and WO2014/152196 disclose pharmaceutical composition of esketamine in the form of the aqueous formulation of esketamine hydrochloride, preferably for nasal administration, for use in the treatment of treatment-refractory or treatment-resistant depression.

[0017] Mucoadhesive oral forms of esketamine and pharmacokinetics of esketamine after oral, intranasal and intravenous administration are described in WO2014/020155.

[0018] K. Jonkman et al., Anesthesiology 127 (4), 675-683, 10, 2017, studied on healthy volunteers the safety and feasibility of delivery of ketamine by inhalation of nebulized esketamine hydrochloride saline solution as a new route of ketamine administration. It has been found that inhaled ketamine bioavailability was reduced due to both dose-independent and dose-dependent impairment of pulmonary uptake. This was related to the high viscosity of esketamine; the viscosity of esketamine is three to four times greater than that of water. Because of this the administration via nebulization will be imprecise and non-reliable.

[0019] Singh et al., Biological Psychiatry 80:424-413, 2016, observed a rapid onset of robust antidepressant effects in patients with treatment resistant depression (TRD) after a 40-minute i.v. infusion of either 0.20 mg/kg or 0.40 mg/kg of esketamine. The lower dose may allow for better tolerability while maintaining efficacy.

[0020] The above illustrates the absolute medical need and importance of development of high-dose ketamine formulation that is both highly effective as well as convenient and easy to everyday self-administration by the patient including self-administration on out-patient basis to ensure high patient compliance. Such a formulation should first of all deliver therapeutic

ketamine dose to the blood, should be characterized with high effectiveness, including rapid therapeutic effect and low risk of undesired effects, such as DP, due to precise dosing. Such a formulation should allow only a minimum level of systemic first-pass metabolites such as norketamine and hydroxylated metabolites, especially assure acceptable (es)ketamine to (es)norketamine ratio, both in view of avoiding reduction of ketamine level actually administered and unwanted metabolites effects.

[0021] The target was to achieve similar ketamine plasma concentration and hence similar antidepressant effect as that by Sing et al. with intravenous infusion of 0.20 mg/kg lasting 40 minutes using route of administration more convenient for a patient and producing less adverse effects.

[0022] The above problems have been solved by the present invention that provides a high-dose and stable dry powder ketamine pharmaceutical composition for use in a method of treatment of depression by pulmonary administration route in a reliable, reproducible and convenient manner.

Summary of the invention

[0023] The invention provides a dry powder pharmaceutical composition comprising ketamine or a pharmaceutically acceptable salt thereof as a medicine for use in a method of treatment of depression by pulmonary administration.

[0024] In another aspect, the invention provides ketamine or its pharmaceutically acceptable salt for use in a method of treatment of depression, wherein ketamine or its pharmaceutically acceptable salt is administered by pulmonary route as a dry powder pharmaceutical formulation.

[0025] In another aspect, the invention provides a method of treatment depression in a subject in need thereof, wherein ketamine or its pharmaceutically acceptable salt is administered to a subject by pulmonary route as a dry powder pharmaceutical formulation.

[0026] The invention will be described in more detail below, with reference to the drawing, wherein:

Figure 1 presents NGI deposition data for the composition of Example 1;

Figure 2 presents NGI deposition data for the composition of Example 2;

Figure 3 presents NGI deposition data for the composition of Example 3;

Figure 4 presents NGI deposition data for the composition of Example 4;

Figure 5 presents NGI deposition data for the composition of Example 5;

Figure 6 presents NGI deposition data for the composition of Example 6;

Figure 7 shows esketamine plasma concentration vs time after administration of various single doses of dry powder composition of Example 2;

Figure 8 shows esketamine plasma concentration vs time after administration of a sequence of single doses of dry powder composition of Example 2; and

Figure 9 presents adverse effect distribution after administration of dry powder composition of Example 2.

Detailed description of the invention

[0027] The object of the invention is a dry powder pharmaceutical composition comprising ketamine or its pharmaceutically acceptable salt as a medicine for use in a method of treatment of depression by pulmonary administration, i.e. administration via pulmonary route.

[0028] Another object of the invention is ketamine or its pharmaceutically acceptable salt for use in a method of treatment of depression, wherein ketamine or its pharmaceutically acceptable salt is administered by pulmonary route as a dry powder pharmaceutical formulation.

[0029] Another object of the invention is a method of treatment of depression in a subject in thereof, wherein ketamine or its pharmaceutically acceptable salt is administered to a subject by pulmonary route as a dry powder pharmaceutical formulation.

[0030] Preferably, in the use according to the invention, esketamine, especially esketamine hydrochloride, is self-administered pulmonary by a patient by inhalation of a dry powder esketamine composition or formulation in a sequence of administrations consisting of multiple single doses (inhalation events), such as at least 3 single doses, each inhalation event consisting of multiple puffs, such as 1, 2, 3 or 4 puffs, preferably in 3 or 4 puffs, said sequences being separated from each other by a break period without any inhalation (rest period). Preferably, such as sequence lasts at least 30 minutes, for example lasts 30 minutes, and includes 3 sequences of administration and break periods between are preferably equal, i.e. are 15 minutes break (rest) period.

[0031] Preferably, in the use according to the invention, esketamine, especially esketamine hydrochloride, is self-administered pulmonary by a patient by inhalation of a dry powder esketamine composition or formulation in a sequence lasting 30 minutes consisting of 3 single doses (inhalation events), each inhalation event consisting of 3 or 4 puffs, wherein each puff corresponds to esketamine nominal dose of 4 mg in the dry powder composition or formulation. Such a composition or formulation is described in Example 2 below. Between such

each inhalation event (single dose) there is provided a break period without any inhalation, preferably there are two equal breaks lasting about 15 minutes, i.e. first single dose is administered at time 0, second single dose is administered after about 15 minutes and the third single dose is administered at 30 minute. Such a sequence allows to obtain plasma concentration profile that provides plasma concentration infusion at the level having antidepressant effect, as known from prior art tests of intravenous infusions.

[0032] According to the invention, the term "ketamine" encompasses racemic ketamine and its enantiomers esketamine and arketamine, both as a free base and pharmaceutically acceptable salts thereof.

[0033] In a preferred embodiment ketamine is esketamine.

[0034] In another embodiment, ketamine is racemic ketamine.

[0035] Preferred pharmaceutically acceptable ketamine salt is hydrochloride.

[0036] In a most preferred embodiment, the composition of the invention comprises esketamine hydrochloride.

[0037] In another embodiment, the composition of the invention comprises racemic ketamine hydrochloride.

[0038] Preferably, in the use according to the invention, ketamine, especially esketamine such as esketamine hydrochloride, is self-administered pulmonary by a patient by inhalation of a dry powder ketamine composition or formulation in a sequence of administrations consisting of multiple single doses (inhalation events), such as at least 3 single doses, each single dose or inhalation event consisting of multiple puffs, such as 1, 2, 3 or 4 puffs, preferably in 3 or 4 puffs, said sequences being separated from each other by a break period without any inhalation (rest period). Preferably, such as sequence lasts at least 30 minutes, for example lasts 30 minutes, and includes 3 sequences of administration and break periods between are preferably equal, i.e. are 15 minutes break (rest) period.

[0039] Preferably, in the use according to the invention, esketamine such as esketamine hydrochloride, is self-administered pulmonary by a patient by inhalation of a dry powder esketamine composition or formulation in a sequence lasting 30 minutes consisting of 3 single doses (inhalation events), each inhalation event consisting of 3 or 4 puffs, wherein each puff corresponds to esketamine nominal dose of 4 mg in the dry powder composition or formulation. Such a composition or formulation is described in Example 2 below. Between such each inhalation event (single dose) there is provided a break period without any inhalation, preferably there are two equal breaks lasting about 15 minutes, i.e. first single dose is administered at time 0, second single dose is administered after about 15 minutes and the third single dose is administered at 30 minute. Such a sequence allows to obtain plasma concentration profile that provides plasma concentration infusion at the level having

antidepressant effect, as known from prior art tests of intravenous infusions.

[0040] The term "medicine" as used herein can be used interchangeably with the term "medicinal product". It should be understood that "medicine" and "medicinal product" have essentially the same meaning in terms of the invention.

[0041] The term "treatment-resistant or treatment refractory depression" (TRD) is well known in the art and means depression in patients not responding to at least two prior attempts of adequate antidepressive treatment using commonly known antidepressant therapies. The term is generally described for example in US8,785,500 and US2015/0056308.

[0042] The term "bipolar disorder" is well known in the art and means a disorder that causes periods of depression and periods of abnormally elevated mood.

[0043] The term "major depression" is well known in the art and means a disorder characterized by at least two weeks of low mood that is present across most situations.

[0044] In one aspect the composition of the invention comprises from 2 mg to 100 mg of ketamine calculated as a free base per nominal unit dose.

[0045] In a particular embodiment, the composition of the invention comprises from 2 mg to 60 mg of ketamine, especially 2 mg to 40 mg of ketamine, such as from 3 mg to 15 mg of ketamine, calculated as a free base, per nominal unit dose.

[0046] In another embodiment, the composition of the invention comprises further one or more additives selected from the group consisting of a carbohydrate bulking agent in the amount of 30 to 95% by weight and a stabilizing agent in the amount of 0.2 - 3% by weight, with respect to the total weight of the composition.

