2. SYNOPSIS

Name of Sponsor/Company:	MAX ZELLER SÖHNE AG
Name of Finished Product:	Alluna® Nacht zum Einschlafen
Name of Active Ingredient:	Ze 91019 (standardised combination of valerian root dry extract and hops cone extract)
Title of Clinical Study:	Randomised, placebo-controlled prospective clinical study to determine the efficacy of sleeping film coated tablets Ze 91019 (Alluna® Nacht zum Einschlafen, valerian/hops) in patients who suffer from sleep disorders in accordance with the ICD 10 compared to valerian or hops mono-extract
Investigator(s)/: Study Centre(s)	01 - Dr. Dr. Ewald Schrader, Praxis für Arzneimittelforschung, Langgasse 8, DE-35415 Pohlheim (Germany) 02 - PD Dr. med. Rüdiger Schellenberg, Talstrasse 29, DE-35625 Hüttenberg (Germany)
Publication Reference(s):	Not applicable
Studied Period:	Part 1: Dr. Dr. Ewald Schrader; Inclusion of 105 patients: First Patient First Visit (FPFV): March, 13th, 2008 Last Patient Last Visit (LPLV): October 09th, 2008 Part 2: PD Dr. med. Rüdiger Schellenberg; Inclusion of 64 patients: First Patient First Visit (FPFV): May 4th, 2010 Last Patient Last Visit (LPLV): March 20th, 2012
Phase of Development:	Phase III
Objective(s):	Primary Objective: To prove the efficacy of Max Zeller Söhne AG valerian/hops combination (Ze 91019), measured by a change in sleep onset latency (SOL) in the hypnogram at the end of the therapy with consideration of the measured value at the start of the therapy. The measurements were made using the portable Quisi® mini-recorder.

Methodology:	Patients with difficulties falling asleep and/or sleeping through the night of non-organic origin according to ICD 10 F 51.0 - F 51.2 were randomly assigned (1:1:1:1) to receive either valerian/hops combination (Ze 91019), valerian mono extract, hops mono extract or placebo. Hypnograms, including the sleep onset latency (primary endpoint), were recorded by the patients at home at baseline and after 4 weeks of treatment. Patients and investigators were blinded during the study. Physical examinations, laboratory assessments (haematology and clinical chemistry) and vital signs were assessed at baseline and at the final visit. Adverse events were recorded at each visit.
Number of Patients:	Planned: 160, Screened 172, Analysed: Safety: 169, ITT: 118; PP1: 93, PP2: 66
Diagnosis and Main Criteria for Inclusion:	Age: ≥ 18 years old. Patients with difficulties falling asleep and/or sleeping through the night of non-organic origin according to ICD 10 F 51.0 - F 51.2. Sleep onset latency (SOL) at baseline > 30 minutes (patients 1-105, Part 1). In an amendment to the protocol the SOL at baseline was changed to ≥ 45 minutes (patients 106-172, Part 2).
Test Product, Dose and Mode of Administration, Batch Number:	Film-coated tablet Ze91019 valerian/hops combination containing 187 mg standardised valerian root dry extract (5 – 8 : 1 methanol 45% m/m) and 41.88 mg hops cones extract (7 – 10: 1 methanol 45% m/m). Two tablets daily, orally, one hour prior to going to bed. Batch 03.2007, expiry date 02.2010 for site 01, Dr. E. Schrader Batch 04.2009, expiry date 03.2012 for site 02, Dr. R. Schellenberg
Duration of Treatment:	Four weeks
Reference Product, Dose and Mode of Administration, Batch Number:	a) Valerian mono extract: Film-coated valerian extract tablet containing 187 mg standardised valerian root dry extract (5 – 8 : 1 methanol 45% m/m). b) Hops mono extract: Film-coated tablet hops extract containing 41.88 mg hops cone extract (7 – 10 : 1 methanol 45% m/m). c) Placebo Two tablets daily, orally, one hour prior to going to bed. Batch 03.2007, expiry date 02.2010 for site 01, Dr. E. Schrader Batch 04.2009, expiry date 03.2012 for site 02, Dr. R. Schellenberg

Criteria for Evaluation:

Efficacy: Difference in the sleep onset latency (SOL), as recorded by Quisi® mini-recorder at baseline and end of treatment, week 4 (primary endpoint) for the ITT,PP1, PP2 - populations, for both centres and for both sexes.

The following secondary endpoints were assessed:

-Difference in wake after sleep onset (WASO)

-Difference in sleep efficiency

- proportion of sleeping stages to sleep period time (REM, stage 1, 2, 3, 4) [%] at day 0 and week4

- Difference in REM latency (time to first REM sleep) [min]

-The CGI (Clinical Global Impression) was assessed at baseline (severity scale) and at the final visit.

-Responder rates were calculated, and response was defined as a reduction of the sleep onset latency (SOL) of ≥ 25% of the baseline value.

Safety: Evaluation of adverse events, outcome of physical examinations, vital signs and haematology/clinical laboratory parameters (haematology and clinical chemistry) at baseline and after 4 weeks.

Statistical Methods:

This study was designed to show superiority of Ze 91019 ("Alluna® Nacht zum Einschlafen", fixed valerian/hops combination) in patients with non-organic sleep disorders over placebo, valerian mono extract and hops mono extract and among each other, respectively. The primary efficacy variable, difference of sleep onset latency (SOL), was evaluated in the ITT, as well as in two PP populations among the 4 treatment arms by hierarchically sequenced null hypotheses. The test procedure terminated once a null hypothesis was accepted. The non-parametric Mann-Whitney-U Test was used as statistical test. Centre- and gender-related differences for the primary endpoint were assessed accordingly. The secondary efficacy variables were analyzed using descriptive statistics.

Summary and Conclusions:

Efficacy Results:

Although the mean reduction of SOL after 4 weeks was highest with valerian/hops (Ze 91019) treated patients no statistically significant improvement could be shown compared to placebo and the mono-extracts with the present methodology and patient numbers.

Safety Results:

The incidence of adverse events was very low (4 AEs reported, SAF n=169). Also the monitoring of vital signs, physical examinations and laboratory parameters did not reveal any safety concerns related to valerian/hops combination, valerian mono extract and hops mono extract.

Conclusions:

In summary, Ze 91019 and its components (valerian and hops mono-extracts) were very well tolerated confirming the safe use of these herbal medicinal extracts. However, the current trial could not show statistically significant effects of the herbal combination on sleep parameters. Due to numerous artefact measurements, as well as missing values only a limited number of evaluable patients could be analysed. Based on these results, further clinical trials have to be re-designed and should include considerably higher patient numbers.

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