Final Report According to the Plan of Clinical Investigation of Medical Devices

CIP (Clinical Investigation Plans)

Clinical investigation title:

Clinical Investigation of the Electrotherapeutic Device for Mesodiencephalic Modulation

Clinical study title:

Application of Mesodiencephalic Modulation (MDM) for Improvement of Microcirculation in Tissues

Clinical Investigation Plan (CIP) reg. no.[1]: **LPME09006C**
Version (revision) no.: R00

FINAL REPORT

pursuant to Act No. 123/2000 Coll., Decree No. 316/2000 Coll. of the Ministry of Health of the Czech Republic and ČSN EN ISO 14155

Final Report reg. no.: **LPME09016C**
Version (revision) no.: **R00**

1 The Plan of Clinical Investigations is a document stating the rationale, objectives, design and proposed analyses, methodology, monitoring, conduct and record keeping of clinical investigations.

Final Report on Clinical Investigation of Medical Devices

1 CONTENT WITH PAGE NUMBERING INCLUDING ANNEXES AND TABLES

2 IDENTIFICATION INFORMATION

2.1 Title, identification number of the contract investigation organisation at which the clinical investigation is executed

Motol Teaching Hospital
Department of Internal Medicine, 2nd Faculty of Medicine, Charles University and Motol TH
Senior consultant: Prof. MUDr. Milan Kvapil CSc., MBA
V Úvalu 84
15006 Prague 5
Czech Republic

2.2 Title of the clinical investigation

Application of Mesodiencephalic Modulation (MDM) for Improvement of Microcirculation in Tissues.

2.3 Title of the clinically investigated medical device:

Device for MDM, type: MDM-2000/1 – Set,
Type BF applied part, electric power supply 230 V, 50 Hz.
SW: MDM-2000/1 (version 3.2)
Producer: ZAT a.s., Příbram, Factory number: 1800004; Class IIb.

2.4 Preclinical testing

It was necessary to comply with the applicable legal regulations for specified markets, especially the EU, when a group of inventions and patents used in the process of development of the medical device was put into practice. We consider the documents proving safety of the device for MDM, type MDM-2000/1 – Set, to be documents of preclinical testing. They include the following as regards:

- *Technical safety: certificate no. 1080798 (ČSN EN 60601-1standard) issued by Electrotechnical Testing Institute*
- *Biological compatibility of the parts coming into contact with a patient (ČSN EN 10993) reports nos. 022-023 (2001) issued by the National Institute of Public Health and report no.13/08/007issued by the National Institute of Public Health on 18 March 2008.*
- *System for process and manufacture quality management according to ČSN EN ISO 13485.*
- *Clinical safety – see the conclusions published in Praktický lékař (2007)*
- *Satisfaction of engineering & legal requirements for a product with a different use: Certificate of a device of a very similar construction designed for a different indication – EC certificate of conformity.*

2.5 Brief characteristics of the clinical investigation, including its outcome

Assessment of changes in microcirculation by applying the method of microcirculation measuring by means of the Doppler principle while using the electrotherapeutic device for MDM.
Assessment of changes in skin temperature.
Assessment of changes in transcutaneous carbon dioxide arising from the use of the electrotherapeutic device for MDM.
Assessment of input and output laboratory results during both phases of a clinical trial.
Assessment of blood pressure values arising from the use of the electrotherapeutic device for MDM.

2.6 Title (corporate name) and registered office of the legal entity assigning the clinical investigation (hereinafter only the "Sponsor"):

ZAT a.s.
K Podlesí 541
261 80 Příbram
IČO (company's identification no.): 45148431

2.7 Name, surname and place of permanent residence of the clinical research worker (hereinafter only the "Investigator"):

Prof. MUDr.Milan Kvapil CSc., MBA; Svárov 88, 273 00 Červený Újezd
MUDr. Erik Hollay; Na Výsledku II 1022/2, 140 00 Prague 4
MUDr.Krýšová Alexandra; Ústavní 600/2, 180 00 Prague 8

2.8 Name, surname and place of residence of the Sponsor's assistant

Prof. MUDr.Zdeněk Zadák, CSc.; Úprkova 670, 500 09 Hradec Králové 9

2.9 Individual parts of the clinical investigation

Assessment of microcirculation by means of the Doppler principle – Periflux device.
Assessment of skin temperature – Periflux device.
Assessment of partial pressure of carbon dioxide in tissues – Periflux device.
Assessment of input and output laboratory results.
Assessment of blood pressure values.

2.10 Date of commencement of the clinical investigation

12 April 2010

2.11 Date of premature termination of the clinical investigation (if applicable)

There was no premature termination.

