Clinical Investigation Plans of Medical Device
CIP (Clinical Investigation Plans)

FINAL REPORT

of Clinical Investigation of Medical Device

Medical device: **Electroterapeutic Device**

Type: **MDM-2000/1 - Set**

Manufacturer: **ZAT a.s., K Podlesí 541, 26180 Příbram VI, Czech republic**

Investigation name:

Clinical Investigation of Electrotherapeutic Device MDM-2000/1 of Mesodiencephalic Modulation

Name of clinical study (investigation):

Using of Mesodiencephalic Modulation (MDM) for Treatment of Diabetic Polyneuropathy Pain

Submitter/Manufacturer: **ZAT a.s., K Podlesí 541, 26180 Příbram VI, Czech republic**

Provider: **University Hospital in Hradec Králové, Sokolská 581, 500 05 Hradec Králové, Czech republic**

Author of report: **prof. MUDr.Luboš Sobotka, CSc.**

Date of elaboration: **20.11.2006**

Clinical Investigation Plans: **LP05011CZ**
Revision: **R02**

Document No.: **LP05038EN**[*)]

Clinical investigations were executed in according with ČSN EN ISO 14155-1.

[*)] *This document No.LP05038EN has been made by translation of the document No.LP05038CZ*
Translation ZAT a.s., correction prof.L.Sobotka, M.D., prof.Z.Zadak M.D., dr.F.Musil M.D.

Content

**) enclosure makes a part of file „Clinical Investigation Documentation“*

1 Registration data

1.1 Provider

University Hospital in Hradec Králové, Sokolská 581, 50005 Hradec Králové
IČO: 00179906
Clinic Gerontological and Metabolic, Head Prof. MUDr. Luboš Sobotka, Csc.

1.2 Title of Clinical Investigation

Using of Mesodiencephalic Modulation (MDM) for Treatment of Diabetic Polyneuropathy Pain

1.3 Name of Medical Device tested

Electrotherapeutic Device MDM-2000/1 - Set

1.3.1 Identification data of Medical Device

Name:	*Electrotherapeutic Device*
Type of device:	*MDM-2000/1 – Set*
Documentation:	*3-2438*
Classification of device:	*active Medical Device class IIb.*
Construction of device:	*Electrotherapeutic Device class I with supplemental part type BF according to ČSN EN 60601-1*
Construction of set:	*Medical electric system according to ČSN EN 60601-1-1*
Serial number:	*MDM-2000/1–Set (No.1500002) (device MDM-2000/1, No.S7 0003)* *MDM-2000/1–Set (No.1500003) (device MDM-2000/1, No.S7 0005)*
Manufacturer :	*ZAT a.s., K Podlesí 541, 26180 Příbram VI, Czech Republic*

1.4 Short description of Clinical Investigation and its results

The main aim of investigation was to evaluate an impact of mesodiencephalic modulation to relief from pain of diabetic polyneuropathy origin.

The investigation was realized with 25 diabetics with defined symptoms of diabetic polyneuropathy. Patients were devided in to two groups. The first group was treated by mesodiencephalic modulation MDM during first hospitalization and after one month (second hospitalization) they where treated with fictitious modulation – placebo (the MDM modulation running at the maximum limit 1 minute). The second group had reverse order of procedures.

Sealed envelopes method was used for randomization of the subjects in to two respective groups.

Two patients interrupted the investigation because they did not accept the second hospitalization (the first of these was starting with mesodiencephalic modulation and the second of these was starting with fictitious modulation).

Influence of mesodiencephalic modulation caused considerable subjective pain relief of all patients. The pain relief was apparent after the third modulation and after fifth modulation all patients experienced significant improvement.

The second aim of investigation was to evaluate possible side-effects of mesodiencephalic modulation. No side-effect was found in some patient. This was confirmed by clinical and laboratory investigations (blood pressure, pulse rate, ECG, blood biochemistry, haematology parameters).

It can be concluded that the mesodiencephalic modulation leads to the reduction of diabetic polyneuropathy pain without side-effects.