[0047] The composition comprises ketamine, especially esketamine hydrochloride, having median particle diameter d50 of 1 - 10 µm, such as 1 - 8 µm, especially 3 µm, d10 of 0.2 - 5 µm and d90 of 3 - 35 µm.

[0048] Median particle size d_{50} is a parameter obtained by laser diffraction technique with dry dispersion using Sympatec HELOS laser diffractometer attached with ASPIROS feeder. For measurement, raw ketamine, especially esketamine hydrochloride, is dispersed with pressure 3.0 bar in total amount of 30 mg per sample.

[0049] The composition is a dry powder formulation for administration using dry powder inhalers. Conventional and typical dry powder inhalers can be used for this purpose.

[0050] The term "dry powder" is known for a skilled person and should be understood in a manner conventional in the art as a solid mix of particles that is fluidized when the patient inhales after actuation of the inhaler device.

[0051] The term "nominal unit dose" in accordance with the invention relates to the ketamine dose as present (loaded) in the composition that is destined for a single administration. The nominal unit dose can be a measured dose of the dry powder to be ready for the patient to take, contained in a single unit, such as a capsule or single compartment in a blister, or a dose to be taken from for delivery from the multi-dose dry powder reservoir.

[0052] The term "emitted dose" relates to the proportion of the nominal unit dose that exits/leaves the device after inhalation by a patient.

[0053] The dry powder pharmaceutical composition or formulation for use according to the invention may comprise further pharmaceutical excipients., i.e. one or more additives selected from the group consisting of a carbohydrate bulking agent (a carrier) in the amount of 30 to 95% by weight and a stabilizing agent in the amount of 0.2 - 3% by weight, with respect to the total weight of the composition.

[0054] Suitable carbohydrate bulking agent (a carrier) can be lactose, D-mannitol, glucose monohydrate, trehalose, especially trehalose dihydrate, erythritol, dextrose, maltose, sorbitol or xylitol. Especially convenient bulking agent is milled lactose, such as lactose monohydrate or anhydrous lactose, especially lactose monohydrate, having suitable granulometry. Suitable granulometry is defined as having dso 30 - 200 μm (Sympatec HELOS) as the main coarse fraction (especially 80 μm). Examples of suitable lactose monohydrate commercial grades are Lactohale 200 (LH200), Lactohale 100 (LH100) and Lactohale 200LP. Various types of inhalers may require appropriate selection of lactose grade most suitable for performance thereof. Such a selection is within common skills of a skilled person.

[0055] Typical amount of the bulking agent in the composition of the invention is 30 - 95% by weight, especially 30 to 80% by weight, with respect to the total weight of the composition.

[0056] Pharmaceutical excipients/additives include also a stabilizer (also called force control agent - FCA), i.e. a substance that reduces adhesion and cohesion. Suitable stabilizers are for example magnesium stearate, lecithin, and aminoacids, such as leucine. Especially preferred stabilizer is magnesium stearate.

[0057] Stabilizer "disturbs" the weak binding forces between the small particles and thus helps to keep the particles separated, reduces self-adhesion of small particles and also adherence to other particles in the formulation if such other particles are present, reduces the adhesion to the inner surfaces of the inhaler, as well as improves rheological properties of powder - powder flowability.

[0058] The amount of the stabilizer in the composition of the invention is 0.2 - 3% by weight, especially 0.8% by weight, with respect to the total weight of the composition.

[0059] Composition or formulation for use according to the invention is prepared by blending in

a high-shear mixer a bulking agent/carrier of suitable granulometry with a stabilizer, and then adding ketamine, especially esketamine hydrochloride, of suitable granulometry and again blending in a high-shear mixer.

[0060] Alternatively, ketamine, especially esketamine hydrochloride, of suitable granulometry is co-processed (blended) with a stabilizer in a high-shear mixer, and then the bulking agent/carrier is added and again mixed in a high-shear mixer.

[0061] The composition is a dry powder formulation for administration using dry powder inhalers. Conventional and typical dry powder inhalers can be used for this purpose.

[0062] The formulation may be administered by three device categories: single-unit dose inhaler in which each dose, such as in a capsule, is loaded into the device before use; a multi-dose reservoir inhaler in which a bulk supply of dry powder with plurality of doses is preloaded into the device; and a multi-unit dose inhaler in which a plurality of single doses are individually sealed in separate compartments such as in a blister cavity, and discharged each time the device is actuated. Preferred is the multi-unit dose inhaler in which a plurality of single doses are individually sealed, such as in the blister, and discharged each time the device is actuated.

[0063] In one embodiment of the use according to the invention as defined above, the medicine for administration via pulmonary route is a blister with plurality of individual nominal unit doses premetered and individually sealed. One preferred example of such an inhaler is Diskus type inhaler.

[0064] In another embodiment of the use according to the invention as defined above, the medicine for administration via pulmonary route is a capsule with a single nominal unit dose.

[0065] In another embodiment of the use according to the invention as defined above, the medicine for administration of a single dose via pulmonary route is a multi-dose powder reservoir.

[0066] The composition for use according to the invention provides emitted dose of at least 1.0 mg of ketamine calculated as a free base, corresponding to 1.2 mg of ketamine hydrochloride.

[0067] The composition for use according to the invention provides the fraction of the dose delivered locally directly to the lungs that is at least 40%, such as from 40 to 50%, especially 40% to 60%, especially up to 85%, of the emitted unit dose.

[0068] Emitted dose is the portion of nominal unit dose that is emitted from the inhaler device and leaves the inhaler device as an aerosol and hence is available to the patient.

[0069] Only part of emitted dose reaches the lungs and thus circulating blood of a patient as the dose delivered to the lungs (also called Fine Particle Dose - FPD) or fraction delivered to the lungs (also called Fine Particle Fraction - FPF). Some part reaches gastrointestinal tract via

oropharyngeal and oral routes, i.e. is swallowed, and is accessible for undesired first-part metabolism.

[0070] It has been surprisingly found that in spite of well-known problems with inhalation dry powder formulation of high doses of an active substance for pulmonary administration, the uniform and stable high-dose ketamine, especially esketamine hydrochloride dry powder composition can be obtained that when administered by pulmonary route provides therapeutic ketamine level in the circulating blood of a patient, i.e. at least 50 to 100 ng/ml, such as 70 to 100 ng/ml, such as 70-80 ng/ml, such as about 100 ng/ml. Therapeutic ketamine level relates to the level in the blood that is effective in the treatment of depression, especially major depressive disorder, such as treatment resistant or treatment-refractory depression, and may be dependent on the subject, gender, age, severity of the disease, the type of the inhaler, and may vary depending on whether ketamine is racemic ketamine or enantiomeric ketamine.

[0071] The fraction of the emitted dose delivered to the lungs is surprisingly high, in contrast with typical inhalation compositions wherein the standard is that only 15 to 20% of the emitted dose is delivered to the lungs.

[0072] The fraction of the emitted dose delivered locally directly to the lungs (also called Fine Particle Fraction - FPF) can be determined using well-known and conventional methods and assays. Such methods and assays include any of those described in European Pharmacopeia 9.0, Chapter 2.9.18, Preparations for inhalation; Aerodynamic assessment of fine particles for determination of Fine Particle Dose. In particular, the Next Generation Pharmaceutical Impactor (NGI) (Ph. Eur. Apparatus E) can be used to assess and control the aerodynamic particle size distribution (APSD). The NGI apparatus is as presented in Figs 2.9.18.-12 and 2.9.18.-13 on page 333 of European Pharmacopeia 9.0.

[0073] Emitted dose and fine particle dose and fraction (FPF and FPD) are strongly dependent on two factors i.e. on the formulation and on the device. For the device the most discriminatory factor for emitted dose is resistance. The resistance of a dry powder inhaler (DPI) is an intrinsic value which depends on the design of the inhalation channel, the metering cup and the air inlets. DPIs can be classified into four resistance groups (low, medium, medium-high, high) with respect to the inhalation flow required to produce a pressure drop of 4 kPa. This value was chosen because it is the one recommended by pharmacopoeia for the in vitro characterization of the dose emitted from a DPI. Additionally for capsule-based DPIs can be limited by the powder retention in the capsule and device, which lead to reduction in the emitted dose.

[0074] Emitted dose testing is relatively straightforward. The device is 'fired' into a sampling apparatus that enables the capture of the measured dose on a filter. The aerodynamic particle size distribution of inhaled products is measured using the technique of multistage cascade impaction, here Next Generation Impactor (NGI). The collected quantity of active ingredient is determined further by HPLC analysis. The inhalers are tested at a predetermined flow rate, and the pressure drop across the inhaler is 4.0 kPa in line with the Ph Eur.

[0075] Efficient particle capture is ensured by coating the particle collection surface of each of stages 1-7, as well as the MOC and the pre-separator base, with a coating substance. The central cup of the pre-separator is filled with adequate diluent.

[0076] After discharging the powder to the NGI (Number of actuations per impactor n=1 for one analysis) by opening the two-way solenoid valve for the required time at flow control which generate pressure drop across the inhaler 4 kPa the following operations are performed:

1. I. Stages 1 to 7 and MOC. Each stage is washed with appropriate diluent (extraction of drug substance). NGI tray loaded with the cups on a Copley Gentle Rocker is gently shaken for 10 minutes.
2. II. Mouthpiece adapter. Deposited inhalation powder on adapter is rinsed with appropriate diluent a volumetric flask and sonicated for 10 minutes.
3. III. Induction port. Deposited inhalation powder from induction port is rinsed with appropriate diluent into a volumetric flask and sonicated for 10 minutes.
4. IV. Preseparator. Deposited inhalation powder from these component is rinsed with appropriate diluent into a volumetric flask and sonicated for 10 minutes. Finally collected samples from each stage of impactor are filtered analyzed by high-performance liquid chromatography

[0077] Composition of for use according to the invention has an appropriate ketamine, in particular esketamine hydrochloride pharmacokinetics profile that enables achievement of approximately 50 to 100 ng/ml of the ketamine plasma concentration over 40 minutes after pulmonary administration directly to the lungs by inhalation. Said plasma concentration corresponds to antidepressive effect. Maintaining this concentration over time mimics 40-minute intravenous infusion known to be effective in depression and well-tolerated.