2.12 Date of termination of the clinical investigation

2 July 2010

2.13 Date of elaboration of the final report on the clinical investigation

24 January 2011

3 LIST OF ABBREVIATIONS AND TERMS WITH DEFINITIONS

MDM - mesodiencephalic modulation
MDM-2000/1 – Set – electrotherapeutic device for mesodiencephalic modulation
Clinical investigation plan – Plan of clinical investigations of a medical device, ref. no. LPME09006C
Procedure - a therapeutic intervention during which a therapeutic current runs through a headset attached to a trial subject's head for the period of 30 minutes
Proband - the technical term describing a trial subject (patient), used especially in the tabular and graphic attachments hereto
Course - completion of 13 procedures in the course of 10 subsequent days (twice a day on 1^{st} – 3^{rd} day, once a day on 4^{th} – 10^{th} day)

Placebo	*- trial subjects are stimulated for a short period of time required for therapeutic current setting, however not longer than for 60s after the beginning of a procedure*
Randomisation	*- random division of trial subjects to A and B groups on the basis of the envelope method*
MVP	*- mean value baseline -placebo*
MVA	*- mean value baseline – active treatment*
MVZP	*- mean value max area (after temperature rise) - placebo*
MVZA	*- mean value max area (after temperature rise) - active treatment*
PZP	*- percentage change - placebo*
PZA	*- percentage change - active treatment*
Ch1	*- channel 1- measuring of microcirculation by means of the optic Doppler principle*
Ch2	*- measuring of skin temperature*
Ch3	*- measuring of transcutaneous oxygen*

4 PROFESSIONAL QUALIFICATION AND EXPERIENCE OF THE INVESTIGATORS

Annex no.10.3 - Curriculum vitaes of the investigators.

5 LIST OF OTHER PERSONS PARTICIPATING IN THE CLINICAL INVESTIGATION

No other persons participated in the actual clinical investigation.
Processing of statistics was executed by Doc. RNDr. Ladislav Pecen, CSc., Ladislav.Pecen@seznam.cz.

6 DATA ON VERIFICATION OF SUITABILITY OF A MEDICAL DEVICE FOR THE DETERMINED PURPOSE OF USE

6.1 Objectives and substantiation

Extension of the purpose of use of the device for MDM – for improvement of microcirculation in tissues.

The objectives of the clinical investigation according to the Plan of Clinical Investigation are as follows:

a) Within the clinical investigation, to verify whether the determined purpose of use of the medical device has been achieved, i.e. to prove the influence of mesodiencephalic modulation on improvement of microcirculation in a trial subject's tissue, especially for the diagnoses according to Article 6.3.3.1, laid down as "Subsidiary Criteria for Including a Trial Subject to the Study";
b) To specify side effects and evaluate whether they represent acceptable risks when the device is used under the conditions of its operation;
c) To verify whether the medical device – MDM-2000/1– Set – is suitable for use in medical care providing, especially as regards its safety and efficiency (functional characteristics)
d) To verify usability and understandability of the Operating Instructions, Doctor's Manual, Package Information Leaflet and functionality and operation of the MDM-2000/1programme of the device, apart from Czech also in English language.

The purpose is also to meet the requirements arising from ISO 13485:2003 standard and Council Directive 93/42/EEC concerning medical devices or Act No. 123/2000 Coll., on medical devices, and Government Order No.336/2004 Coll., that lays down technical requirements for medical devices.

According to the declaration made by the producer of MDM, the physical method is a non-pharmacological therapy that normalises reactions of an organism to defects caused by functional as well as organic diseases. MDM uses effects of special electric signals leading to selective activation of regulatory structures of a brain to correct the adaptation system of an organism. This causes excretion of biologically active substances to the blood circulation system intended to regenerate functional activity of bodily organs and tissues. Defective microcirculation is a part of a whole range of morbid conditions. Favourable influencing of microcirculation is a necessary precondition for returning damaged tissues back to their normal functioning.

According to the bibliography in the PUBMED database, MDM may be listed among non-invasive electrophysiological methods. MDM is based on stimulation of the central nervous system by defined electrical stimuli. The quality of microcirculation plays a critical role in the interaction between the blood flow and tissues. Acute chronic diseases may influence parameters of microcirculation.

The clinical investigation focused on proving the influence of the used device for mesodiencephalic modulation on peripheral microcirculation in patients who may be expected, on the basis of a diagnosis, to suffer from defective microcirculation of peripheral tissues. These defects are a collerate of so called endothelial dysfunction occurring in arteriosclerosis, diabetes mellitus with high frequency. Another cause of the microcirculation defect may be traumatizing influence of vibrations (work with pneumatic machines) and an after-effect of cold (frostbites, burns, etc).