1.5 Submitter

ZAT a.s., K Podlesí 541, 26180 Příbram VI, Czech Republic
IČO: 45148431

1.6 Submitter's Entrusted Person

ing.Václav Náprstek, Čechovská 122, 26101 Příbram VIII

1.7 Submitter's Assistant
Prof.MUDr.Zdeněk Zadák, CSc., Úprkova 670, 50009 Hradec Králové 9

1.8 Investigators
Prof. MUDr. Luboš Sobotka, CSc., K Osadě 730, 50009 Hradec Králové 9 (Principal Investigator)
MUDr. Alena Šmahelová, Ph.D., Borek 11, 53401 Holice v Čechách (Investigator)
MUDr. František Musil, Ph.D., Hoděšovice 87, 53401 Holice v Čechách (Investigator)

1.9 Ethics Committee
Ethics Committee of University Hospital in Hradec Králové, Sokolská 581, 50005 Hradec Králové

1.10 Particular parts of Clinical Investigation
1. *The selection of patients and informing them about Clinical Investigation. Informed Consent was signed all patients who participate in the study.*
2. *Admission of patients to the Department of metabolic care and gerontology in Hradec Králové*
3. *Mesodiencephalic modulation or fictitious modulation (according to randomization) – 13 procedures during 10 days of hospitalisation*
4. *Discharging of patients from Department of metabolic care and gerontology. One month stay at home*
5. *Second admission of patients to Department of metabolic care and gerontology*
6. *Fictitious modulation or mesodiencephalic modulation (according to randomization) – 13 procedures during 10 days of hospitalisation*
7. *Discharging of patients from Department of metabolic care and gerontology*

1.11 Start of Clinical Investigation
24.11.2005

1.12 Early termination of Clinical Investigation

1.13 End of Clinical Investigation
25.05.2006

2 List of abbreviations and definitions

MDM - mesodiencephalic modulation
Placebo – fictitious modulation
BP - blood pressure
PR - pulse rate
ALT – alaninaminotranspherase
AST – aspartátaminotranspherase
ALP – alcaline phosphatase
Clinical Investigation – for purposes of this document replaces " clinical trial"
MD - Medical Device
Study subject - participant of Clinical Investigation who fulfills criteria for participation in the study

3 Investigator´s qualification and practice

Enclosure No.0 Curicculum Vitae of Principal Investigator

4 List of persons cooperated at Clinical Investigation

Prof. MUDr. Luboš Sobotka, CSc.
MUDr. Alena Šmahelová, PhD.
MUDr. František Musil, PhD.

Hana Melicharová
Ing. Jiří Knížek, CSc. – statistics

5 Evaluation of pertinence Medical Device for intended rational use

5.1 Aims and reasons

The main aim was evaluation of impact of mesodiencephalic modulation to algic symptoms of diabetic polyneuropathy. This disease is very difficult-to- treat and painful for the patient. Pharmacotherapy is expensive and it´s effect is not clear.

Mesodiencephalic modulation according to literature data is the method which could be used as full method for the treatment of the pain of diabetic polyneuropathy origin.

Special device for mesodiencephalic modulation is used for the treatment.

5.2 Related legal enactment and recommendation public body and authorized persons

Abiding MDD Directive 93/42/EEC on Medical Device and national legislative.

5.3 Clinical Investigation Plan

Evidence number of Clinical Investigation Plan (CIP): LP 05011CZ
Name of clinical study (investigation):
Using of Mesodiencephalic Modulation (MDM) for Treatment of Diabetic Polyneuropathy Pain

Czech language documentation of Medical Device was translated in to English and Russian language. This documentation was used during the clinical study to evaluate the quality of translations.

5.3.1 Description of Clinical Investigation Plan

The procedure of random cross-over study was specified by Clinical Investigation Plan for 25 patients with algic symptoms of diabetic polyneuropathy. Patients were registered for the study after the information about aims of study and after signing the Informed Consent with participation in the study.
Subsequently subjects were randomized into those who starts mesodiencephalic modulation or the fictitious modulation – placebo (only one minute MDM modulation - maximum) using the sealed envelopes method. The impact MDM of placebo on the pain relief was evaluated using eight degree scale – see enclosed Protocol of Participant in the Clinical Study.

5.3.2 Control group

It is random cross-over study where each patient is self-creating control.

5.3.3 Randomisation

Submitter made randomization of patients to the two same groups A,B by random method of sealed envelopes (first half of cards was group A and second half was group B; numbering envelopes, shuffling and inserting of the chosen cards into envelopes; sealing of envelope). The result of randomization was insertion of chosen envelope into numbered file (Protocol of Participant in the Clinical Study). Using of envelopes by Investigator is following:

All envelopes were still placed in the designated place at Assistant of Clinic Head.
Envelope was opened and closed purely by doctor (Investigator).