[0078] The present invention will now be with reference to the accompanying examples, which are not intended to be limiting.

Examples

General manufacturing procedure:

[0079] A sum of lactose monohydrate and magnesium stearate are sieved through 0.25 mm mesh and mixed in high-shear mixer for 3 minutes. Obtained mixture is sieved with active substance through 0.5 mm mesh and mixed in high-shear mixer for 5 minutes.

[0080] To eliminate electrostatic charges, antistatic PE bags are used during the process.

Vacuum filling process (blisters):

[0081] Vacuum-drum technology dose forming process is used for blister filling. The blister cavity is in volume range of 15 to 45 mm^3 (especially ca. 30 mm^3). Powder which is filled into cavity is in amount of 10 - 30 mg (especially 23 mg).

[0082] During process parameters of vacuum-drum device are:

Vacuum pressure: -0 - 500 mBar, especially 50 - 400 mBar

Fluidization pressure: - 0.1 - -0.4 Bar

Fluidization time: 50 - 2000 ms, especially 50 -300 ms

Filling time: 50 - 700 ms, especially 50 - 400 ms

Sealing time: 100 - 600ms

Sealing tests of filled blisters are performed under vacuum.

[0083] Finally, the blister strips are coiled into the medical device.

Filling process (capsules):

[0084] Capsules to be filled are placed in the sockets closed ends down. Powder is discharged from the dosator and comes directly to the capsules. The powder with which the capsules are to be filled is placed in the dosator, may be tamped and discharged into the capsules.

[0085] During the process parameters of capsule filling device are:

Rotation: 1- 70 rpm

Tamping high: 1 - 10mm

Dosator high: 1 - 250mm

[0086] Finally, the filled capsules are mounted into the medical device.

Ketamine dry inhalation powder for blisters and capsules

[0087] The following compositions has been prepared in accordance with the above general procedure in the scale of 0.9 kg.

Example 1

Component	Amount (mg/unit)
Esketamine hydrochloride	3.45 (corresponds to 2.99 mg esketamine)
Lactose monohydrate LH200 LP	19.16
Magnesium stearate	0.39

Example 2

Component	Amount (mg/unit)
Esketamine hydrochloride	4.61 (corresponds to 4 mg esketamine)
Lactose monohydrate LH200 LP	18.20
Magnesium stearate	0.18

Example 3

Component	Amount (mg/unit)
Esketamine hydrochloride	5.06 (corresponds to 4.39 mg esketamine)
Lactose monohydrate LH200 LP	17.581
Magnesium stearate	0.359

[0088] The compositions have been found uniform in accordance with requirements of Ph.Eur.2.9.40. Average esketamine hydrochloride content (n=10) was in the range 92.5% - 107.5% of nominal dose.

[0089] The process has been found scalable to the scale of 1.8 kg.

[0090] Aerodynamic Particle Size Distribution (APSD) test of the compositions of the Examples 1, 2 and 3 of the invention.

[0091] The compositions of Examples 1, 2 and 3 of the invention have been tested using the Next Generation Pharmaceutical Impactor (NGI) (Ph. Eur. Apparatus E) in accordance with the procedure for powder inhalers.

[0092] The results of the tests are presented in Table 1 below and in Figure 1 (Example 1), Figure 2 (Example 2) and Figure 3 (Example 3) of the drawing, wherein upper diagrams present APSD data for the whole NGI and bottom diagrams present APSD data for stages 1-7 and MOC. The following abbreviations are used for the results of the tests:

MA - mouth adapter

T- induction port

PS - Pre-separator

S1-S7 - stages of NGI

MOC - micro-orifice collector

ISM - Impactor sized mass; mass entering the impactor excluding non-sizing portions

MMAD (μm) - mass median aerodynamic diameter. Defined as the diameter at which 50% of the particles by mass are larger and 50% are smaller.

GSD - geometric standard deviation. Measure of the spread of an aerodynamic particle size distribution

FPF - fine particle fraction (%)

FPD - fine particle dose

Table 1. NGI deposition data

Example No	1	2	3
MA [mg]	0.043	0.194	0.074
T	0.166	0.713	0.740
PS	0.598	0.262	0.825
S1	0.063	0.157	0.179
S2	0.193	0.599	0.541
S3	0.308	0.538	0.588
S4	0.243	0.392	0.345
S5	0.112	0.201	0.179
S6	0.061	0.121	0.105
S7	0.048	0.087	0.070
MOC	0.037	0.054	0.054
ISM (mg)	1.00	1.99	1.88
Total Mass on Impactor (mg)	1.07	2.15	2.06
Total Mass on System (mg)	1.87	3.32	3.70
Mass on Impactor/Actuation (mg)	1.07	2.15	2.06
Mass on System/Actuation (mg)	1.87	3.32	3.70
FPD ≤5.0 mcm (mg) esketamine	1.0	1.7	1.6
FPF ≤5.0 mcm (%)	49.0	51.0	44.0
MMAD (mcm)	2.6	2.9	3.0
GSD	1.8	1.8	1.8

[0093] The obtained results showed a product with expected quality attributes.

[0094] The composition of the invention demonstrated appropriate homogeneity and a very high level of fine particle fractions, with:

FPF > 49%, FPD 1.0 mg; and emitted dose: 2.3 mg, for Example 1

FPF > 47%, FPD: 1.7 mg; and emitted dose: 3.6 mg, for Example 2, and

FPF > 44%, FPD: 1.6 mg; and emitted dose: 3.9 mg, for Example 3.

Esketamine dry inhalation powder for capsules

[0095] The following compositions has been prepared in accordance with the above general procedure in the scale of 0.9 kg.

Example 4

Component	**Amount (mg/unit)**
Esketamine hydrochloride	5.00 (corresponds to 4.34 mg esketamine)
Lactose monohydrate LH200 LP	19.8
Magnesium stearate	0.2

Example 5

Component	**Amount (mg/unit)**
Esketamine hydrochloride esketamine)	10.00 (corresponds to 8.67 mg
Lactose monohydrate LH200 LP	39.6
Magnesium stearate	0.4

Example 6

Component	**Amount (mg/unit)**
Esketamine hydrochloride esketamine)	20.00 (corresponds to 17.34mg
Lactose monohydrate LH200 LP	79.2
Magnesium stearate	0.8

[0096] Aerodynamic Particle Size Distribution (APSD) test of the compositions of Examples 4, 5 and 6 of the invention.

[0097] The compositions of Examples 4, 5 and 6 of the invention have been tested using the Next Generation Pharmaceutical Impactor (NGI) (Ph. Eur. Apparatus E) in accordance with the procedure for powder inhalers.

[0098] The results of the tests are presented in Table 2 below and in Figures (Example 4), Figure 5 (Example 5) and Figure 6 (Example 6) of the drawing, wherein higher diagrams present APSD data for the whole NGI and lower diagrams present APSD data stages 1-7 and MOC.

Table 2. NGI deposition data

Example No	4	5	6
MA [mg]	0.090	0.174	0.329
T	0.655	1.328	2.877
PS	0.262	0.774	1.838
S1	0.368	0.669	1.621
S2	0.915	1.505	3.293
S3	0.631	1.057	2.270
S4	0.449	0.705	1.386
S5	0.273	0.414	0.719
S6	0.167	0.300	0.505
S7	0.108	0.214	0.374
MOC	0.061	0.166	0.283
ISM (mg)	2.61	4.36	8.83
Total Mass on Impactor (mg)	2.97	5.03	10.45
Total Mass on System (mg)	3.98	7.30	15.49
Mass on Impactor/Actuation (mg)	2.97	5.03	10.45
Mass on System/Actuation (mg)	3.98	7.30	15.49
FPD ≤5.0 mcm (mg) esketamine	2.4	3.9	7.9
FPF ≤5.0 mcm (%)	59	54	51
MMAD (mcm)	3.0	3.0	3.2
GSD	1.9	1.9	2.6

[0099] The obtained results showed a product with expected quality attributes.

[0100] The invented formulation demonstrated appropriate homogeneity and a very high level of fine particle fractions, with:

FPF > 59%, FPD 2.4 mg; emitted dose: 4.2 mg, for Example 4

FPF > 54%, FPD: 3.9 mg; emitted dose: 7.1 mg, for Example 5, and

FPF > 51%, FPD: 7.9 mg; emitted dose: 16.5 mg, for Example 6.

[0101] The dry powder pharmaceutical composition of the invention provided emitted esketamine hydrochloride dose at the level up to 97%, such as up to 85% of the nominal dose and at least 40% of fine particle fraction (fraction delivered to the lungs) for emitted esketamine dose.

Example 7

Pharmacokinetics of inhaled esketamine dry powder in healthy volunteers

[0102] Esketamine hydrochloride dry powder formulation of Example 2 was administered to healthy volunteers pulmonary, i.e. directly to the lungs using dry powder inhaler (DPI) (by self-administration).

