Synopsis for Clinical Trial Report Version 1.0 from October 4, 2024

Synopsis Version 1.0

Efficacy of Magnesium Orotate in Patients with HFrEF in terms of the Influence of NTproBNP – a Prospective, Monocentric, Randomized, Double-Blind, Placebo-Controlled Cross-over Study. MACH 2

(Magnesium orotate in severe congestive heart failure – Part 2)

EudraCT No.: 2016-004600-53

Trial ID: RBK03-16-00389

Phase II

Sponsor:

Wörwag Pharma GmbH & Co. KG

Trial Site:

Robert Bosch Hospital

Department of Cardiology

CONFIDENTIAL

SYNOPSIS

NAME OF SPONSOR Wörwag Pharma GmbH & Co. KG **NAME OF FINISHED PRODUCT** *magnerot® CLASSIC N* **NAME OF ACTIVE INGREDIENT(S)** Magnesium orotate dihydrate		**INDIVIDUAL TRIAL TABLE REFERRING TO MODULE 5 OF THE CTD** Volume: Not applicable Page: Not applicable	**(FOR NATIONAL AUTHORITY USE ONLY)**
Title of Trial	MACH 2 – Efficacy of Magnesium Orotate in Patients with HFrEF respect to the Influence of NTproBNP - a Prospective, Monocentric, Randomized, Double-Blind, Placebo-Controlled Cross-Over Study Original title: Wirksamkeit von Magnesium-Orotat bei Patienten mit HFrEF in Bezug auf den Einfluss von NTproBNP - eine prospektive, monozentrische, randomisierte, doppelblinde, Placebo-kontrollierte Cross-over Studie. MACH2 (Magnesium orotate in severe congestive heart failure - Part 2)		
Investigator(s)	Prof. Dr. med. [redacted] (Principal Investigator) Dr. med. [redacted] (Deputy Investigator)		
Trial centre(s)	Robert Bosch Hospital GmbH, Department of Cardiology Auerbachstr. 110, 70376 Stuttgart Germany		
Publication	N/A		
Trial period	FPFV: November 21, 2019 LPLV: September 4, 2023 Recruitment stop due to COVID19 pandemic 06.04.2020 – 22.06.2020	Phase of development:	Phase II
Current protocol	Version 4.0, June 20, 2022		
Protocol amendments	Amendment 4.0; 20.06.2022: Principal investigator and deputy change, extension of trial duration Amendment 3.1; 01.10.2020: Extension of trial duration, adjustment of statistics details. Amendment 3.0; 07.06.2019: In- and exclusion criteria change Amendment 2.0; 31.01.2019: In- and exclusion criteria change Amendment 1.3; 10.07.2018 Principal investigator change Amendment 1.2; 28.05.2018 Implementation of changes required for regulatory approval Amendment 1.1; 22.03.2018 Implementation of changes required for regulatory approval Initial protocol 1.0; 16.03.2017		

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Objectives	Primary Objective: The primary aim is to show that a significant reduction in NTproBNP can be achieved by regularly taking magnesium orotate compared to placebo. Secondary Objectives: The aim is to show that magnesium orotate is superior to placebo with regard to • improving the symptoms of heart failure • improving the NYHA classification • increasing the LVEF • improving the symptoms, measured on the basis of the KCCQ questionnaire • reducing the hospitalization rate due to heart failure, cardiac decompensation or myocardial infarction • improving the participant's subjective quality of life, measured according to EQ-5D-5L
Safety criteria	• Assessment of AE/SAE • Clinically significant changes in the laboratory parameters at the investigator's discretion
Methodology	This is a prospective, randomized, double-blind, placebo-controlled trial in cross over design.
Number of participants	Planned: 30 Randomized: 30 Dropped out: 3 Analysed per protocol: 27
Diagnosis and main criteria for inclusion	• Male or female patients ≥ 18 years • Participants with chronic heart failure who have been receiving stable treatment according to current guidelines for at least 3 months • NYHA Class II-IV • LVEF ≤ 45 % • NTproBNP ≥ 600 pg/ml (most up-to-date value in the last 3 months) • Willingness to refrain from consuming alcohol while participating in the study

