Randomized, first in human, double-blind, placebo- and active comparator-controlled 3-way crossover study in healthy male subjects (part 1), and a subsequent parallel open label study in healthy male and female subjects and MS patients (part 2), to assess the safety, pharmacokinetics and pharmacodynamics of 2B3-201.

Published: 18-10-2013
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Primairy objective:• To determine the safety, tolerability and pharmacokinetics of 2B3-201, and in comparison to free methylprednisolone hemisuccinate and placebo;Secundairy objective:• To determine the pharmacodynamic effects of 2B3-201 on CNS...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Demyelinating disorders
Study type	Interventional

Summary

ID

NL-OMON40606

Source
ToetsingOnline

Brief title
Safety, PK and PD study with 2B3-201.

Condition

- Demyelinating disorders

Synonym
Multiple sclerosis, nerve disease

Research involving
Human

Sponsors and support

Primary sponsor: to-BBB technologies BV
Source(s) of monetary or material Support: to-BBB technologies BV

Intervention

Keyword: liposomes, methylprednisolone, Multiple sclerosis, pharmacology

Outcome measures

Primary outcome

Safety Variables and Endpoints: Safety will be assessed by evaluating the following: Adverse events, Concomitant medications, Safety clinical laboratory tests (standard serum chemistry and hematology), Urinalysis, Physical examination, Vital signs, ECG

Pharmacokinetic variables: Area under the plasma concentration-time curve (AUC), Maximal observed plasma drug concentration (Cmax), Time to maximum observed plasma drug concentration (tmax), Half-life (t *), Volume of distribution (Vd), Clearance

Secondary outcome

Pharmacodynamic variables: The following pharmacodynamic variables will be measured: NeuroCart test battery (cohorts 1-3 only) will include: Pharmaco-EEG,

Maze Learning, Visual Verbal Learning Test, Stroop test, Adaptive tracking, VAS Bond & Lader and VAS Bowdle, Saccadic and smooth pursuit Eye Movements.

Other pharmacodynamic outcome measures will include: Serum cortisol concentration, serum ACTH concentration, serum osteocalcin concentration, blood lymphocyte count, fasting serum glucose concentration, complement factors, Ig-E

Cohorts 8 and 9: also EDSS, MSFC, sleep questionnaire, MP-AEQ questionnaire and neurological examination.

Study description

Background summary

Glucocorticoids are a class of steroid hormones that have anti-inflammatory and immunosuppressive activities and are among the most commonly prescribed drugs for the treatment of autoimmune disorders such as multiple sclerosis (MS) and neuro-inflammatory conditions such as CNS lupus, childhood epilepsy, viral encephalitis and bacterial meningitis.
A new compound, glucocorticoid methylprednisolon encapsulated in GSH-PEG liposomes. is being developed. This compound is expected to improve uptake by the blood-brain barrier, and reduce peripheral side-effects.

Study objective

Primairy objective:
• To determine the safety, tolerability and pharmacokinetics of 2B3-201, and in comparison to free methylprednisolone hemisuccinate and placebo;

Secundairy objective:
• To determine the pharmacodynamic effects of 2B3-201 on CNS functioning in comparison to free methylprednisolone hemisuccinate and placebo;
• To determine the pharmacodynamic effects of 2B3-201 on the HPA-axis hormones in comparison to free methylprednisolone hemisuccinate and placebo;
• To determine the influence on fasting blood glucose of 2B3-201 in comparison to free methylprednisolone hemisuccinate and placebo;
• To determine the influence on osteocalcin concentrations of 2B3-201 in comparison to free methylprednisolone hemisuccinate and placebo.
• To determine the influence on lymphocyte count of 2B3-201 in comparison to free methylprednisolone hemisuccinate and placebo.

