A two-phased, randomized, double blind, placebo-controlled study of ECP002A (*9-THC) to determine safety, tolerability and efficacy in Multiple Sclerosis patients suffering from spasticity and pain.

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Primary objective:*Evaluation of the efficacy of ECP002A (*9-THC) on spasticity in patients with MSSecondary objectives:*Evaluation of the efficacy of ECP002A (*9-THC) on pain in patients with MS*Evaluation of the tolerability of ECP002A (*9-THC) in...

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

Summary

ID

NL-OMON37947

Source
ToetsingOnline

Brief title
ECP002A (*9-THC) in MS patients

Condition

- Demyelinating disorders

Synonym
MS, multiple sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Echo Pharmaceuticals
Source(s) of monetary or material Support: Funded by the sponsor (Echo Pharmaceuticals)

Intervention

Keyword: Multiple Sclerosis, pain, spasticity, tetrahydrocannabinol

Outcome measures

Primary outcome

Treatment phase: the difference between patients treated with ECP002A (*9-THC)

and patients treated with placebo in the H-reflex/M-wave amplitude ratio as

measured by peripheral nerve stimulation of the tibial nerve

Secondary outcome

Pharmacodynamics:

o severity of spasticity based on a daily diary assessment by the subject on a

0*10 spasticity numerical rating scale (NRS)

o severity of spasticity based on the modified Ashworth scale in lower limb

muscles affected by spasticity

o severity of patient disability based on the Kurtzke expanded disability

status scale (EDSS)

o severity of spasticity: based on the RM-test performed on the muscle of the

lower limb

o severity of spasms based on a daily diary assessment by the subject on a 1*5

numerical spasm frequency scale

o severity of pain based on the short form McGill pain questionnaire (SF-MPQ)

o the patients global impression of change (PGIC) in their disease (seven point

scale)

o the Pittsburgh sleep quality index (PSQI)

o the timed 25 feet (T25FW)

o SDST (attention)

o fatigue severity scale (FSS)

o Guy*s neurological disability scale (GNDS)

o visual analogue scale (VAS) Bowdle (feeling high, internal perception,

external perception)

o VAS Bond & Lader (alertness, mood and calmness)

o body sway

o heart rate

o inflammatory disease markers:MMP-8, MMP-9, TIMP-1, IL-12p40, IL-23, IL-17a,

IL-10, IL-6 and TNF*

Pharmacokinetics:

o steady state Cmax, AUC0-last, tmax

o population pharmacokinetic profile

PK-PD:

o establishment of a PK-PD model for the effect of ECP002A (*9-THC) on

spasticity in MS

Tolerability:

o adverse events

o vital signs

o safety laboratory

Study description

Background summary

The endogenous cannabinoid system appears to be tonically active in the control of spasticity and cannabinoids have been proposed as therapeutic options for spasticity in multiple sclerosis (MS) because of their ability to reduce the subjective feeling of spasticity. Cannabinoids have been shown to modulate motor cortical excitability probably through presynaptic cannabinoid receptors CB1 that control the release of neurotransmitters from axonal terminals. *9-tetrahydrocannabinol (*9-THC) is one of the cannabinoids in the Cannabis sativa plant and a direct agonist of the cannabinoid receptor CB1.
Oral bioavailability of *9-THC is variable and the current formulation is expected to have superior pharmacokinetic properties to previous formulations, leading to more stable *9-THC plasma levels without high peaks which will beneficially influence the occurrence of side effects.

Study objective

Primary objective:
*Evaluation of the efficacy of ECP002A (*9-THC) on spasticity in patients with MS

Secondary objectives:
*Evaluation of the efficacy of ECP002A (*9-THC) on pain in patients with MS
*Evaluation of the tolerability of ECP002A (*9-THC) in patients with MS
*Establishment of a PK-PD model for the effect of ECP002A (*9-THC) on spasticity in patients with MS

Study design

*This will be a two-phased study consisting of a dose-finding (PK-PD) phase and a treatment phase
*I
n the dose-finding phase the effect of an escalating dose of ECP002A (*9-THC) on spasticity will be determined in a randomized placebo-controlled two-way cross-over fashion. Patients will visit the outpatient clinic on two occasions and will receive an escalating dose of ECP002A (*9-THC) or placebo. Spasticity will be scored objectively and subjectively, as will psychotropic effects of *9-THC. Plasma levels of ECP002A (*9-THC) will be measured.