The quality of microcirculation is one of decisive parameters of correctly functioning peripheral tissues. It is influenced by conditions of chronic and acute diseases. Microcirculation is studied in great detail, whereas the only possible examination was biomicroscopy until recently.

6.2 Bibliographic references to related legal regulations and recommendations of state authorities, authorized persons or other persons with respect to the clinical investigation in question

Act No.123/2000 Coll., on medical devices (as amended)
Government Order No.336/2004 Coll., that lays down technical requirements for medical devices (as amended)
Council Directive 93/42/EEC concerning medical devices (as amended)
Decree No. 316/2000 Coll. of the Ministry of Health of the Czech Republic, on particulars of the final report on a clinical evaluation of a medical device (as amended)
ČSN EN ISO 14155-1 Clinical investigations of medical devices for human subjects - Part 1: General Requirements(as amended)
ČSN EN ISO 14155-2 Clinical investigations of medical devices for human subjects - Part 2: Clinical investigation plan (as amended)
Decree No.501/2000 Coll., on the forms and methods of reporting adverse incidents of medical device (as amended)

6.3 Clinical Investigation Plan

Reference number of the Clinical Investigation Plan (CIP): LPME09006C
Study title: Application of Mesodiencephalic Modulation (MDM) for Improvement of Microcirculation in Tissues

In the course of clinical investigations, the Sponsor changed its authorized representative for clinical investigations. The originally authorized representative was Ing. Václav Náprstek, the newly authorized representative is Ing. Jaroslav Neužil. This change was properly reported to the Ethics Committee of the Motol TH as an administrative change.

6.3.1 Description of the Clinical Investigation Plan

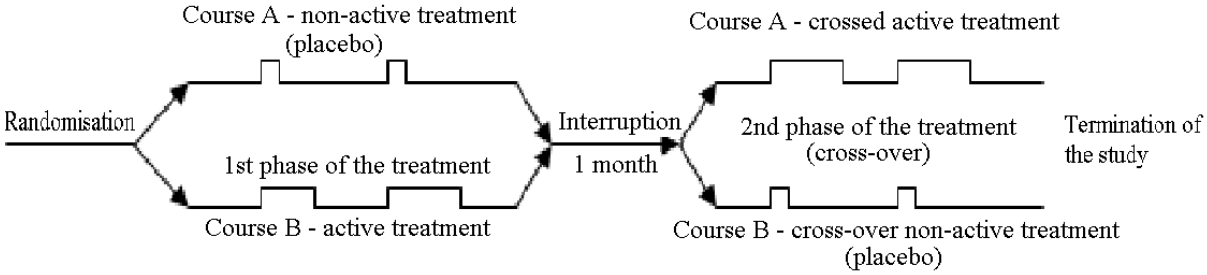
Randomised division of trial subjects to two groups (A and B) on the basis of the envelope method.

Course – 13 procedures in 10 subsequent days, twice a day on 1st – 3rd day, with the interval of 6-18 hours between procedures, once a day on 4th – 10th day, with the interval of 18-30 hours.

1st course (phase) group A non-active treatment (placebo), group B active treatment
30 days interruption between the 1st and 2nd phase.

2nd course (phase): group A active treatment, group B non-active treatment (placebo).

Measuring of microcirculation in every course always after 1,2,6,8,10,13 procedure,
(out of which 1st measuring always before the 1st procedure, the other measuring sessions follow always after a completed procedure).



6.3.2 Selection of the control group

The control group comprises of the monitored patients in the placebo phase – a patient plays the control role for himself/herself.

6.3.3 Population for the clinical investigation

6.3.3.1 Criteria for including patients or healthy persons who fulfil the function of the reference group and who will voluntarily undergo the clinical investigation (hereinafter only the "trial subjects")

- *Legal capacity.*

- *Trial subjects with Type 1 or Type 2 diabetes regardless of its treatment, presence of diabetic microangiopathy in diabetic neuropathy, with or without trophic defects.*
- *Absence of contraindications.*

Subsidiary criteria for including a trial subject to the Study:

- *Atherosclerosis of limb arteries*
- *Functional disorders of upper limbs (Raynaud's disease)*
- *Trophic defect in microcirculation disorders*
- *Diabetic microangiopathies in diabetic neuropathy with or without trophic defects*
- *Diabetic nephropathy*
- *Defective microcirculation in diabetic retinopathy*

Defective microcirculation is usually evident especially in subjects suffering from Type 1 and Type 2 diabetes. For this reason diabetics were usually included to the clinical investigation.