[0103] One puff of dry powder formulation contained 4.6 mg of esketamine hydrochloride, corresponding to 4 mg of esketamine free base and excipients 18.22 mg of lactose monohydrate and 0.18 mg of magnesium stearate.

[0104] A single dose was an inhalation events consisting of 1 to 6 puffs, i.e. 4 to 24 mg of esketamine free base nominal dose.

[0105] In part A of the study, designed as a one-centre single ascending dose, the medicine was delivered in a single dose once daily (up to 6 consecutive puffs) to 18 healthy volunteer subjects. Subjects were divided into 6 cohorts, cohorts receiving 1, 2, 3, 4, 5 or 6 puffs in a single doses (inhalation events), respectively. Collection of blood samples for determination of esketamine and esnorketamine concentration and calculation of pharmacokinetic parameters was performed for up 24 hours following the start of the test.

[0106] The aim of the study was to determine the amount of puffs needed to obtain plasma concentration similar to that sufficient to achieve antidepressant effect as for 0.20 mg/kg 40 minutes intravenous infusion. It can be predicted on the basis of literature data that this corresponds to concentration at 40 min of infusion between about 60 to 100 ng/ml. It was also the aim to determine the number of puffs that allow to avoid a sharp peak of plasma concentration that is considered an important factor inducing adverse psychomimetic and dissociative effects.

[0107] The results of the part A of the test are presented on Figure 7 that shows esketamine plasma concentration over time after administration of various single doses of dry powder composition of Example 2. As it can be seen, the number of puffs that allows to obtain plasma esketamine concentration sufficient for antidepressant effect and without sharp peak of said concentration was determined to be 1 to 4 puffs, corresponding to 4 to 16 mg of esketamine free base nominal dose.

[0108] Therefore, a single dose (inhalation event) consisting of 1 to 4 puffs was selected for the next Part B of the test.

[0109] In part B of the study the composition of Example 2 was administered to 12 healthy volunteer subjects divided into 4 cohorts in four different single doses each cohort (i.e. each single dose consisting of 1, 2, 3 or 4 puffs, respectively) in one day in the administration sequence consisting of three administrations of single dose (inhalation event) in the period of 30 minutes, Between inhalation events there were 15 minutes break periods, i.e. first single dose was administered at 0 min., second single dose was administered at 15 min, and third single dose was administered at 30 min.

[0110] The aim of Part B was to investigate pharmacokinetic properties of esketamine following different dosing schemes in healthy subjects and determine the scheme that enables achievement of the appropriate plasma concentration over time to mimic the 40-minute intravenous infusion (part B),

[0111] The results of the of the part B of the test are presented on Figure 8 that shows esketamine plasma concentration over time after administration of various single doses of dry powder composition of Example 2 in a sequence of 3 administrations of single doses during 30 minutes. Figure 8 shows also (the area between two bold black lines) a simulation of esketamine plasma concentration after 0.2 mg/kg 40 minutes i.v. infusion.

[0112] As it can be seen form Fig. 8, sequence of administration of 3 single doses consisting of 3 or 4 puffs allowed to obtain plasma concentration profile mimicking quite well esketamine intravenous infusion at the level corresponding to antidepressant effect.

[0113] Both in Part A and Part B of the study the adverse effects were monitored and assessed by a psychiatrist. The summary of the adverse effects is presented in Fig. 9. As can be seen, no serious effects were observed, all adverse effects being assessed as mild, occasionally moderate. Psychomimetic effects were transient, lasting up to 30 minutes following administration. There were no discontinuations due to adverse effects or toxicity.

[0114] The above shows that pulmonary administration of esketamine, i.e. directly to the lungs is a promising way of treating depression, in particular TRD, by convenient self-administration by a patient. Plasma concentration profile is quite smooth, consistent with a target profile and safe for chronic administration.

REFERENCES CITED IN THE DESCRIPTION

Cited references

Patent documents cited in the description

- US20070287753A1 **[0013]**
- DE102007009888 **[0014]**
- WO2013138322A **[0015]**
- WO2014143646A **[0016]**
- WO2014152196A **[0016]**
- WO2014020155A **[0017]**
- US8785500B **[0041]**
- US20150056308A **[0041]**

Non-patent literature cited in the description

- **G. SERAFINI et al.**The Role of Ketamine in Treatment-Resistant Depression: A Systematic ReviewCurrent Neuropharmacology, 2014, vol. 12, 444-461 **[0004]**
- **K. JONKMAN et al.**Anesthesiology, 2017, vol. 127, 4675-683 **[0018]**
- **SINGH et al.**Biological Psychiatry, 2016, vol. 80, 424-413 **[0019]**

Patentkrav

1. Farmaceutisk tørpulversammensætning omfattende ketamin eller farmaceutisk acceptabelt salt deraf til anvendelse i en behandling af depression, via direkte indgivelse til lungerne via pulmonal rute.

2. Ketamin eller farmaceutisk acceptabelt salt deraf til anvendelse i en behandling af depression, hvor ketamin eller det farmaceutisk acceptable salt deraf indgives via pulmonal rute som en farmaceutisk tørpulversammensætning eller som en inhalerbar farmaceutisk tørpulverformulering.

3. Sammensætning eller ketamin til anvendelse ifølge krav 1 eller 2, hvor det farmaceutisk acceptable salt er hydrochlorid.

4. Sammensætning eller ketamin til anvendelse ifølge et hvilket som helst af kravene 1 til 3, hvor ketamin er esketamin-hydrochlorid.

5. Sammensætning eller ketamin til anvendelse ifølge et hvilket som helst af kravene 1 til 4, hvor sammensætningen omfatter fra 2 mg til 100 mg mikroniseret ketamin beregnet som en fri base per nominel enhedsdosis.

6. Sammensætning eller ketamin til anvendelse ifølge krav 5, hvor sammensætningen omfatter fra 2 mg til 40 mg mikroniseret ketamin beregnet som en fri base per nominel enhedsdosis.

7. Sammensætning eller ketamin til anvendelse ifølge krav 6, hvor sammensætningen omfatter 4 mg mikroniseret esketamin beregnet som en fri base per nominel enhedsdosis.

8. Sammensætning eller ketamin til anvendelse ifølge et hvilket som helst af kravene 1 til 7, hvor sammensætningen omfatter et eller flere tilsætningsstoffer valgt fra gruppen bestående af et kulhydratfyldemiddel i en mængde fra 30 til 95 vægt-% og et stabiliseringsmiddel i en mængde fra 0,2 – 3 vægt-%, i forhold til den samlede vægt af sammensætningen.

9. Sammensætning eller ketamin til anvendelse ifølge et hvilket som helst af kravene 1 til 8, hvor sammensætningen omfatter ketamin med gennemsnitlig partikeldiameter d50 på 1 - 10 µm, d10 på 0,2 - 5 µm og d90 på 3 - 35 µm, som målt med laserdiffraktionsteknik.

10. Sammensætning eller ketamin til anvendelse ifølge et hvilket som helst af kravene 5 til 9, hvor sammensætningen tilvejebringer emitteret dosis på mindst 1,0 mg ketamin beregnet som en fri base, svarende til 1,2 mg ketamin-hydrochlorid.

11. Sammensætning eller ketamin til anvendelse ifølge krav 10, hvor fraktionen af den emitterede dosis leveret til lungerne er mindst 40%.

12. Sammensætning eller ketamin til anvendelse ifølge et hvilket som helst af kravene 1 til 11, hvor sammensætningen til indgivelse via pulmonal rute er omfattet i en blisterpakning med en flerhed af individuelle nominelle enhedsdoser præ-doseret og forseglet individuelt.

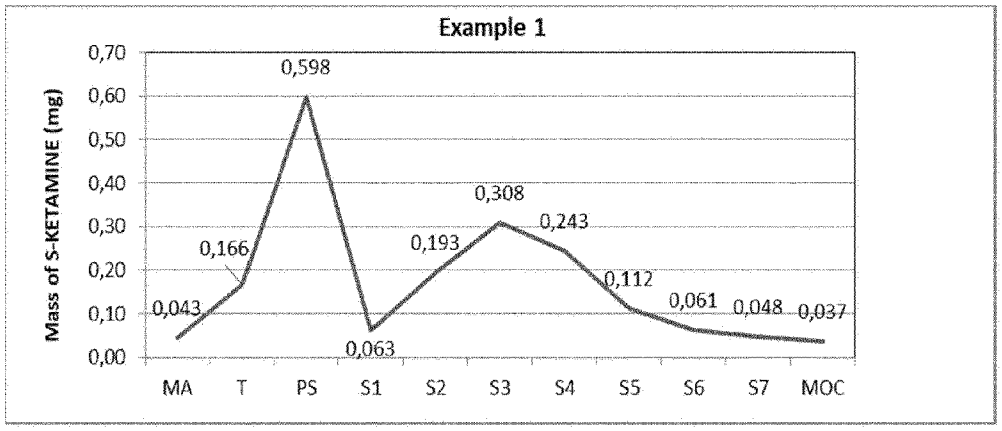
13. Sammensætning eller ketamin til anvendelse ifølge et hvilket som helst af kravene 1 til 11, hvor medicinen til indgivelse via pulmonal rute er omfattet i en kapsel med en enkelt nominel enhedsdosis.

14. Sammensætning eller ketamin til anvendelse ifølge et hvilket som helst af kravene 1 til 11, hvor medicinen til indgivelse via pulmonal rute er omfattet i en flerdosispulverbeholder.