*
Based on the pharmacokinetics and pharmacodynamic response of the individual patient, an individual dosing regimen will be generated.
*In the treatment phase, the individual dose as determined based on the dose-finding phase will be given in a randomized placebo-controlled two-group, parallel, trial. The treatment period will be 4 weeks.
*
Treatment arms (in the treatment phase):
o ECP002A (*9-THC) at an individually predetermined dose
o Matching placebo

Intervention

ECP002A (*9-THC)

Study burden and risks

The risk of participation includes the possible side-effects of the study drug (i.e. tachycardia, feeling high, changed perception of time, disturbance in attention, drowsiness, nausea) and findings during test (i.e. positive test result for hepatitis B, hepatitis C or HIV)

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subject is legally competent;
2. Subject is eighteen years of age or older;
3. Subject is able to speak, read and understand the local language of the investigational site, is familiar with the procedures of the study, and agrees to participate in the study program by giving oral and written informed consent prior to screening evaluations;
4. Subject has a diagnosis of progressive (primary or secondary) Multiple Sclerosis according to the revised McDonald criteria;
5. Subject has a disease duration of more than 1 year as defined by a diagnosis of MS at least one year prior to inclusion in the trial;
6. Subject has clinically stable disease > 30 days.

Exclusion criteria

1. Baseline Expanded Disability Status Scale (EDSS) score < 4.5 or > 7.5;
2. Subject does not have spasticity in at least one of the lower limbs as defined by an Ashworth score * 2;
3. Subject has a body mass index (BMI) below 18 or above 28.5 kg/m2;
4. Subject has a presence or a significant history of any cardiac or vascular disorder, asthma or other pulmonary disease, major gastrointestinal abnormalities, peptic ulceration, hepatic, psychiatric, haematological (including bleeding disorders), endocrine, renal, or major genitourinary disease or neurological disease other than MS or uses any kind of concomitant medication that - in the opinion of the investigator - may interfere with the study;
5. Subject has a (history of) a significant medical disorder that may pose a risk for the subject or jeopardize the aims of the study, based on medical history, physical examination, ECG and safety laboratory parameters;
6. Subject has a presence or history of clinically significant psychiatric illness in first degree relatives;
7. History of sensitivity / idiosyncrasy to THC, compounds chemically related to these compounds, or excipients which may be employed in the study or to any other drug used in the past;
8. Subject is currently a regular user (including *recreational uses*) of any illicit drugs, except for cannabis, or has (a history of) drug or alcohol abuse (alcohol consumption > 40 grams/day or 4 units/day);
9. Subject smokes more than 10 cigarettes or 2 cigars or 2 pipes per day and/or not able or not willing to refrain from smoking on study days;

10. Subject is a habitual and heavy consumer of caffeinated beverages (more than 6 cups of coffee or equivalent/day) at the time of the study and/or is not able to refrain from use of (methyl) xanthines (e.g. coffee, tea, cola, chocolate) from 12 hours prior to dosing until the end of the study day;
11. Unable/unwilling to refrain from all use of grapefruit from 2 weeks prior to the first dose until the last study day and/or unable/unwilling to refrain from all use of quinine containing products from 2 days prior to the first dose until discharge;
12. Positive alcohol breath test at screening or admission and/or unable/unwilling to refrain from alcohol use from 48 hours before each study day until the last blood sample has been drawn;
13. Positive urine screen at screening for other drugs than THC or benzodiazepines, i.e., cocaine, opioids, MDMA, methamphetamine and amphetamines;
14. Positive urine drug test, including THC prior to first dosing;
15. Positive test result on hepatitis B surface antigen, hepatitis C antibody or HIV antibody test;
16. Participation in an investigational drug study within 90 days prior to the first dose and during the entire study period;
17. Donation of blood/plasma outside limits of Sanquin Blood Supply Foundation guidelines;
18. Premenopausal women not using one of the monophasic oral contraceptives (including Diane-35), who are unable or unwilling to also skip the pill/ring-free week, from the screening until the end of the first study phase and during the second study phase;
19. Pregnant and/or breastfeeding subjects;
20. Clinically significant history of use of CNS medication as judged by the investigator.
21. Unable to stay in the Netherlands for more than four weeks.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	02-03-2011
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	delta-9-tetrahydrocannabinol
Generic name:	Namisol

Ethics review

Approved WMO Date:	09-11-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-01-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-01-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-10-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-02-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	17-02-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-03-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-05-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-11-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-11-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2010-022033-28-NL
CCMO	NL34443.029.10