Subjects suffering from the following diagnoses were usually included to the clinical investigation:

- *Atherosclerosis of limb arteries*
- *Diabetic microangiopathies in diabetic neuropathy with or without trophic defects*
- *Diabetic nephropathy*
- *Defective microcirculation in diabetic retinopathy*
- *Hypertension*
- *Ischaemic heart disease*

Detailing of trial subjects, including specification of their respective diagnoses, is set forth in Annex No. 10.9.6.

6.3.3.2 The criteria for excluding a trial subject from the clinical investigation

Participation of a trial subject in another study
Active pulmonary tuberculosis
Presence of a metal object in the cranial cavity
Epilepsy
State after an organ transplantation
Psychoses
Schizophrenia
Invasive reconstruction intervention (during the term of the Study)

6.3.3.3 Registration of subjects of the clinical investigation (name, surname)

Source data on individual trial subjects are set forth in the respective file of the Study Participant Record.
24 subjects were included in the clinical investigation upon its commencement. Subject no. 5 withdrew in the middle of the clinical investigation without giving any specific reason, therefore the withdrawal cannot be evaluated as any negative adverse effect of the method whatsoever. Subject no. 25, who completed only the active phase, was newly included to the study instead of subject no. 5.
Hence, the total number of participants in the clinical investigation was 25 subjects.

6.3.3.4 Detailed characteristics of a subject of the clinical investigation
Subjects with Type 1 or Type 2 diabetes, regardless of its treatment, presence of diabetic microangiopathy in diabetic neuropathy, with or without trophic defects. The detailed characteristics of trial subjects are set forth in the table attached hereto as Annex no. 10.9.6.

6.4 Medical care provided to subjects of the clinical investigation

Baseline internal examination
Checks of laboratory results before the beginning and at the end of every course, regular checks of blood pressure before and after execution of the MDM procedure.

6.4.1 Identification data of the applied medical device, appliance

a) Device for MDM, type : MDM-2000/1 - Set, type BF applied part, electric power supply 230V, 50Hz, SW: MDM-2000/1 (version 3.2)
Producer: ZAT a.s., Příbram; Factory number: 1800004; Class: IIb

b) Periflux PF 5000 device – Vascular laser - Doppler device, Software 1.20
Producer: Perimed; Factory/serial number: 1211; Class: IIa

c) Periflux PF 5000 device - Vascular laser - Doppler device, Software 1.20
Producer: Perimed; Factory/serial number: 1725; Class: IIa

6.4.2 Previous and current therapies of the clinical investigation subject
Chronic therapy of trial subjects kept.

6.4.3 Treatment regime during the clinical investigation
Ambulatory application of procedures and measuring of microcirculation or hospitalization.

6.5 Variable quantities characterizing efficiency and safety of a medical device

6.5.1 Determination of the level of efficiency and safety
The Study did not primarily assess safety of the medical device.

Documents on the device safety from preclinical investigations:
- *Technical safety: Certificate no.1080798 issued by Electrotechnical Testing Institute,*
- *Biological compatibility: Reports no.022-023 (2001) issued by the National Institute of Public Health and report no. 12/08/007 issued by the National Institute of Public Health on 18 March 2008,*
- *Clinical safety: see previous studies with MDM.*

6.5.2 Primary evaluated values
Measuring of microcirculation defects by means of a device on optic Doppler principle:
- measured in PU (Perfusion Unit).

Measuring of skin temperature with a contact thermometer in exactly defined places:
- measured in °C.

Measuring of transcutaneous oxygen.

6.5.3 Description of the measuring methods and analysis of suitability of their application

Microcirculation was measured with Periflux 5000 device + Perisoft software of the Perimed company, designed to be used for measuring of microcirculation on the "principle of laser-Doppler measuring of blood perfusion".

The device works on the optic Doppler principle. It uses laser beams of a low performance, with wave lengths of 543nm, 633 and 780nm, which enable to detect cells (mostly erythrocytes, sporadically leucocytes).

The device was equipped with a module for measuring of skin temperature and transcutaneous oxygen

- measuring before the 1st procedure, furthermore after 2,6,8,10,13 procedure,

- beginning of measuring not later than within 10 minutes after the end of a procedure,

- measuring of at rest recording for about 15 minutes until values get stabilised (variability of 5-20 minutes),

-after stabilisation of the recording at rest, warming to the skin temperature of 44°C and measuring for 10-15 minutes until values get stabilised (variability of 10-20 minutes).