More detailed specification is in the Enclose No.9.8.

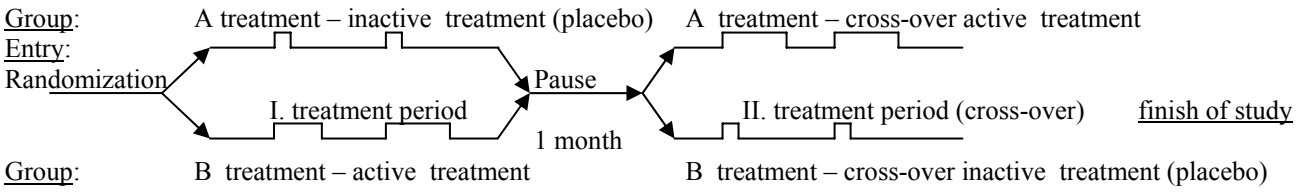
5.3.3.1 Using of envelope of random method and enlistment of patient to the group

- *Doctor doing the treatment of patient by MDM (modulation, placebo) is opening the envelope.*
- *He inscribes in the card indicating the group the number of envelope by blue pen and he notes the group so that nobody knows only him the enlistment of patient.*
- *After he puts card back to the envelope and closes it so that is impossible to find out enlistment of patient to the group otherwise than by again opening. Closed envelope he hands-over to hands Head's Assistant.*
- *He fills the number of envelope in the content of file.*
- *Every envelope is used only onetime and after finishing of study it becomes the part of file of Protocol of Participant in the Clinical Study.*
- *Random running is not impact in the case that patient has not finished the study because for next patient is used new envelope.*

By reason of identification of subjects are in the report stated: patient ordinal number, patient initials and case-record number.

5.3.3.2 Progress chart of treatment after separating patients to the groups A/B and specification of placebo

The active treatment: pass through 13 procedures during 10 days (1.-3. day twice daily, 4.-10. day once daily). One procedure runs 30 minutes.
The placebo: patients are stimulated short time necessary for setting of optimal electric current in according to procedure stated in the Doctor guide. After finding of optimal electric current for patient the doctor setups rate 0mA and will be finished whole procedure. Named procession has to be finished (setup rate 0mA) until 60seconds after starting procedure.



5.3.4 Population for Clinical Investigation

Participants of Clinical Investigation were patients (next "subject evaluation") who fulfill criterions for participation (vide the Protocol of Participant in the Clinical Study).

5.3.4.1 Criterions for enlistment of subject evaluation

Registered in the study were diabetics with type 1 or 2 with diabetic polyneuropathy and algic symptoms. Exclusion criterions for the study were diabetics younger 18 years and older 80 years, pregnant women or women supposing pregnancy, patients in other study and patients with acute decompensation of diabetes, severe liver- disease, acute renal failure, severe renal disease, dyshaemopoesis, disorders in haemocoagulation parameters , acute infectious disease, malignant and benign tumors, epileptics, psychotics, patients with eye disorders, patients with metal thing in area of skull or cranial cavity.

5.3.4.2 Criterions for exclusion of subject evaluation

- *undesirable effects*
- *patient's decision about discontinue in the study*

5.3.4.3 Identification of subject evaluation

All information about the subject evaluation, which are not possible publish in the Final Record by reason of protection of personality, are registered in the Protocol of Participant in the Clinical Study. This file is identified by participant's number, patient initials and case-record number. Each subject evaluation was indicated by name of group (A or B) at the end of study. The name of group was inscribed in the Protocol when whole study was finished. Code identifiers intended for working and publication of data are ordinal number of patient and group.

5.3.4.4 Detailed characteristic of subject evaluation

The subject evaluation were patients with algic symptoms of diabetic polyneuropathy who agried with the enlistment in the study. Overall 25 patients were enlisted in the study. They were stabilized patients with diabetes type 1 or 2.