• To determine the influence on activation of complement factors en inflammation parameters during infusion of 2B3-201, in comparison to free methylprednisolone hemisuccinate and placebo.
• To determine and compare the safety, tolerability, pharmacodynamics and pharmacokinetics of 2B3-201 amongst the different study populations: healthy male and female subjects and MS patients.
• To determine and compare the safety, tolerability and pharmacokinetics of 2B3-201 with and without hydroxypropyl β-cyclodextrins in the infusion bag in healthy male subjects
• To optimize the infusion schedule for 2B3-201 with or without the addition of an anti-histaminic drug to minimize the likelihood of mild to moderate allergic infusion reactions .
• To determine the change in clinical outcome measures at 1, 2, 4 and 8 weeks after a single dose of 2B3-201 in patients with MS having an acute disease exacerbation

Study design

This study is a randomized, first-in-human, double-blind, placebo- and active comparator- controlled study, followed by an open label single infusion study in healthy male and female subjects, and MS patients.
A total of 54 volunteers will be divided over 8 cohorts with ascending dose in cohorts 1-3 and a dose of 450 mg in cohorts 4, 6 and 8, 300 mg in cohort 6 and either 300 or 450 mg in cohort 7 (based upon results of cohorts 4-6). The dose of cohort 9 will be based on results of cohorts 1-8. Safety and PK-data of cohort 1 will be analyzed before dose escalation to cohort 2.

Cohorts 1-3 follow a 3-way cross over study design with 7 days wash-out between study periods.
A screening and CNS-training session will be planned up to 21 days prior to the first study period.
For each study period, subjects will arrive at CHDR in the evening of day -1 (around 21.00 hr) prior to the day of dosing. Study medication will be administered in the morning of day 0. Subjects will stay for a period of approximately 45 hours and leave CHDR in the morning (around 12.00 hr) of day 1. At days 2 and 3 they will visit CHDR for blood samples.
A follow-up visit is scheduled approximately 7 days after last dose administration.
The total study duration from screening to follow up visit for the subjects is up to 11 weeks.

Cohorts 4-6 will have an open label, single dose of 2B3-201.
A screening session will be planned up to 21 days prior to the first study period.
Subjects will arrive at CHDR in the evening of day -1 (around 21.00 hr) prior to the day of dosing. Study medication will be administered in the morning of day 0, for cohort 4 and possibly for cohort 6 with clemastine as pretreatment.

Subjects will stay for a period of approximately 45 hours and leave CHDR around 17.00 hr on day 1. At days 2 and 3, for cohort 4 and 5 also on days 4, 5 and 6, they will visit CHDR for blood samples.
A follow-up visit is scheduled approximately 7 days after dose administration.
The total study duration from screening to follow up visit for the subjects is up to 5 weeks.

Cohort 7 will be a two-way cross over study with open label treatments of 2B3-201 and methylprednisolone.
A screening session will be planned up to 21 days prior to the first study period.
Subjects will arrive at CHDR in the evening of day -1 (around 21.00 hr) prior to the first study period. Study medication will be administered in the morning of day 0, possibly with clemastine as pretreatment. Subjects will stay for a period of approximately 45 hours and leave CHDR in the morning (around 17.00 hr) of day 1. At days 2, 3, 4, 5 and 6 they will visit CHDR for blood samples. After a 14 day wash out period they will have a similar study period.
A follow-up visit is scheduled approximately 7 days after last dose administration.
The total study duration from screening to follow up visit for the subjects is up to 7 weeks.

Cohorts 8 and 9 will have an open label, single dose of 2B3-201 in MS patients. Subjects will arrive at CRU in the morning of day 0, at around 08:00. Study medication will be administered, possibly with clemastine as pretreatment. Subjects will stay for a period of approximately 10 hours and leave in the evening (around 18.00 hr) of day 0. They will have a home visit at days 1, 2, 3, 4, 5, 6, 9 and 11 for blood samples.
Follow-up visits are scheduled approximately 1, 2, 4 and 8 weeks dose administration.
The total study duration from screening to follow up visit for the subjects is up to 9 weeks.

Intervention

Cohort 8: 2B3-201 with 450 mg methylprednisolone.
cohort 9: dose will be based on cohorts 1-8, and not higehr than 450 mg.