6.6 Securing of credibility of data from the clinical investigation

Trial subjects were monitored on a daily basis.

The ill were not informed whether it was a fictitious modulation or a real mesodiencephalic modulation. In addition to this, the cross-over design of the Study enabled us to distinguish the group which was treated fictitiously in the first phase from the group which was treated by means of mesodiencephalic modulation, while the monitored subjects did not have their own experience with mesodiencephalic modulation in the first phase.

An investigator filled daily records into the Study Participant Record according to the instructions set forth in the Directions for Document Use in the file of the Study Participant Record which was established for every participant meeting the conditions of participation.

The source data are available for inspection.

6.7 Applied statistics methods

The SAS (Statistical Analysis Software, version 9.1, Carry USA). The basic model for the applied cross-over design is the GLM (general linear model), with the effects of a phase, a period, sequence of periods and a subject, where the effect of a subject is nested in a sequence because every subject has only one sequence according to the randomisation. For the purposes of the statistical evaluation, all data differing from the average of a subject in question by more than 10 % were left out as regards microcirculation parameters. The result of the statistical significance of a sequence was found for native and cleaned data. Only the measuring at the end of application were included in the statistical evaluation of the method's effect; a relative change, expressed in per cents, was compared against values before application of the method (placebo) as well as absolute changes.

6.8 Data on evaluation of the effect of a medical device as declared by its producer with respect to the specified purpose of use

Within the scope of the investigations, it may be pronounced that the "Operating Instructions" manual attached by the producer fully meets the requirements of clinical use.

6.8.1 Analysed datasets on the medical device

Referential documents for the medical device:

a) *Investigator's Manual for the Clinical Investigation (ref.no. LPME09007C)*
b) *Operating Instructions for the MDM-2000/1 – Set Medical Device (in Czech) - (ref.no. LPME09010C)*
c) *Operating Instructions for the MDM-2000/1 – Set (in English) (ref.no. LPME09011A)*
d) *Doctor's Manual (in Czech) (ref.no. LPME09012C)*
e) *Doctor's Manual (in English) (ref.no. LPME09013A)*
f) *Package Information Leaflet – cotton pads (in Czech) (ref.no. LPME09029C)*
g) *Package Information Leaflet – cotton pads (in English) (ref.no. LPME09031AC)*
h) *Package Information Leaflet – NS1 headset (in Czech) (ref.no. LPME09030C)*
i) *Package Information Leaflet – NS1 headset (in English) (ref.no. LPME09032A)*
j) *Declaration of Conformity(ref.no. LPME09017C)*

During the clinical investigations, it was verified that all the directions set forth in the Operating Instructions and related documents were understandable, and the MDM-2000/1 – Set electrotherapeutic device performed operations as expected. Other detailed information on the tested electrotherapeutic device is set forth in the Questionnaire for the Investigator contained in Annex no. 10.6.

6.8.2 Evaluation of the methods of application of a medical device

The method of application corresponds to the purpose of the device and the localization of its effect. As regards its application in practice, it is important that the device may be used not only in recumbent patients but also in sitting persons. The method must be applied in a calm environment, without any disturbing perceptions.
No unpleasant or undesirable feelings on the side of trial subjects were recorded.

6.8.3 Outcomes concerning efficiency and suitability of a medical device as regards the determined purpose

The outcome of the statistical significance of a sequence was found for native (uncleaned) data as well as cleaned data. For the purposes of the statistical evaluation, all data differing from the average of a patient in question by more than 10 % were left out as regards microcirculation parameters. After the statistical native and cleaned data had been compared, it was found that the acquired outcome was true with a 95% probability, but on the other hand that 5 % need not correspond to reality => the statistical evaluation of native and cleaned data proved 95 % conformity.

The absence of statistically evaluated data in Annexes Nos. 10.9.1 and 10.9.2 is caused by exclusion of the data which differed by more than 10 % from the average of a patient in question, and also by withdrawal of subject no. 5 (he withdrew in the middle of the clinical investigation) and subject no. 25 (he withdrew after termination of the first phase).

Subjects suffering from the following diagnoses were included in the clinical investigation:

- *Atherosclerosis of limb arteries*
- *Diabetic microangiopathies in diabetic neuropathy with or without trophic defects*
- *Diabetic nephropathy*
- *Defective microcirculation in diabetic retinopathy*
- *Hypertension*
- *Ischaemic heart disease*

The detailed characteristics of trial subjects are set forth in the table attached hereto as Annex no. 10.9.6.
From its beginning, the design of the clinical investigation was focused on the indication which was, under this clinical investigation, evaluation of the influence of the studied method on changes of microcirculation in tissues. Efficiency was investigated with a focus on defects of microcirculation, not with a focus on individual diagnoses. The obtained results give evidence of the detected changes in microcirculation.