5.4 Medical care for subject evaluation

Patients were hospitalized in the ward A of Department of metabolic care and gerontology *University Hospital in Hradec Králové. These patients were observed by standard regime including dietary meal and therapy in according with the disorder.*

5.4.1 Previous and existing therapy of subject evaluation

Patients were treated by insulin or peroral antidiabetic drug. Formerly the half of these patients was treated by pharmacotherapy of diabetic polyneuropathy. It means infusion with thioctic acid or Gabapentinum (preparation Neurontin). Before enlistment in the study all patients had subjective problems and last pharmacotherapy was halted minimally 1 month before starting study. Rem.: pharmacotherapy was not halted by reason of study but by reason of its ineffectiveness (Gabapentinum) or it was not effectual (thioctic acid infusion). Other therapy (hypertension , heart failure treatment, etc.) was not changed during the study.

5.4.2 Medical regime during clinical investigation

Patients were treated by insulin or peroral antidiabetic drug and their long-term using medicaments. Hospitalized patients had diabetic diet. Hospital-regime and frequency of doctor´s round was in accord with common standard.

5.5 Variable quantities characterizing effect and safeness of Medical Device

5.5.1 Determination rate of effect and safeness

Evaluated parameter was the relief from pain caused by using mesodiencephalic modulation or fictitious modulation. Patients were biochemically checked always before starting and after finishing stay in hospital. Before and after each procedure blood pressure, pulse rate and ECG record were taken from each patient.

5.5.2 Primary values evaluated

Primary aim was monitoring relief from pain caused diabetic polyneuropathy by means of eight-ratio scale what characterizing scale of improvement.

5.5.3 Describe of measuring method and analysis of pertinence using

At the patients was monitored subjective improvement of polyneuropathic pain by means of eight-ratio scale. It was recorded in the Protocol of Participant in the Clinical Study. Concretely patients were asked for recording their subjective condition following:

unchanged – 0 points

slightly changed – 2 points

half relief – 4 points

expressive change – 6 points

or they are without problems against their condition before hospitalizing – 8 points

1, 3, 5 a 7 points means values between named scale of pain (e.g. 1 – condition without changes up and to slight change).

Subjective pain sensation always was in comparison with condition before starting mesodiencephalic modulation or fictitious modulation.

The pain scale is using standardly during evaluation of subjective pain sensation. For the purpose of Clinical Investigation named scale was suitable and it follows from result of Clinical Investigation. Evaluation of pain by means of the scale was easy executable, understandably and uniquely determined for all patients.

5.6 Reliability of Clinical Investigation data

Patients were monitored daily and they filled the scale always after the mesodiencephalic modulation or the fictitious modulation. Patients were not notified of kind of mesodiencephalic modulation or fictitious modulation. Beyond cross-over design of study allows differentiate of groups. The first group what had fictitious treatment in the first phase and the second group what had active mesodiencephalic modulation, whereas in the first phase monitored subject had not own experience with mesodiencephalic modulation. Simultaneously the Principal Investigator did not know to what group the patients were registered.

Daily records Investigator filled in the Protocol of Participant in the Clinical Study according with Instructions for Documents Using named in the file in the Protocol of Participant in the Clinical Study.

5.7 Using of statistical methods

Numerical data were tested according to lay-out. In the case of the normal lay-out was used T-test, event. Aspin-Welch Test. In the case of the abnormal lay-out were used the tests non-parametric – Mann Whitney Test and Kolmogorov - Smirnov Test. The subjective scale pain was evaluated by means of non-parametric – Mann Whitney Test and Kolmogorov- Smirnov Test. The subjective data are stated as the medianus and as the maximum effect of therapy. Simultaneously was statistical evaluated the effect of both subgroups it means the subgroup what starting with the fictitious modulation and the subgroup what starting with the mesodiencephalic modulation. The aim of this investigation was exclude the possible alteration of the results through rank of the procedures.

Statistical evaluation was executed by means of software NCSS (www.ncss.com) at the Institute Medical Biophysics of Medical Faculty of Charles University in Hradec Králové by ing. Jiří Knížek , Csc. Every statistical evaluation has special record enclosed to the Final Report.

5.8 Investigation effectiveness of Medical Device in light of purpose rational use

5.8.1 Analyzed data sets for Medical Device

Sets of information for Medical Device were complete. Those information sufficiently informed Investigators at following language version: Czech, English and Russian.

5.8.2 Investigation of the ways of Medical Device application

The mesodiencephalic modulation with using two electrodes placing on the area forehead and the area nape. This process is stated by manufacturer and its realization was without problems.