15. Sammensætning eller ketamin til anvendelse ifølge et hvilket som helst af kravene 1 til 14, hvor en patient selv står for pulmonal indgivelse af ketamin, fortrinsvis esketamin, via inhalation af en tørpulver-ketaminsammensætning eller –formulering i en sekvens af indgivelser bestående af flere enkeltdoser, for eksempel såsom en sekvens på mindst 3 enkeltdoser, idet hver enkeltdosis består af flere pust, såsom 1, 2, 3 eller 4 pust, fortrinsvis 3 eller 4 pust, idet nævnte sekvenser er adskilt fra hinanden af en pause uden nogen inhalation.

16. Sammensætning eller ketamin til anvendelse ifølge krav 15, hvor indgivelsen omfatter sekvensen af esketamin i tre enkeltdoser bestående af 3 eller 4 pust i en periode på 30 minutter, idet enkeltdoser er adskilt af pauser på 15 minutter, hvor hvert pust svarer til en nominel esketamin-dosis på 4 mg i tørpulver-sammensætningen eller -formuleringen.

DRAWINGS



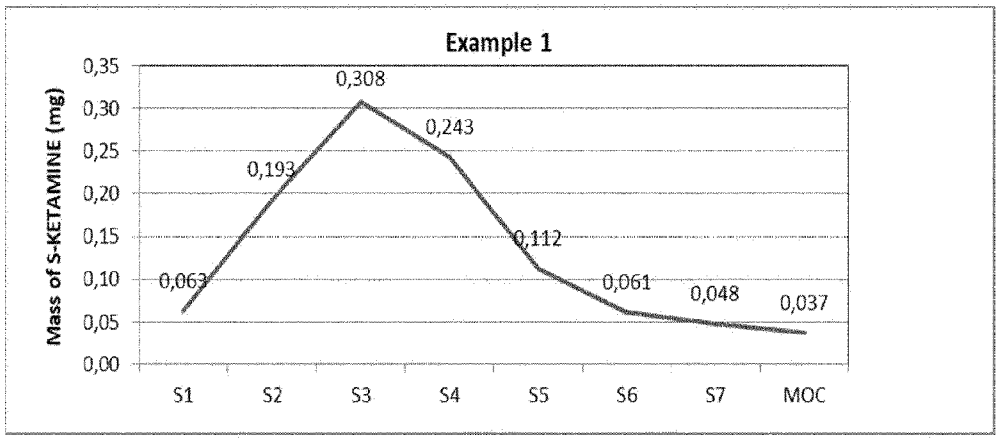
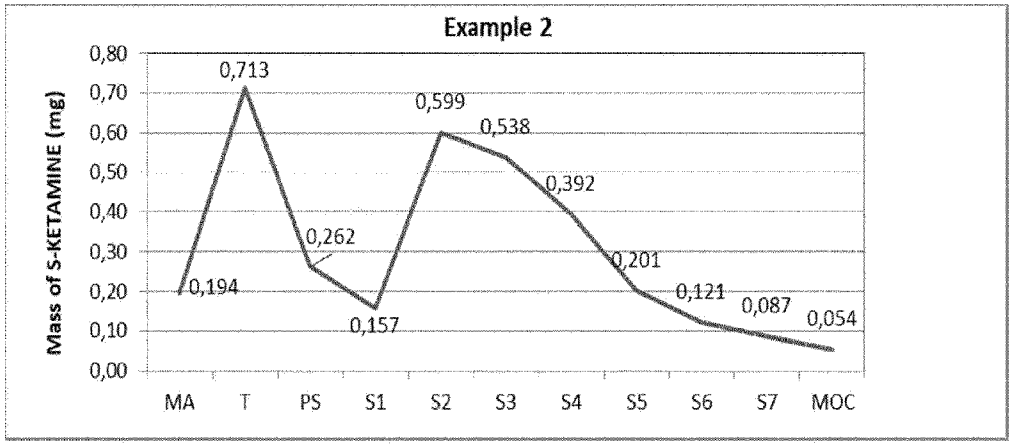


Fig. 1


Example 2
Mass of S-KETAMINE (mg)
0,80
0,70
0,60
0,50
0,40
0,30
0,20
0,10
0,00
0,713
0,599
0,538
0,392
0,262
0,201
0,194
0,121
0,087
0,157
0,054
MA
T
PS
S1
S2
S3
S4
S5
S6
S7
MOC

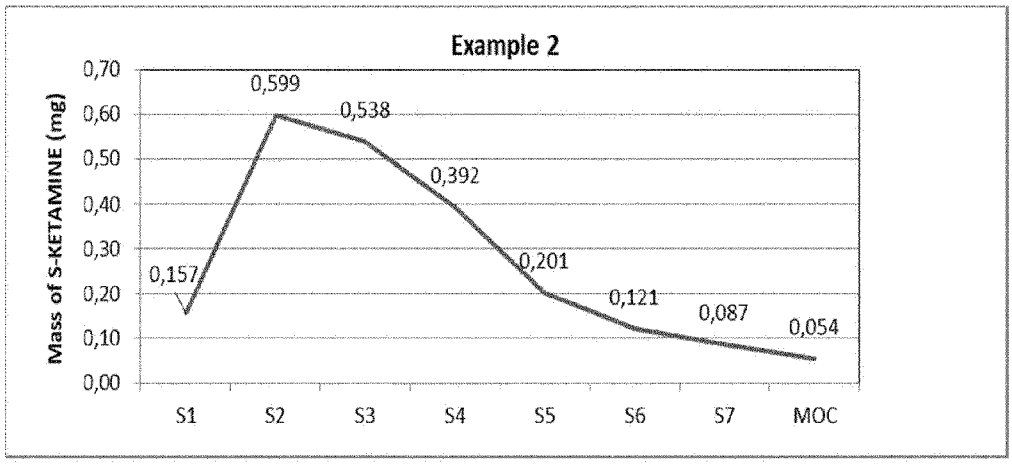
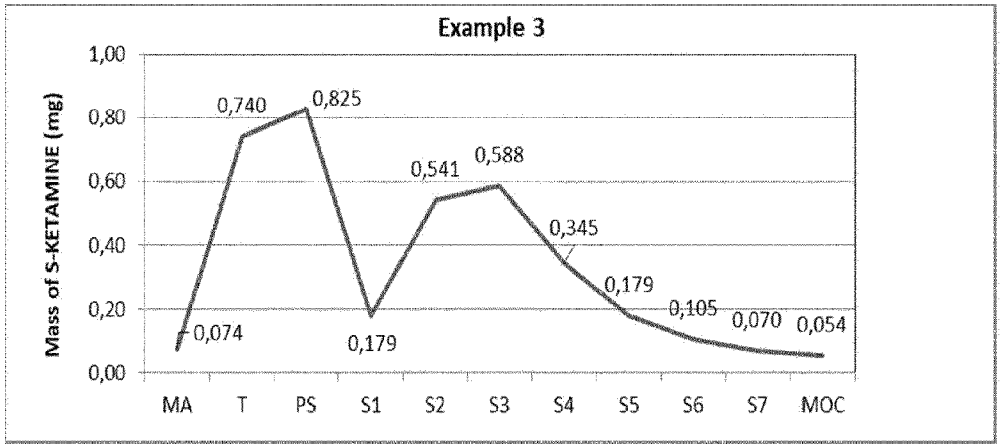

Example 2
Mass of S-KETAMINE (mg)
0,70
0,60
0,50
0,40
0,30
0,20
0,10
0,00
0,599
0,538
0,392
0,157
0,201
0,121
0,087
0,054
S1
S2
S3
S4
S5
S6
S7
MOC

Fig. 2


Example 3
Mass of S-KETAMINE (mg)
1,00
0,80
0,60
0,40
0,20
0,00
0,740
0,825
0,541
0,588
0,345
0,179
0,105
0,070
0,054
0,074
0,179
MA
T
PS
S1
S2
S3
S4
S5
S6
S7
MOC