No optimal value has been determined for microcirculation as a whole that could be used as a baseline deviations (if any) from which could be subsequently measured and evaluated to unambiguously determine whether there has been an improvement or deterioration. The value of microcirculation of every individual subject is an individual quantity which changes in every person depending on many factors (e.g. age, condition, performed activities, etc). During the measuring executed as a part of the clinical investigations, we were monitoring changes in microcirculation during individual phases of treatment and evaluated the results obtained during active treatment vs. placebo. The evaluation of measured values is showed in Annexes Nos. 10.9.3 and 10.9.4.

A detailed analysis of the skin temperature after temperature rise did not show any statistically or clinically significant differences, which proves that the conditions for measuring of microcirculation were standardised. Changes in microcirculation in skin after the method has been applied were not statistically significant when the active phase was compared to placebo. Neither any significant influence on microcirculation during an individual period was proved. However, a sequence had a statistically significant influence on percentual changes in microcirculation under the basic conditions and after a temperature rise ($p=0.0045$) and also the influence of a period was statistically significant ($p=0.0379$). Percentual changes in perfusion are in A group/period 1/1071.54 (506.36) % and A/period 2/ 1301.85(663.2) % , in group B/period 1/ 989.83 (394.46) % and B/period 2/ 1053.34(463.75)% after a temperature rise. It shows that when there was an active phase in the first period, microcirculation was positively influenced especially in the second period with the placebo phase, and when placebo was applied in the first phase, there was no influence in the active phase during the second period. In evaluating the influence of the phase sequence it was hence proved that in patients with the first phase – active (period 1) the percentual change in the parameters of perfusion in the second phase – placebo (period 2) is statistically significantly bigger in comparison with the second group in which this sequence was inverse. The descriptive statistics show that the influence of a period is given by the active

phase-placebo sequence. The findings could suggest the possibility that the effect of the method on microcirculation will appear only after 30 days have lapsed. A detailed analysis of outcomes and discussion are set forth in Annex No. 10.11.3.

Oxymetric measurements show a tendency to better values in the active phase, nevertheless, these changes do not achieve any statistical significance. Differences in the averages of the oxymetric measurements are in the first phase as follows: 76.36 in the placebo phase, 83.84 in the active phase; in the second phase as follows: 55.79 in the placebo phase, 79.30 in the active phase. The total average of oxymetric measuring is 64.32 in the placebo phase, and 81.55 in the active phase. As standard deviations show, the variability of results is high (in total 64.32±103.25 in the placebo phase, 81.55± 109.12 in the active phase). The differences in oxymetric measurements are also in median values – in total 35.39 in the placebo phase, 53.02 in the active phase. The statistical significance of differences, if they exist in the population, could be proved by a study with a higher number of patients or narrower input criteria. A detailed analysis of the results and a discussion are set forth in Annex No. 10.11.3.

Glycaemia did not change in any statistically significant manner, only the glycated haemoglobin changed – during the active phase its absolute value was dropping down and, on the contrary, during the placebo phase it was increasing. The difference expressed in the absolute difference was a growth by 0.29 % on average (median 0.2) in the placebo phase and decrease by -0.36 on average (median 0.4) in the active phase. Changes during the phase of placebo application are not clinically significant, however, changes during the active phase are contrarily very significant. The reason is not only the absolute difference, but especially the fact that the values were taken at the beginning and at the end of a phase, i.e. within the interval of 10 days; hence, the change in the compensation must have been considerable. However, the design of the study does not allow this positive finding to be explained. It may be expected that a higher number of patients or narrower input criteria may lead to explanation of the obtained positive finding. Specification of such criteria is one of suitable ideas for determination of the "Follow up" concept (see Article 8).
A detailed analysis of the results and a discussion are set forth in Annex No. 10.11.3.

As a control of adverse effects (if any) of the mesodiencephalic modulation influence on microcirculation, trial subjects' subjective feelings were evaluated as a part of the clinical investigation. During the test, an investigator was asking trial subjects whether they felt or did not feel any improvement. Obtained answers are recorded in the "Study Participants Records" file. No subjective signs of aggravation were detected. The characteristics of the subjects participating in the clinical investigation are set forth in Annex No. 10.9.6.

6.8.4 Interaction and its potential incidence

No interaction incidence was detected. No other devices were applied. Subjects were treated with common antidiabetics, antihypertensives and hypolipidemics. We may exclude interaction for these groups of drugs.