5.8.3 Results of effectiveness and pertinence in light of purpose rational use

The Clinical Investigation results show evidence of significant subjective improvement of pain symptoms of diabetic polyneuropathy. The improvement was caused by using Electrotherapeutic Device MDM-2000/1 – Set.

5.8.4 Interaction and its possible occurrence

During the study was not indicated interaction with others medical process.

During the study was not indicated interaction with others medical devices.

5.9 Investigation of safeness of Medical Device in light of evaluated subjects

5.9.1 Results of monitoring and other monitoring connected with safeness evaluated Medical Device.

During using of Medical Device were monitored vital functions of patients including ECG before and after MDM.

Source data of patients are stated in the pertinent file of Protocol of Participant in the Clinical Study. The values of microalbuminuria and glycosylated hemoglobin were not investigated at whole extent (it means at all 4 investigations) connecting 6 from 25 patients who starts the study. During statistical evaluation took view of it and this fact has not impact on the evaluation of the effect MDM.

Undesirable side effects were not found during using device in light subjective changes and objective investigation, even were not found changes in pursued measurements which characterizing vital functions of patient.

A - Blood pressure:

In the Graph No. 4.1, 4.2, 5.1, 5.2 are stated the values of systolic and diastolic pressure pursued at the particular patients. This Graphs shows that MDM and fictitious (placebo) modulation had not significant impact on the blood pressure values.

In the Graph No. 6.1, 6.2, 7.1 and 7.2 are stated the values of blood pressure (systolic and diastolic) before and after MDM and before and after fictitious (placebo) modulation pursued of all patients after procedures. Also this Graphs shows that MDM and fictitious (placebo) modulation had not significant impact on the blood pressure value.

B - Pulse rate:

The values of pulse rate were not influenced by means of mesodiencephalic modulation and fictitious (placebo) modulation. This Graph shows No. 8 where is illustrated pulse rate before and after the modulation (MDM or placebo) at the particular patients.

C - ECG curve is not changed by means of MDM. Sinus rhythm was registrated of all patients. It persisted after mesodiencephalic and also after placebo modulation.

At the close of this part it is possible to state that MDM using for modulation of diabetic polyneuropathy symptoms was safe and there have been found-out no undesirable effects for patients during whole time application.

5.9.2 Laboratory investigation of each subject evaluation

There have been scanned no undesirable effects made by device using both for biochemical parameters and for haematology parameters which have been monitored before MDM or fictitious modulation and after its finishing – 10. day MDM, vide the Tables Enclosure 9.2.

Haematology changes

Neither MDM nor placebo modulation did lead to no undesirable effects, vide Tables 6.

B – Biochemical changes

As you may vide in Table 3 and 5 that MDM did not affect monitored biochemical parameters used for monitoring of liver function, renal function, metabolism of lipids and glucose.

It is visible from the above mentioned results, that MDM carried on during 13 sitting at 10-day interval has lead to no undesirable effects.

The patients indicated feeling of gentle tingling in the area of electrodes during modulation. This feeling never grown up to effect that could lead to modulation interrupting (vide Doctor guide) and article 5.3.3.2.

5.9.3 Undesirable incidents

No one was registered.

6 General summary and conclusion

6.1 Aims of clinical study

1. *to prove MDM effectivity for treatment of painful diabetic polyneuropathy symptoms*
2. *to find-out the method has not undesirable effects or symptoms for cardiovascular apparatus and if the treatment by MDM negatively affect biochemical parameters that characterized homeostasis, liver function, renal function, lipid metabolism and diabetes compensation*

Study has been realized with 25 patients who suffered from painful form of diabetic polyneuropathy. The mentioned patients were hospitalized at Metabolic ward of Department of metabolic care and gerontology. They were randomized into 2 groups by method of sealed envelops after their signing of Informed Agreement:

- *group that has started with fictitious modulation (placebo) and after one-month break there was realized true MDM*
- *group that has started with true MDM and after one-month break there was realized fictitious MDM (placebo)*

MDM was realized exactly according to instructions that has been supplied by manufacturer placebo modulation consists of short time action which did not reach to intensity of true MDM. Only doctor who applied MDM knew to which type of group the patient has been placed. Other members of team even the patient have not been informed about character of modulation (true versus placebo). Before each one application and after its finishing there were taken blood pressure in standing and lying position to each patient and there was monitored ECG. Pulse rate has been established on the base of electrocardiography curve. There was taken blood from each patient before starting up of