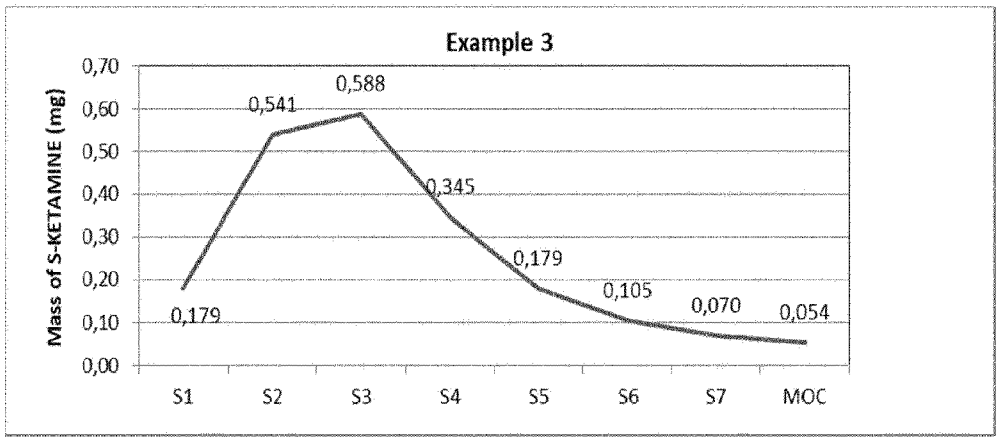
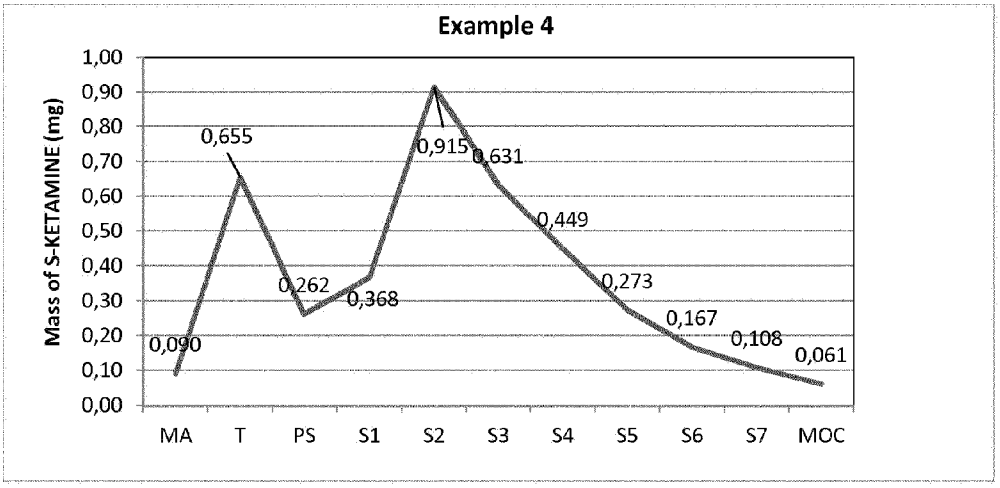

Example 3
Mass of S-KETAMINE (mg)
0,70
0,60
0,50
0,40
0,30
0,20
0,10
0,00
0,588
0,541
0,345
0,179
0,105
0,070
0,054
0,179
S1
S2
S3
S4
S5
S6
S7
MOC

Fig. 3


Example 4
Mass of S-KETAMINE (mg)
1,00
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0,80
0,70
0,60
0,50
0,40
0,30
0,20
0,10
0,00
0,090
0,655
0,262
0,368
0,915
0,631
0,449
0,273
0,167
0,108
0,061
MA
T
PS
S1
S2
S3
S4
S5
S6
S7
MOC

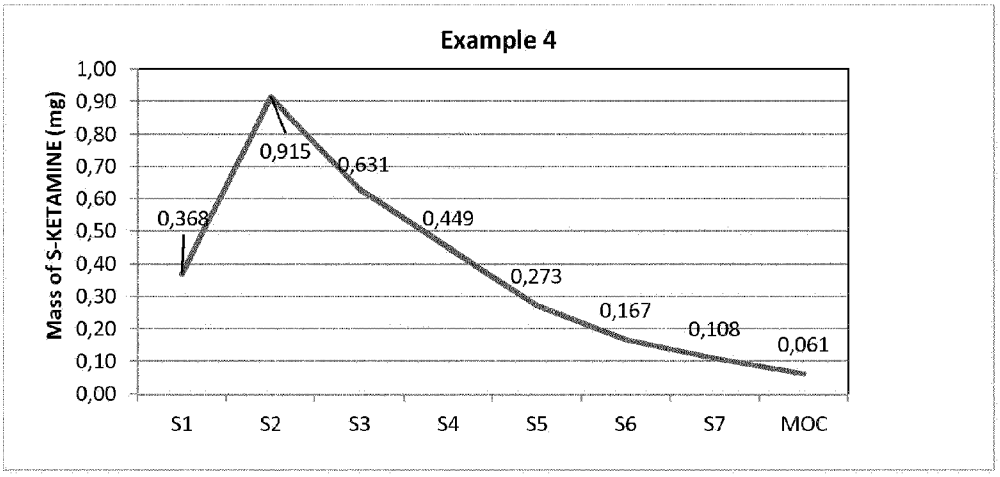
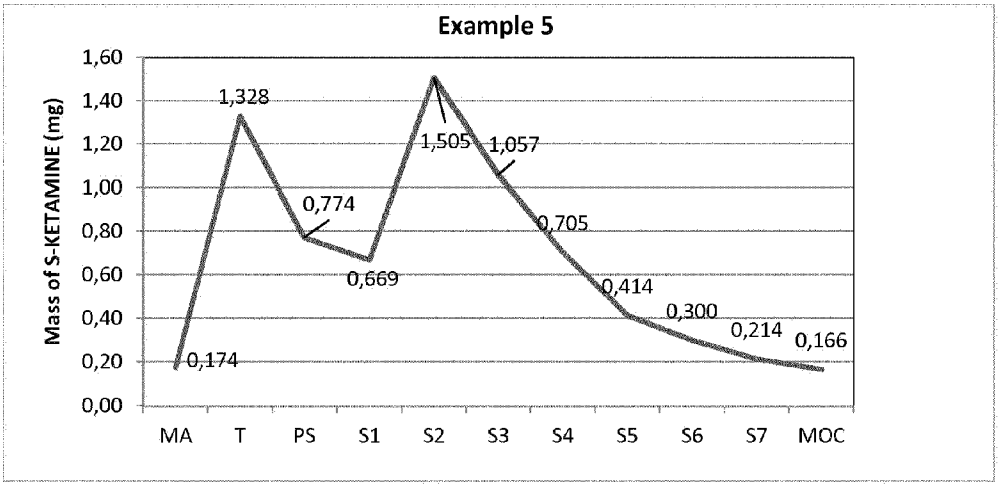

Example 4
Mass of S-KETAMINE (mg)
1,00
0,90
0,80
0,70
0,60
0,50
0,40
0,30
0,20
0,10
0,00
0,368
0,915
0,631
0,449
0,273
0,167
0,108
0,061
S1
S2
S3
S4
S5
S6
S7
MOC

Fig. 4


Example 5
Mass of S-KETAMINE (mg)
1,60
1,40
1,20
1,00
0,80
0,60
0,40
0,20
0,00
1,328
0,774
0,669
1,505
1,057
0,705
0,414
0,300
0,214
0,166
0,174
MA
T
PS
S1
S2
S3
S4
S5
S6
S7
MOC

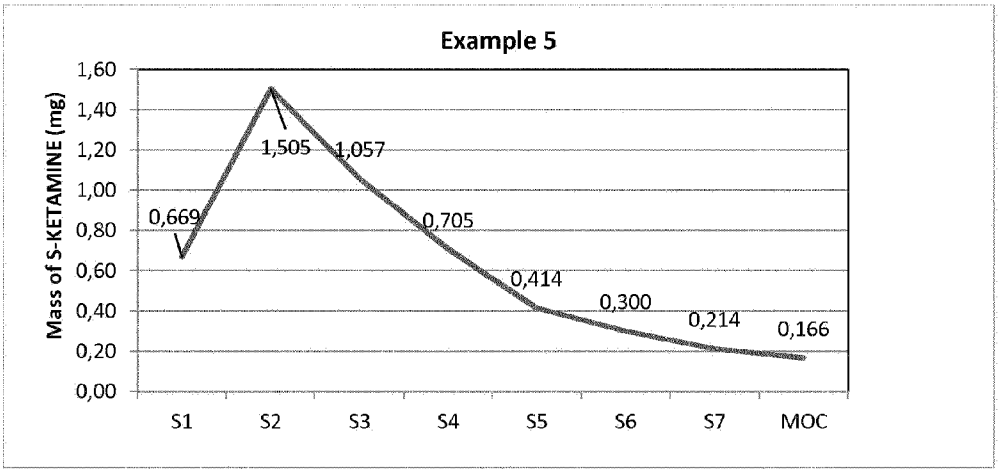
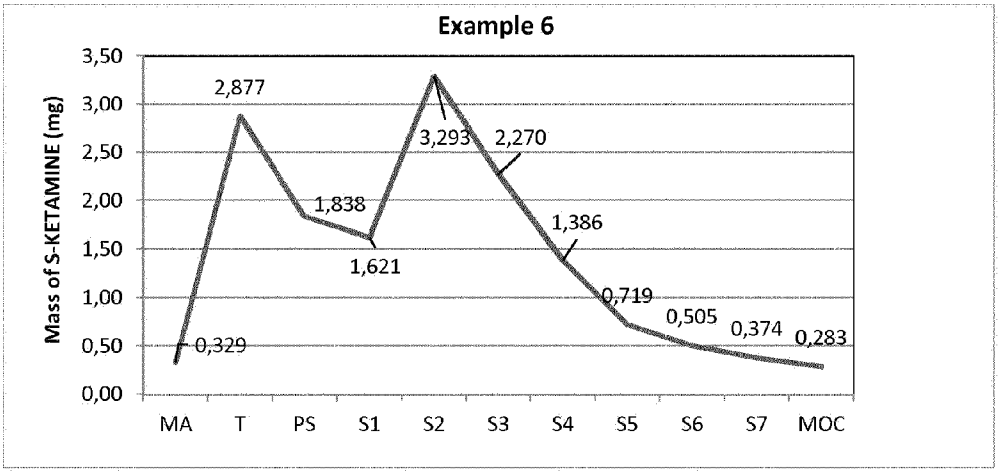
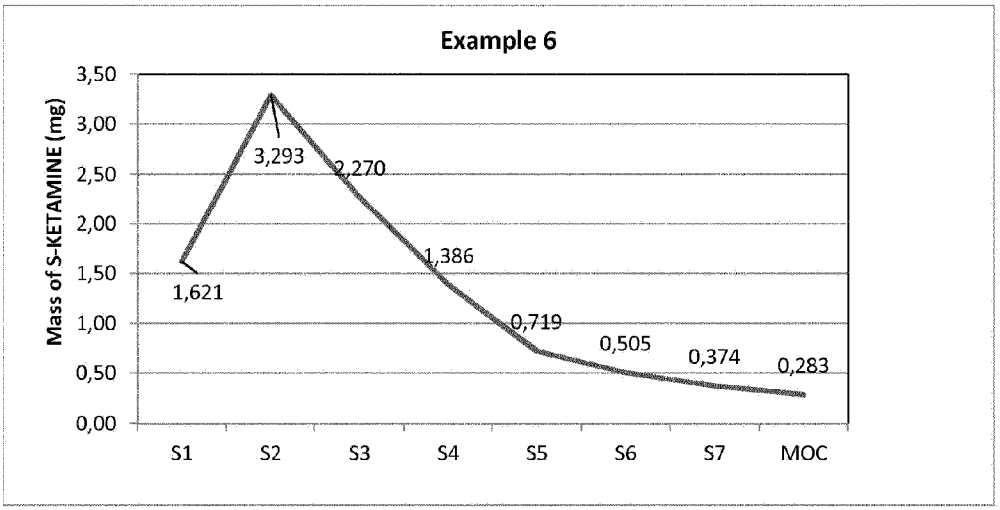