6.9 Evaluation of safety of a medical device as regards subjects of the clinical investigation

No adverse incident was detected.
No adverse event was detected.

6.9.1 Results of monitoring of vital functions, physical finds and other observations related to safety of the tested medical device
Vital functions, physical finds, blood pressure values and EKG were not influenced by MDM.
Data on the measured values are set forth in the respective file of the Study Participant Record. A complete survey of the measured blood pressure values is set forth in Annex No.10.9.1.

6.9.2 Laboratory evaluations or, alternatively, chemical analyses

6.9.2.1 Laboratory examinations of individual subjects of the clinical investigation
Annex no. 10.9.2 – The values of measuring of biochemical indicators

6.9.2.2 Evaluation of the laboratory values
Annex no. 10.9.2 - The values of measuring of biochemical indicators

6.9.3 Adverse events
None were detected.

7 GENERAL SUMMARY AND CONCLUSION

The clinical investigation had the character of a pilot project (the first clinically relevant testing of a widely defined set of subjects with the aim to verify the basic hypothesis).The result of a detailed statistical analysis proved that the parameters of the main outcome (influence on microcirculation) were loaded with a high intraindividual and interindividual variability. On the basis of statistical evaluation of the results obtained from measuring it may be concluded that the parameters used for evaluation of microcirculation were statistically significantly better after a lapse of time for the first active phase in the second placebo phase. It may be concluded from this finding that the influence of the method becomes evident after the interval of 30 days have lapsed after its application.

A detailed discussion on the results is in Annex No. 10.11.3, representation of the results is provided in the tabular and graphic annexes (see Article 0).

A significant finding from the clinical viewpoint is the fact that during the clinical investigation no adverse effect was detected. The method of mesodiencephalic modulation proves to be very safe.

On the basis of the results arising from the Clinical Study, the MDM method may be recommended as a device having a positive impact on microcirculation in peripheral tissues in the long-run; the method may be recommended to be included among the methods of physical therapy or balneotherapy, as the case may be.

8 DISCUSSION

It may be expected that if a narrower definition of the treated cases was used, it would be possible to prove, with a lower variability of obtained parameters, convincing statistical

results concerning the influence of mesodiencephalic stimulation on the parameters of microcirculation in tissues. A detailed discussion on the results is in Annex No. 10.11.3. Taking into account the very encouraging results of the Clinical Investigation, the Sponsor will develop the "Follow up Plan" aimed at improving microcirculation in tissues. The document describing the "Follow up Plan", including all data necessary for its implementation will have been drawn up by 30 June2011 at the latest.

9 INVESTIGATORS' STATEMENT ON THE FINAL REPORT

The final report was drawn up in accordance with legal regulations, approved Study Protocol, and on the basis of obtained results that were statistically evaluated.

10 ANNEXES TO THE FINAL REPORT ON CLINICAL INVESTIGATIONS

Annexe number and title:

10.1 Written consent of the competent Ethics Committee with execution of clinical investigations

Affirmative opinion of the Ethics Committee on the clinical assessment of a medical device according to Record No.LPME09006 as of 8 December 2009, ref. no. EK-2026/09

10.2 Statement by the competent Ethics Committee

Statement by the Ethics Committee on the "Application for a statement on executed clinical investigations by the Ethics Committee of the Motol TH" as of 28 January 2011, file no. 0322/2011

10.3 CVs of investigators *)

10.4 Informed consent, including advice and information on how the informed consent was obtained *)

Before the study commenced, a subject had received understandable information in accordance with the "Information for a Patient" Annex; the education was recorded in documentation by the educating doctor and a subject received a copy of the document.

After such understandable education, a subject, in case he or she agreed with the Study and its terms and conditions, signed the "Informed Consent" that makes a part of health documents as law obliges if a subject has been hospitalised, and an annex to the Study Participant Record; a subject received one copy of the consent.

10.5 A sample of the Study Participant Report file*)

10.6 Questionnaire for investigators

10.6.1 Prof. MUDr. M. Kvapil, CSc., MBA – Subjective evaluation of the clinical investigation documents and application of the MDM-2000/1 – Set electrotherapeutic device

10.6.2 MUDr. A. Krýšová - Subjective evaluation of the clinical investigation documents and application of the MDM-2000/1 – Set electrotherapeutic device

10.6.3 MUDr. Erik Hollay - Subjective evaluation of the clinical investigation documents and application of the MDM-2000/1 – Set electrotherapeutic device

10.6.4 Z. Martínková - Subjective evaluation of the clinical investigation documents and application of the MDM-2000/1 – Set electrotherapeutic device

10.7 Clinical Investigation Plan *)

10.8 Original documentation for a medical device*)

The following documentation in Czech and English language versions.