Study burden and risks

Methylprednisolone dosing: short-term use can induce sodium retention-related weight gain and fluid accumulation, hyperglycemia and glucose intolerance, gastrointestinal side effects (primarily with oral use), and mood changes, such as insomnia and anxiety, cognitive side effects with impaired memory and occasionally even psychosis. Moreover, chronic administration may lead to decreased bone density, thinning of skin, cataract, diabetes and susceptibility

to infectious diseases due to their immune suppressive effect.

2B3-201 dosing: The risks associated with the administration of 2B3-201 to humans have not yet been identified, because this compound has not yet been studied in humans.
2B3-201 is a glutathione PEGylated liposomal methylprednisolone formulation designed to enhance the sustained delivery of methylprednisolone (MP) to the brain. The different entities of this formulation have all previously been extensively studied, including methylprednisolone, glutathione, PEGylated liposomes and glutathione PEGylated liposomes.

The active compound of 2B3-201,(i.e. MP), is a well-known glucocorticoid with anti-inflammatory and immunosuppressive characteristics, and a commonly prescribed drug for acute treatment of neuro-inflammatory diseases such as multiple sclerosis (MS). The side-effects associated with methylprednisolone are mentioned earlier in this paragraph.

Clemastine has as major side effects: headache, fatigue, sleepiness, sleeplessness, dizziness, dry mouth, gastralgia, nausea, diarrhoea, obstipation.
Venapuncture: Inserting a catheter for the administration the study drugs and for taking blood for testing may cause pain and discomfort such as bleeding, bruising, dizziness, fainting, inflammation of the vein and infection.

We don't expect any advantages for the subjects in this study. The development of 2B3-201 may contribute to the possibilities is the treatment of (CNS) autoimmune disorders.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Healthy subjects (cohorts 1-7):
1. Healthy male (cohorts 1-6) and female (cohort 7) subjects, 18 to 45 years of age, inclusive. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, and urinalysis.
2. Body mass index (BMI) between 18 and 30 kg/m2, inclusive, and with a minimum weight of 50 kg.
3. Able to participate and willing to give written informed consent and to comply with the study restrictions.;MS subjects (cohorts 8 and 9)
1. Age: 18 to 65 years, both men and women.
2. Patients with relapsing multiple sclerosis (RMS), defined as below, with an acute exacerbation, who in the opinion of the treating physician should undergo a 3 - 5 day course of high dose methylprednisolone;
o Patients with Relapsing Remitting Multiple Sclerosis (RRMS).
o Patients with Secondary Progressive Multiple Sclerosis (SPMS) and superimposed relapses.
o Patients with clinically isolated syndromes (CIS) who show dissemination of lesions in time (DIT) and space (DIS) on MRI scans according to the 2010 McDonald criteria.
3. Able to participate and willing to comply with the study restrictions. Understands and signs the written informed consent prior to any of the testing under this protocol, including screening tests and evaluations that are not considered part of the subject's routine care.

Exclusion criteria

Healthy volunteers (cohorts 1-7):
1. Subjects not willing to use contraception, for the duration of the study and for 3 months after the last dose.
2. Positive test for drugs at screening or pre-dose.