Example 5
Mass of S-KETAMINE (mg)
1,60
1,40
1,20
1,00
0,80
0,60
0,40
0,20
0,00
0,669
1,505
1,057
0,705
0,414
0,300
0,214
0,166
S1
S2
S3
S4
S5
S6
S7
MOC

Fig. 5


Example 6
Mass of S-KETAMINE (mg)
3,50
3,00
2,50
2,00
1,50
1,00
0,50
0,00
2,877
1,838
3,293
2,270
1,386
1,621
0,719
0,505
0,374
0,283
0,329
MA
T
PS
S1
S2
S3
S4
S5
S6
S7
MOC


Example 6
Mass of S-KETAMINE (mg)
3,50
3,00
2,50
2,00
1,50
1,00
0,50
0,00
3,293
2,270
1,386
1,621
0,719
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0,374
0,283
S1
S2
S3
S4
S5
S6
S7
MOC

Fig. 6

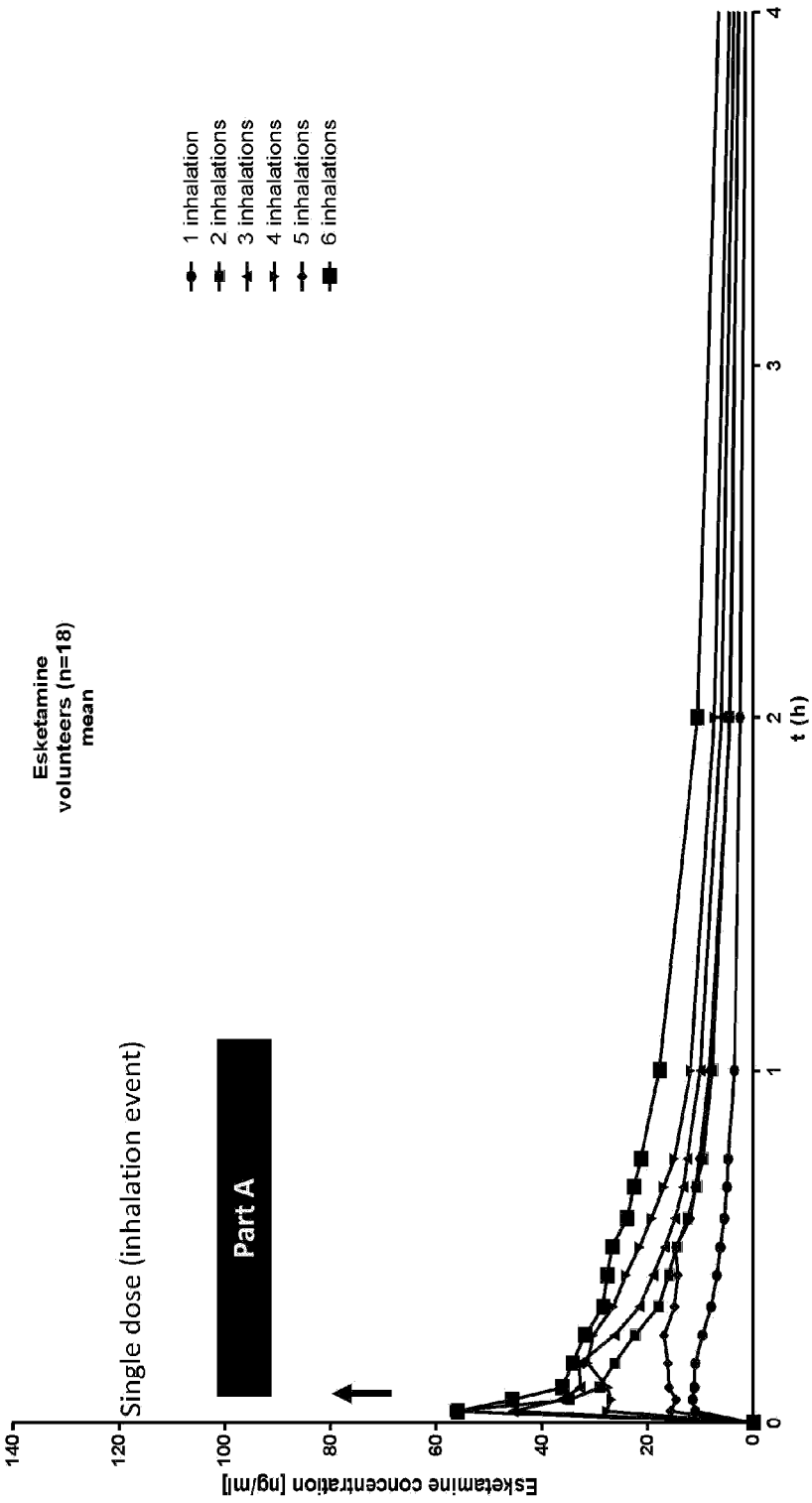
Esketamine volunteers (n=18) mean
1 inhalation
2 inhalations
3 inhalations
4 inhalations
5 inhalations
6 inhalations
Single dose (inhalation event)
Part A
Esketamine concentration [ng/ml]
t (h)
0
20
40
60
80
100
120
140
0
1
2
3
4

Fig. 7

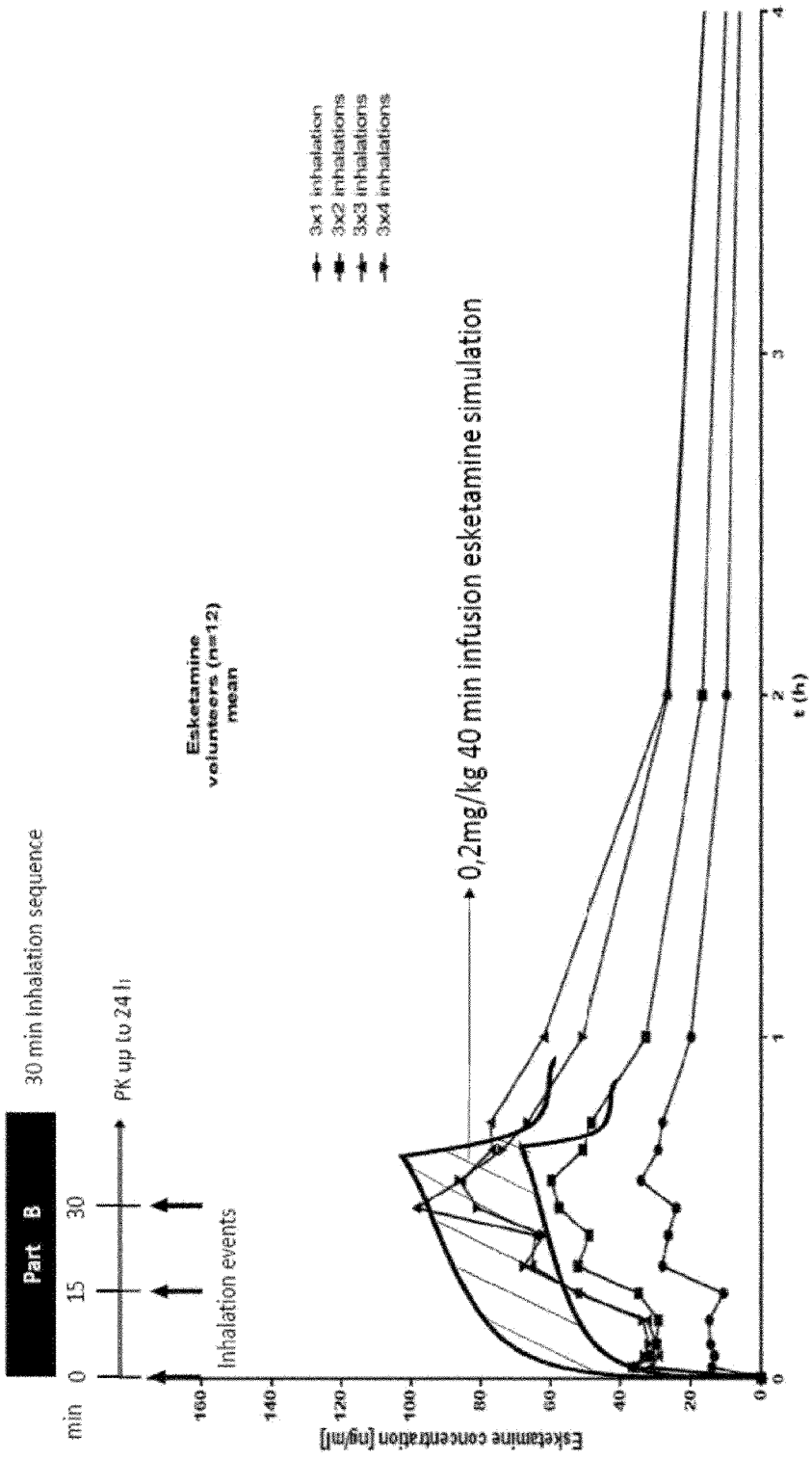
Part B
30 min inhalation sequence
min 0 15 30
PK up to 24 h
Inhalation events
Esketamine volunteers (n=12) mean
0,2mg/kg 40 min infusion esketamine simulation
3x1 inhalation
3x2 inhalations
3x3 inhalations
3x4 inhalations
Esketamine concentration [ng/ml]
t (h)