- *Operating Instructions*
- *Doctor's Manual*
- *Package Information Leaflet - Headset*
- *Package Information Leaflet - Pads*

10.9 Tables and charts based on data obtained from the clinical investigation

10.9.1 Table: Values obtained from the measuring of microcirculation by means of the Doppler principle – the Periflux device

10.9.2 Table: Values obtained from the measuring of biochemical indicators (blood count, biochemistry – serum, urine + sediment)

10.9.3 Chart: The average value of the percentual change in microcirculation

10.9.4 Chart: Percentual changes in microcirculation (after temperature rise vs. baseline)

10.9.5 Statistical evaluation of measured values by means of the SAS (Statistical Analysis Software, version 9.1, Carry USA)

10.9.6 Table: Overview of basic characteristics of individual subjects

10.10 Bibliography *)

As a part of the Clinical Investigation, the Sponsor submitted the following professional publications, attached as Annexes Nos. 22 – 28 to the "Clinical Investigation Plan":

- *Annex No. 22 Publication in Praktický lékař (2007)*
- *Annex No. 23 Publication on experiments and MDM in English (1999 – 2000)*
- *Annex No. 24 Publication in English (1995 – 2004)*
- *Annex No. 25 New Physical Technologies in Diabetic Complications Treatment - Symposium (2009)*
- *Annex No. 26 Results of application of MDM in the Russian Federation (1986 – 2009)*
- *Annex No. 27 Microcirculation – measuring, clinical experience*
- *Annex No. 28 Microcirculation – preclinical research*

In this case ***the above specified bibliography was not included in the Clinical Investigation Plan with the aim to develop a critical bibliographic research related to the defined purpose of use of the tested medical device and the proposed method of application,*** *but only with the aim to provide support information to investigators as regards the following:*

- *Application of the MDM-2000/1 – Set medical device and its use in the treatment by mesodiencephalic modulation method;*
- *The executed Clinical Investigation during which the MDM-2000/1 – Set medical device was used to treat complications related to diabetic polyneuropathy;*
- *Application of the mesodiencephalic modulation method in the Russian Federation;*
- *Determination of possible complications caused by defective microcirculation (e.g. arterial defects, chronic venous insufficiency, defects in critical states, etc);*
- *The method of measuring of defects in microcirculation based on the "principle of laser-Doppler measuring of blood perfusion" by means of the Periflux device*

10.11 Appendices, especially

10.11.1 Copies of contracts concluded between the Sponsor and Sponsor's Assistant and the Investigator and the Contract Investigation Organisation at which the clinical investigation was executed *)

10.11.2 The randomisation scheme and codes enabling to identify subjects of the clinical investigation and the respective application of the medical device *)

10.11.3 A detailed scientific analysis of the clinical investigation progress, including the methodology of evaluation, analysis of results and discussions, and bibliography

10.11.4 Report on Control No.02-01-11/123-00/KZZP (issued by: SÚKL, Prague; on 28 February 2011)

10.12 Publications

- *"Influence of Mesodiencephalic Modulation on the Dermal Microcirculation" abstract accepted for presentation in the form of a poster at the Diabetologic Congress in Luhačovice, held as a part of "The 47th Diabetologic Days in Luhačovice" held on 14 – 16 April2011 (Luhačovice, The Elekta Municipal Culture Centre)*
- *No other publications have been drawn up on the basis of the clinical investigation.*

**) – The Annex makes a part of the file of documents for the clinical investigation*

Final Report on Clinical Investigation of Medical Devices

Representatives of the contract investigation organisation:

JUDr. Ing. Miloslav Ludvík, MBA
Director
(Motol Teaching Hospital)

Prof. MUDr. Milan Kvapil, CSc., MBA
Principal investigator
(Motol Teaching Hospital)

MUDr. Alexandra Krýšová
Investigator
(Motol Teaching Hospital)

MUDr. Erik Hollay
Investigator
(Motol Teaching Hospital)

Sponsor's assistant:

prof.MUDr.Zdeněk Zadák, CSc.
Sponsor's assistant

Sponsor's representatives:

Ing. Jaroslav Scharf
Chairman of the Board of Directors
(ZAT a.s.)

Ing. Vladislava Česáková
Management executive officer
(ZAT a.s.)

Ing. Ivo Tichý
Commercial and Implementation executive officer
(ZAT a.s.)

Ing. Jaroslav Neužil
Authorized representative for clinical investigations
(ZAT a.s.)

In …… Date ……