3. History (within 3 months of screening) of alcohol consumption exceeding 2 standard drinks per day on average (1 standard drink = 10 grams of alcohol). Alcohol consumption will be prohibited during study confinement and at least 48 hours before screening, before dosing, and before each scheduled visit.
4. History or symptoms of any significant disease including (but not limited to), neurological, psychiatric, endocrine, cardiovascular, respiratory, gastrointestinal, hepatic, or renal disorder.
5. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.
6. Systolic blood pressure (SBP) greater than 140 or less than 90 mm Hg, and diastolic blood pressure (DBP) greater than 90 or less than 50 mm Hg.
7. Use of any medications (prescription or over-the-counter [OTC]), vitamin, mineral, herbal, and dietary supplements within 21 days of study drug administration. Exceptions are paracetamol (up to 4 g/day).
8. Use of CYP3A4-inhibiting drugs, including quinine containing drinks (bitter lemon and tonic water) is prohibited within 21 days of study drug administration
9. Subject has used grapefruit, grapefruit juice, grapefruit-containing products, Seville oranges, or pomelo-containing products, within 14 days prior to day -1.
10. Clinically significant abnormalities, as judged by the investigator, in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis). In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility or judged to be clinically irrelevant for healthy subjects.
11. Participation in an investigational drug or device study within 3 months prior to screening.
12. Donation of blood over 500 mL within three months prior to screening.
13. Concomitant disease or condition that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the subject in this study.
14. Smoker of more than 10 cigarettes per day prior to screening or who use tobacco products equivalent to more than 10 cigarettes per day.
15. Clinically significant abnormal ECG, as judged by the Investigator.
16. Current infection or inflammation study within 1 month prior to screening
17. Recent vaccinations study within 3 months prior to screening.
18. Positive Mantoux test of 5 mm or more.
19. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, or multiple drug allergies (non-active hay fever is acceptable).
20. Unwillingness or inability to comply with the study protocol for any other reason.
21. Any subject who is pregnant or breastfeeding. A urine pregnancy test should be performed in female subjects of childbearing potential (defined as < 2 years after last menstruation and not surgically sterile) prior to the start of the study treatment.
22. For female subjects of childbearing potential (defined as < 2 years after last menstruation and not surgically sterile) and male subjects who are not surgically sterile or with female partners of childbearing potential: absence of effective, non-hormonal means of contraception (intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal gel) will be a contraindication. ;MS patients (cohorts 8 and 9)
1. Previous acute exacerbations, and/or corticosteroid treatment or ACTH < 1 month before present exacerbation.
2. Hypersensitivity to methylprednisolone.

3. Prior use of immunosuppressive treatments / disease-modifying drugs (DMDs) other than interferon-beta, glatiramer acetate, fingolimod or teriflunomide within 12 months of the index episode.Subjects may continue their current therapy with interferons, glatiramer acetate, fingolimod, dimethylfumarate or teriflunomide throughout the course of the study.
4. Non-steroidal anti-inflammatory agents, including salicylic acid, should be avoided during the administration of the steroid therapy. If absolutely necessary they are permitted for subjects to treat interferon side effects, when the patient is not responding to acetaminophen/paracetamol.
5. Current or recent (within 30 days of first study treatment) treatment with any other investigational drug or participation in any other investigational study
6. Evidence of psychiatric illness
7. History of any significant cardiac, gastrointestinal, hepatic, pulmonary, renal or active immunosuppressive disease.
8. Immune deficiency or any other medical conditions that would preclude corticosteroid therapy.
9. Any patient who is pregnant or breastfeeding. A urine pregnancy test should be performed in female subjects of childbearing potential (defined as < 2 years after last menstruation and not surgically sterile) prior to the start of the study treatment.
10. For female subjects of childbearing potential (defined as < 2 years after last menstruation and not surgically sterile) and male subjects who are not surgically sterile or with female partners of childbearing potential: absence of effective, non-hormonal means of contraception (intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal gel) will be a contraindication.
11. Physical examination results or laboratory findings that may interfere with the planned treatment, affect patient compliance or place the patient at a high risk of treatment-related complications.
12. Known hypersensitivity to any of the excipients in 2B3-201 (e.g. PEG, Cholesterol, HSPC or GSH).

Study design

Design

Study type:	Interventional
Intervention model:	Other
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-11-2013
Enrollment:	54
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	2B3-201
Generic name:	2B3-201
Product type:	Medicine
Brand name:	Solu-medrol
Generic name:	methylprednisolone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	tavegyl
Generic name:	clemastin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	18-10-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-10-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-01-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	17-03-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-04-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-05-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-06-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-07-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-08-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-11-2014
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2013-004077-28-NL
CCMO	NL46479.056.13