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Test product, dose and mode of administration, batch number	3x3 tablets (4500 mg/d) for 4 weeks, followed by 3x2 tablets (3000 mg/d) for 8 weeks oral intake of *magnerot*® CLASSIC N (Magnesium orotate dihydrate) Bulk batch numbers: 16L058 and 20J077
Reference therapy, dose and mode of administration, batch number	3x3 tablets for 4 weeks, followed by 3x2 tablets for 8 weeks oral intake of Placebo Bulk batch numbers: 16L089 and 2084C01
Duration of treatment	Each participant should undergo treatment for a total of 8 months, (= 32 weeks). The Phase 1 (either verum or placebo) of the study should last for 12 weeks per participant, followed by an 8-week washout phase. The Phase 2 (either verum or placebo) should also last for 12 weeks per participant.
Criteria for evaluation	<u>Efficacy:</u> The primary aim of the study was to demonstrate that a significant reduction in NTproBNP can be achieved by the regular intake of magnesium orotate for 12 weeks, compared to placebo. The following secondary endpoints have been evaluated to further evaluate efficacy: Symptoms of heart failure (body weight, ankle oedema, nocturia, cyanosis, dyspnea, angina pectoris, anasarca) NYHA classification Left ventricular ejection fraction measured by echo cardiography Heart failure specific quality of life measured with KCCQ questionnaire Quality of life measured with EQ-5D-5L Hospitalization rate due to heart failure, cardiac decompensation or myocardial infarction <u>Pharmacokinetics:</u> Pharmacokinetics is evaluated by measuring plasma magnesium. <u>Safety:</u> Safety is evaluated by evaluation (serious) adverse events and clinically significant laboratory findings.

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Statistical methods	The primary analysis of this trial is the per protocol analysis. All parameters were evaluated descriptively at all available survey times, depicting sample size, mean, standard deviation, minimum, maximum, 25th and 75th percentiles, and median for metric data, as well as frequency and percentage for categorical data. Primary and further endpoints were analysed using Wilcoxon rank test for not normally distributed variables, paired t-test for normally distributed variables and McNemar or Bowker's symmetry test for categorial variables. All statistical tests are two-sided and a significance level of 5% was used. The statistical programming was done with IBM SPSS Statistics 29 (SPSS Inc. an IBM Company, Chicago, IL) and R (R Core Team 2024), R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

SUMMARY CONCLUSIONS

DEMOGRAPHICS

30 of 67 screened participants were included in the trial. During the first cross-over phase, 2 and in the second cross-over phase 1 participant dropped-out from the study. The primary analysis was the per protocol analysis, which included 27 individuals of those 18 (67 %) were male and 9 (33 %) were female. Median age was 66 years (IQR 56 – 77) with a median BMI of 26.3 kg/m^2 (IQR 24 – 30.4). 17 (63 %) were non-smokers, 8 (30 %) ex-smokers and 2 (7 %) participants were actively smoking. Median NTproBNP was 1186 pg/ml (IQR 894 – 2126) and LVEF 38 % (IQR 26 – 40).

Separating demographics and baseline characteristics by the 2 randomization groups (placebo-magnerot and magnerot-placebo), reveals differences in median age (73 vs 59 years), median BMI (25.8 vs. 28.5 kg/m^2), median NTproBNP (1375 vs. 1160 pg/ml) and median LVEF (31 vs. 39 %) at visit 1, respectively. Those differences were statistically not significant, however may have clinical relevance and indicate slightly higher disease severity in the group that received placebo first**.**

EFFICACY RESULTS

Primary endpoint - NTproBNP: For the primary endpoint NTproBNP, a significant carry-over effect was identified (significant difference between the baseline visits of the first intake phase (V1) and the second intake phase after wash-out (V4)). This carry-over effect occurred only within the group who received first placebo. Therefore, the primary endpoint was analysed only exploratory. A post-hoc linear mixed-model analysis, with carry-over effect and period-effect as covariates did not show any significant covariate effects.

Median of NTproBNP decreased about 70 pg/ml (IQR -291 – 174) from 1056 pg/ml (IQR 679 – 2085) to 897 pg/ml (IQR 603 – 1876) under magnerot within 12 weeks. However, there was no statistical significance against

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placebo. The decrease under placebo was numerically higher with median 199 pg/ml (IQR -368 – 18) reduction from 1297 pg/ml (IQR 847 – 2094) to 1117 pg/ml (IQR 767 – 1801).

Observing the group receiving first magnerot showed a significant reduction of NTproBNP (p=0.022) between baseline (V1) and after 12-week intake (V3). In this group, NTproBNP was almost back to study start with only small placebo effects in the placebo intake phase. However, the group, receiving first placebo showed strong placebo effects in the placebo intake phase (p=0.075) and no reductions under magnerot in the second intake phase. Overall, the reductions of NTproBNP within the first 12 weeks could be prone to general placebo effects.