Fig. 8

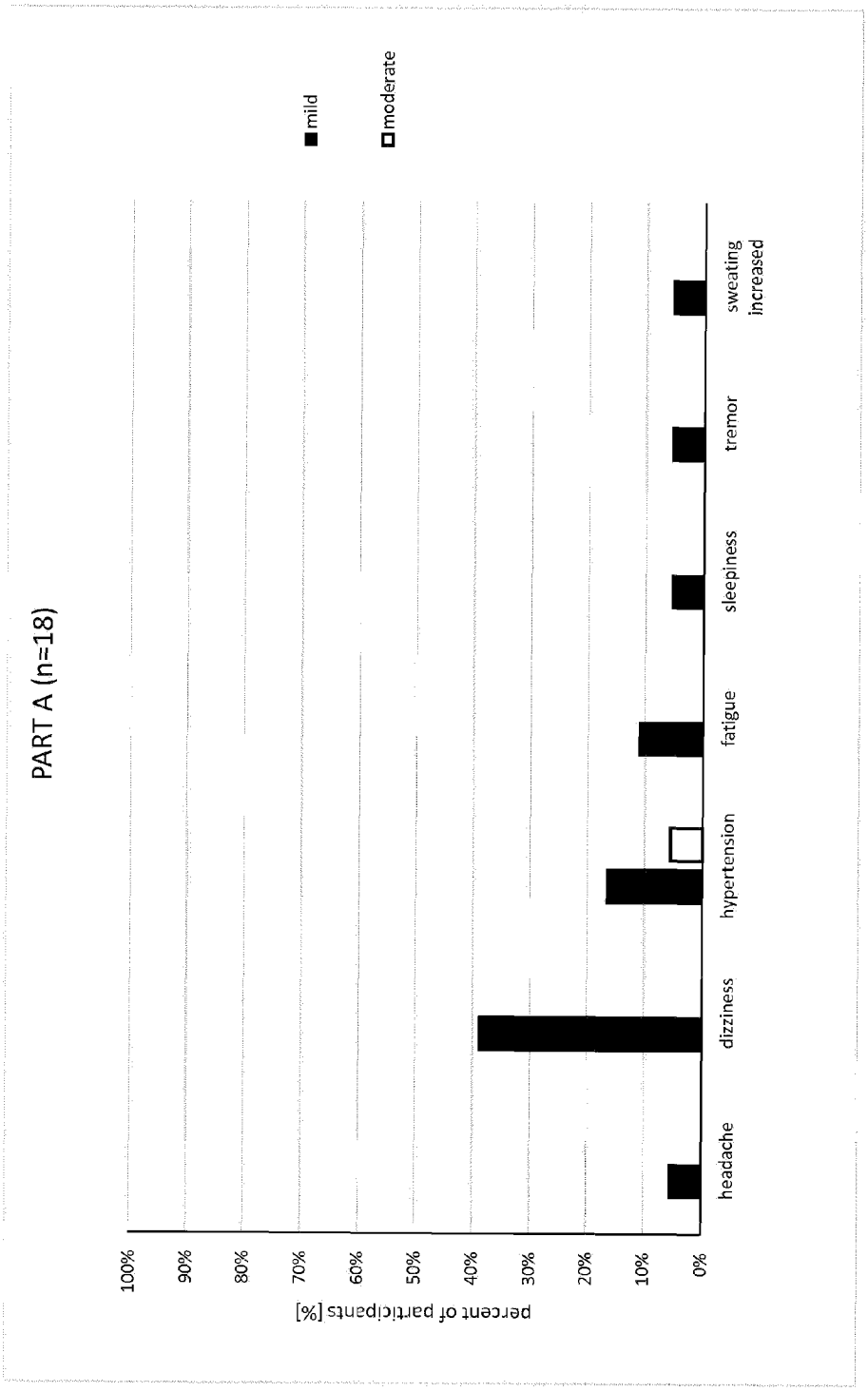
PART A (n=18)
mild
moderate
percent of participants [%]
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
headache
dizziness
hypertension
fatigue
sleepiness
tremor
sweating increased

Fig. 9

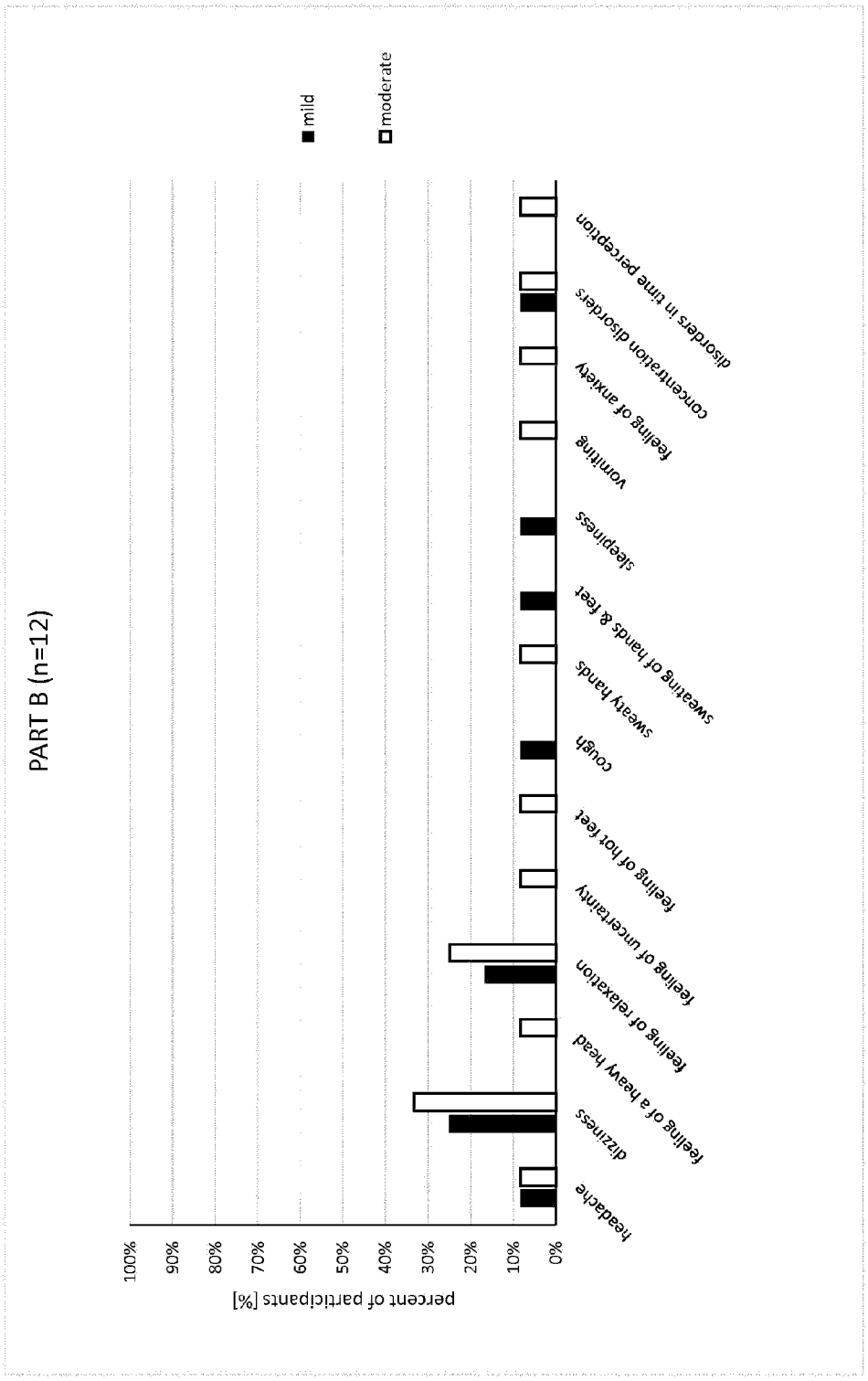
PART B (n=12)
mild
moderate
percent of participants [%]
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
headache
dizziness
feeling of a heavy head
feeling of relaxation
feeling of uncertainty
feeling of hot feet
cough
sweaty hands
sweating of hands & feet
sleepiness
vomiting
feeling of anxiety
concentration disorders
disorders in time perception

Fig. 10