1. Synopsis

Name of Sponsor Echo Pharmaceuticals	
Name of Finished Product Namisol®	
Name of Active Ingredient Δ^9-tetra-hydro-cannabinol (Δ^9-THC)	
Title of Study A two-phased, randomized, double blind, placebo-controlled study of ECP002A (Δ^9-THC) to determine safety, tolerability and efficacy in Multiple Sclerosis patients suffering from spasticity and pain	
Investigator G.J. Groeneveld, MD, PhD	
Study centre Centre for Human Drug Research	
Publication (reference): N/A	
Studied period (years): 2011 – 2013 **Date of first enrollment:** 24-Mar-11 **Date of last completed:** 22-Apr-13	**Phase of development:** Phase 2A
Primary Objective – Evaluation of the efficacy of ECP002A (Δ^9-THC) on spasticity in patients with MS **Secondary Objectives** – Evaluation of the efficacy of ECP002A (Δ^9-THC) on pain in patients with MS – Evaluation of the tolerability of ECP002A (Δ^9-THC) in patients with MS – Establishment of a PK-PD model for the effect of ECP002A (Δ^9-THC) on spasticity in patients with MS	
Methodology – This was a two-phased study consisting of a dose-finding (PK-PD) phase and a treatment phase – In the dose-finding phase the effect of an escalating dose of Namisol® on spasticity was determined in a randomized placebo-controlled two-way cross-over fashion. Patients were to visit the outpatient clinic on two occasions and received an escalating dose of Namisol® or placebo. Spasticity was scored objectively and subjectively, as were psychotropic effects of Namisol®. Plasma levels of Namisol® and its metabolites 11-OH-THC and THC-COOH were measured. – Based on the pharmacokinetics and the pharmacodynamic response of the individual patient, an individual dosing regimen was generated. – In the treatment phase, the individual dose as determined based on the dose-finding	

phase was administered in a randomized placebo-controlled two-group, parallel, trial. The treatment period was 4 weeks.

- Treatment arms (in the treatment phase):
  - Namisol® at an individually predetermined dose
  - Matching placebo

Number of patients / subjects (planned and analysed):
24 subjects were planned and randomized, 23 subjects completed the treatment phase and were subsequently included in the analyses.

Diagnosis and main criteria for inclusion:
Patients eligible for inclusion were to be 18 years of age or older and had to have:

- A diagnosis of progressive (primary or secondary) multiple sclerosis
- A disease duration > 1 year as defined by a diagnosis of MS at least one year prior to inclusion in the trial
- A baseline Expanded Disability Status Scale (EDSS) score between 4.5 and 7.5
- Spasticity in at least one of the lower limbs as defined by an Ashworth score ≥ 2
- Clinically stable disease > 30 days

Test product, dose and mode of administration, batch number:
Namisol® was orally administered as tablets of 1.5 mg and 5.0 mg.

- Batch number 1.5 mg = 26754/26764
- Batch number 5.0 mg = 26756/26756

Duration of treatment:
Subjects were randomized to a four week treatment phase.

Reference therapy, dose and mode of administration, batch number:
N/A

Criteria for evaluation:
Efficacy:
Primary endpoint:

- the difference in the severity of spasticity: defined by the H-reflex/M-wave amplitude ratio between the subjects who received Namisol® and the subjects who received placebo

Secondary endpoints:

- the difference in the severity of spasticity based on a daily diary assessment by the subject on a spasticity numerical rating scale (NRS), between the subjects who received Namisol® and the subjects who received placebo
- the difference in the severity of spasticity as measured by the modified Ashworth scale in lower limb muscles affected by spasticity between the subjects who received Namisol® and the subjects who received placebo
- the difference in the severity of patient disability in multiple sclerosis as measured by the Kurtzke expanded disability status scale (EDSS), between the subjects who received Namisol® and the subjects who received placebo
- the difference in severity of spasticity: defined by the RM test between the subjects who receive Namisol® and the subjects who received placebo.
- the difference in the severity of spasms based on a daily diary assessment by the