A sensitivity analysis including only those participants without having a significant change of cardiac concomitant medication or a relevant serious adverse event, did also not show any significant differences between magnerot and placebo. Similarly, there were no differences between the treatments in terms of NTproBNP in a subgroup with high or low NTproBNP at baseline, with or without a relevant change in cardiac concomitant medication, an LVEF greater than or less than/ equal to 40 % or participants with AEs with potential influence on NTproBNP or atrial fibrillation or none of those.

Secondary endpoints: None of the secondary endpoints showed significant treatment effects. Numerically, but neither significant nor clinically significant, under magnerot median LVEF improved by 1% (IQR -3 – 4). This numerical change was similar in the subgroup with participants having lower NTproBNP at baseline and in the subgroup with participants having LVEF ≤ 40 %. Neither NYHA classification, symptoms of HF (weight, nocturia, cyanosis, dyspnea, angina pectoris, ankle edema, anasarca) or hospitalization, showed relevant changes under magnerot. Subjective quality of life (QoL) assessed with the cardiomyopathy questionnaire overall summary score (KCCQ-OSS) and clinical summary score (KCCQ-CSS) did not show significant differences between magnerot and placebo.

Numerically, but neither significant nor clinically significant, under magnerot median KCCQ OSS improved by 1.77 score points (IQR -2.344 – 5.208) on a scale between 0 and 100 points and remained stable under placebo (median=0.0 points, IQR -5.729 – 4.687). Also, QoL assessed with the more general EQ-5D-5L questionnaire did not show significant differences. Under magnerot EQ-5D-5L VAS, which ranges from 0-100, improved by trend after 12 weeks (p=0.077) and was stable under placebo (p=0.731). The median showed an improvement of 1.0 points (IQR 0 – 10) under magnerot compared to placebo (median=0.0, IQR -5 – 5). The EQ index, ranging from -0.59 to 1, was stable under both, magnerot and placebo and showed no significant differences in quality of life. None of the subgroup analyses found any statistically significant effects in secondary endpoints.

Magnesium: Median plasma magnesium was with 0.84 mmol/l (IQR 0.76 – 0.89) at the beginning of magnerot treatment and 0.85 mmol/l (IQR 0.79 – 0.91) at the beginning of placebo treatment, within reference range at the beginning of both treatments. The reference range for magnesium ranges between 0.7 – 1.0 mmol/l. Median

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plasma magnesium increased by trend (p=0.05) under magnerot, compared to placebo. Increase was 0.03 mmol/l (IQR -0.01 – 0.06) under magnerot while slightly decreasing under placebo (median=-0.01, IQR -0.05 – 0.05).

SAFETY RESULTS

Within the current study, 27 participants (90%) suffered from an adverse event under magnerot, which was comparable to 24 participants (80%), suffering from an adverse event under placebo. In the wash out phase also 24 participants (80 %) suffered from an adverse event. Thirteen adverse events (12.5 %) of 104 adverse events under magnerot and similar 10 adverse events (9.6 %) of 104 adverse events under placebo were assessed by investigator as related to the investigational medicinal product. All related adverse events were mostly mild to moderate gastrointestinal complaints. Musculoskeletal, connective tissue, and bone disorders were substantially higher with placebo (17.3 % of AEs, 11 participants) compared to magnerot (3.8 % of AEs, 4 participants). Most of these events involved muscle cramps affecting various parts of the body, particularly the legs and feet. This could be due to the known effects of magnesium on reducing muscle cramps. Only one of the severe adverse events occurred under placebo, three severe events occurred during wash out. In total, 31 adverse events out of 300 were serious. Out of these 1 occurred under placebo and 15 occurred under magnerot in 5 participants. The remaining SAEs (N=15) occurred under wash-out (N = 6) or for two participants after end of trial (N = 9). None of the serious adverse events were rated as related to the investigational medicinal product. Serious adverse events were mainly linked to worsening of the underlying disease.

The compliance of investigational medicinal product intake was > 80% for all completing participants.

Safety laboratory parameters of kidney function were slightly more likely to be clinically significant after taking magnerot compared to placebo. During an observation, the investigator explained these findings with the worsening of the disease and magnerot was rated to have no influence on these findings.

CONCLUSION

In the current small sample population, suffering from mild to moderate, stable chronic heart failure, no effects of magnerot on NTproBNP or symptoms of heart failure could be shown. However, magnerot in the used dose was able to maintain magnesium levels with reference range and reduce musculoskeletal adverse events. No serious adverse events occurred, which were assessed by investigator as related to magnerot or placebo. Due to the small sample size, data variability plays a strong role, which makes it impossible to draw clear conclusions about the treatment.

DATE OF THE REPORT VERSION 1.0: October 04, 2024

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