This Summary of Clinical Study Report is provided for patients and healthcare professionals to demonstrate the transparency efforts of the Menarini Group. This document is not intended to replace the advice of a healthcare professional and can't be considered as a recommendation. Patients must always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document can not be considered as prescribing advice.

The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Investigators:	A list of participating investigators can be found in Appendix 16.1.4.	
Clinical Trial Centers:	2 centers: 1 center in Germany for tilting-table tests 1 center in France for parabolic flights	
Publication:	Planned	
Studied Period (Years): Date of First Enrolment: Date of Last Completed:	 05/03/2008 14/07/2008	**Phase of Development:** Phase I Trial
Sponsor's Responsible Person:	[redacted]	
Authors of the Synopsis:	[redacted]	
Objectives:	Primary objective: The aim of both study parts (tilting-table tests and parabolic flights) was to investigate possible influences of nebivolol on microcirculation parameters under micro-g conditions. Secondary objectives: Influences of nebivolol on heart rate, blood pressure and facial heat distribution. Moreover a standard model for drug testing under micro-g conditions was to be investigated.	

Methodology:

Primary efficacy variable:

Measurement of microcirculation using O2C (LEA Medizintechnik)

Secondary efficacy variables:

- Blood pressure, heart rate using HealthLab System (Koralewski Elektronik)
- Heat distribution in the face using Thermal Imaging Camera (Thermocam FLIR Systems)

No. of Subjects:

Tilting-table tests

	planned			realized				
	total	M	CD	total	M		CD	
	n	n	n	n	n	%	n	%
Randomized	16	16	16	16	16	100.0	16	100.0
Evaluable - safety	16	16	16	16	16	100.0	16	100.0
- efficacy								
- ITT	16	16	16	16	16	100.0	16	100.0
- PP	16	16	16	16	16	100.0	16	100.0

Parabolic flights

	planned			realized				
	total	M	CD	total	M		CD	
	n	n	n	n	n	%	n	%
Evaluable - safety	4	4	–	4	4	100.0	–	–
- efficacy								
- ITT	4	4	–	4	4	100.0	–	–
- PP	4	4	–	4	4	100.0	–	–

M = Medication, CD = Comparator Drug, ITT = Intention To Treat, PP = Per Protocol

Diagnosis / Indication and Main Criteria for Inclusion:	Diagnosis / Indication: NA (healthy volunteers) Main criteria for inclusion: • Age 20–45 years • The subject is healthy as judged by the responsible physician, with no clinically significant abnormality identified during the screening evaluation or medical history, including ECG • Non-smoker • The subject is willing and able to participate in both study parts (tilting-table test part and parabolic flight part) • Positive standard medical check-up for parabolic flight • The subject has a normal cardiovascular adjustment during tilting-table tests • The subject is willing to restrain a normal fluid supply before the tilting-table tests without a subjective feeling of thirst
Test Product, Dose, **Mode of Administration, Batch-No.:**	Nebilet® Active ingredient: nebivolol Dose: 5 mg Mode of administration: oral, in the evenings Batch-no.: D0608021 (tilting-table test part) D0608022 (parabolic flight part)
Duration of Treatment for Each Subject:	Tilting-table test part: Cross-over 7 days nebivolol/placebo, 7 days wash-out, 7 days placebo/nebivolol Parabolic flights: 7 days nebivolol before parabolic flight experiments
Reference Therapy, Dose, Mode of Administration, Batch-No.:	Placebo Active ingredient: none Dose: 5 mg Mode of administration: oral, in the evenings Batch-no.: D0608021 (tilting-table test part)
Criteria for Evaluation: **Efficacy:**	• • Primary efficacy parameters: • Intra-individual changes and changes from baseline (for tilting-table tests) of microcirculation parameters [oxygen saturation, hemoglobin (relative) and blood flow (relative)] • Parameters were calculated separately for temple and shinbone

	(tibia) in two different depths of the skin layer (up to 0.2 cm and 0.8 cm skin layer depths). • Secondary efficacy parameters: • Intra-individual changes and changes from baseline (for tilting-table tests) of parameters of the HealthLab system (systolic and diastolic blood pressure and heart rate)
Safety:	• Incidence of adverse events • For the parabolic flight part, change of vital parameters between the pre- and post-flight day • Change of clinical status (physical examination) in the conduct of the study
Statistical Methods:	The statistical analysis was performed for only one analysis population (full analysis population), which comprises all 16 subjects who participated in the study. • Although efficacy variables have been classified as primary and secondary variables, the statistical analysis was regarded as exploratively. • All variables were analyzed descriptively. • In addition, test-statistical analyses (only for the tilting-table test part) were performed solely exploratively for both primary and secondary efficacy parameters. • Two-tailed significance tests at a significance level of $\alpha = 0.05$ were carried out. Null hypothesis (H0) and alternative hypothesis (H1) were as follows: • H0: $\mu Neb = \mu Plac$ • H1: $\mu Neb \neq \mu Plac$ • where μNeb = expected value of the efficacy variable after treatment with nebivolol and $\mu Plac$ = expected value of the efficacy variable after treatment with placebo. • To assess treatment and possible carry-over effects the Grizzles two-stage model was applied.

SUMMARY - CONCLUSIONS

Efficacy Results

Mean values of the microcirculation parameters (oxygen saturation, relative hemoglobin and relative blood flow) of the temple measurements decreased during pull-up (approx. 1.8 g), increased during injection phase (0 g) and decreased between pull out (approx. 1.8 g) and post phase (approx. 1 g). When measured on shinbone, changes of microcirculation parameters were in the opposite direction, which may reflect the head-wards shift of body fluids even after a relative short period of 20 seconds of zerogravity.

Microcirculation parameters assessed during the tilting-table test showed changes in the same manner. Therefore, it is concluded that the tilting-table test represents a useful and valuable model for simulations of microgravity and may be used for further tests when selecting suitable drugs for a space pharmacy.

The parallel course of blood pressure and heart rate values during tilting-table and parabolic flight underlines the suitability of the tilting-table test as a simulation model for microgravity and also for testing clinical effects of drugs.

Safety Results

In total, 30 treatment emergent adverse events (TEAEs) occurred in 9 subjects during both study parts. Thereof, causally related TEAEs occurred in 4 subjects.

In both parts, tilting-table and parabolic flight part, 5 subjects each experienced TEAEs (17 vs. 13 TEAEs). During the parabolic flight part there was no related TEAE, most TEAEs may more likely be ascribed to transdermal scopolamine for motion sickness prevention prior to the parabolic flight.

None of the TEAEs during the tilting table part was judged as *severe*. Most frequently mentioned TEAEs were *headache* in 3 subjects (including one placebo subject), *vertigo, asthenia* and *tiredness* each in 2 subjects.

Summing up, safety data suggest a good tolerability of nebivolol during tilting-table as well as parabolic flight for healthy normotensive volunteers.

Conclusion

Overall, it is concluded that the tilting-table tests as well as parabolic flights seem to be attractive and comparable models to test pharmaceutics in astronauts prior to space flight, and that the highly selective β-1-receptor nebivolol, after further testing during short, mid- and long-term missions, seems to be at least one promising candidate for a space pharmacy.

To further evaluate the suitability of the simulation models tilting table and parabolic flight and to analyze clinical effects of nebivolol application under real and simulated micro-g conditions, randomized clinical trials with larger sample sizes and sufficient power for a statistical proof are needed.

Date of the Report: November 04, 2009