subject on a spasm frequency scale, between the subjects who received Namisol® and the subjects who received placebo
- the difference in the severity of pain based on the short form McGill pain questionnaire (SF-MPQ), between the subjects who received Namisol® and the subjects who received placebo
- the difference in the patient's global impression of change (PGIC) in their disease between the subjects who received Namisol® and the subjects who received placebo
- the difference in the quality of sleep as determined by the Pittsburgh sleep quality index (PSQI), between the subjects who received Namisol® and the subjects who received placebo
- the difference in the walking distance as determined by the timed 25 feet walk test (T25FW) between the subjects who received Namisol® and the subjects who received placebo
- the difference in attention span as determined by the SDST, between the subjects who received Namisol® and the subjects who received placebo
- the difference in level of fatigue as determined by the fatigue severity scale (FSS), between the subjects who received Namisol® and the subjects who received placebo
- the difference in the level of disability as determined by Guy's neurological disability scale (GNDS) between the subjects who received Namisol® and the subjects who received placebo
- the difference in inflammatory state as defined by inflammatory disease markers MMP-8, MMP-9, TIMP-1, IL-12p40, IL-23, IL-17a, IL-10, IL-6 and TNFα between the subjects who received Namisol® and the subjects who received placebo
- the difference in level of neurodegeneration as defined by change from baseline of the level of neurofilaments between subjects who received Namisol® and the subjects who received placebo (*results described in separate addendum)*
- population pharmacokinetics sampling (POP-PK) to establish the pharmacokinetic parameters at steady state in this patient population
- the difference in subjective mood as determined by the visual analogue scale (VAS) as described by Bowdle (feeling high, internal perceptions, external perceptions) between the subjects who received Namisol® and the subjects who received placebo
- the difference in postural stability as determined by the Body sway (mm) between the subjects who received Namisol® and the subjects who received placebo
- the difference in heart rate between the subjects who received Namisol® and the subjects who received placebo

Safety:

Vital signs:
- Systolic and diastolic blood pressure (mmHg)
- Heart rate (BPM)
- Temperature (°C)

ECG
- HR
- PR interval
- QRS interval
- QT interval
- QTcF

- QTcB

Biochemistry
Hematology
Physical examination

Statistical methods
All pharmacodynamic endpoints are summarised (mean and standard deviation of the mean, median, minimum and maximum values) by treatment and time, and are presented graphically as mean over time, with standard deviation as error bars. All repeatedly-measured PD endpoints are analyzed using a mixed effect model with fixed effects treatment, time and treatment by time and random effect subject and, if available, the average baseline value as covariate.

EFFICACY RESULTS:
The primary endpoint of this study, H/M ratio, did not show a significant treatment effect of Namisol®. Secondary, objective measures for spasticity (Ashworth, RM test) did also not demonstrate a significant difference between treatment and placebo groups. However, secondary subjective measures of the severity of experienced spasticity and pain did show a treatment effect. The objective endpoints for clinical improvement (EDSS, GNDS, Timed 25ft Walk) and the subjective endpoints for clinical improvement (PGIC, PSQI) were not significantly different between Namisol® and placebo. The objective and subjective endpoints for undesirable effects (VAS Bond & Lader, VAS Bowdle, SDST, Body sway) did not show significant deleterious effects.

These findings are in line with what has been reported previously related on the effects of cannabinoids in patients with MS.

SAFETY RESULTS:
The observed adverse event profile is in line with what is known from previous studies investigating the effects of Δ^9-THC. The adverse events that were observed and considered treatment-related were mild in nature. Therefore the safety findings indicate overall good tolerability for this oral formulation of Δ^9-THC.

CONCLUSION:
This study demonstrates that Namisol® exerts a similar effect on spasticity and pain as other Δ9-THC formulations. In line with previous reports, spasticity and pain appear to be influenced by THC through higher-level CNS modulation of perception of spasticity rather than of spasticity itself.

Date of the report: 23-DEC-13