MDM or fictitious (placebo) modulation consecution. The taken blood was scanned for haematology and biochemical indicators which can confirm eventual undesirable effect of MDM to human body (blood count, quantity of leukocytes and blood platelets, liver's tests, mineralogram, creatinine and lipid level). Glycaemia level was scanned for each patient too. Glycaemia level did not made a part of study because there have been applied therapy (peroral antidiabetic or insulin and its analogs) with the view to reach the optimal diabetes compensation. Patient´s diabetes treatment has got a priority character and that is why it is not possible to evaluate the glycaemia level as the parameter depending on MDM.

All patients have signed Informed Consent and true or fictitious MDM was started for them. Two patients did not appear for second hospitalization. The first of them passed fictitious (placebo) modulation only, the second one passed true modulation. Study interruption for these two patients was not made by undesirable effects or by negative experience with treatment but by fact the patients did not want to be hospitalized for second time already.

Totally 25 patients have participated in study and 23 people finished it. On the base of our study results it is possible to give replies for two basic questions which made aim of monitoring.

1. ***To prove effectivity of MDM*** *during treatment of painful polyneuropathy symptoms. The treatment effect was monitored by numerical line from number 0 to number 8. 0 – means no effect of treatment, 8 – patient´s pains has been completely relieved – vide more detailed description in article 5.5.3. Individual data are mentioned in Tables No. 1 and 2. It is demonstated in Tables that every patient registered regeneration of its health. Between patients there was no one patient who registered no regeneration of its subjective problems since the middle of hospitalization (it is from 7. modulation). Table illustrates individual data concerning patients whereas 1. part shows placebo modulation and 2. part shows true modulation. The difference between fictitious and true modulation was evident since 2. day already. Graphs No. 1 and 2 show medianus and maximal values of each patient. Graf No. 3 shows medianus for whole group of patients after each one modulation. The difference between placebo and MDM was significant as for each patient and as well for whole group. There was no evident difference of effect in case the treatment was started by fictitious or by true modulation (group A and B) – vide more detailed protocols of statistical evaluation. Data were evaluated by non-parametric tests (vide article No. 6.7 and enclosed protocols of statistical survey). Data confirm highly significant MDM effect to problems of patients suffered by diabetic polyneuropathy.*

In fine of this part it is possible to state that MDM led to improvement of pain level for everyone patient. After procedure finishing was registered slightly improvement of problems for one patient, three patients registered improvement that reached ½ of primary pains and the rest of patients described improvement as expressive.

2. ***To find-out if MDM has any negative impact to patients****. In patients were monitored basic biochemical parameters that characterized homeostasis (mineralogram, renal function, urea, creatinine, uric acid, liver´s tests and lipid metabolism). The mentioned parameters were monitored always before and after 10 days hospitalisation at Department during this time was made 13 modulations (vide Tables No. 3, 4, 5, 6) in patients. As demonstated in Tables patients have got no significant changes of biochemical parameters. Low decrease of calcium and cholesterol of placebo group was significant only and we have no explanation for it. Unambiguously possible to say MDM did not affect biochemical parameters monitored by us.*

Individual statistic evaluation of each parameter (Protocol) makes a part of Enclosure No. 9.2.

3. ***Impact of MDM to blood pressure level, pulse rate and ECG changes at patients.*** *Every patients have got sinus rhythm before MDM starting up. Rhythm was not affected neither fictitious nor true modulation in the event of no-one patient. ECG has been monitored always before and after fictitious respectively true MDM and in the event of no one patient the changes of ECG curve was found-out. Pulse rates levels are showed in graph No. 8. Levels of blood pressure in standing not even in*

lying position were not affected by MDM. Levels of pulse rate pressure are shown in Graphs No. 4 – 7 as for each patient and as well for whole group of patients during each one modulation. On the base of this part it is possible to close up that MDM had no negative effect for some our patients. This fact is confirmed by reality till the time of this report writing up was no-one complication registered after MDM.

In fine it is possible to state that MDM in expressively way positively affected diabetic polyneuropathy symptoms. We did not registered acute changes in biochemical parameters monitored by us not even in blood pressure levels. ECG was not changed during procedures.

6.2 Medical Device evaluation

6.2.1 Accompanying documents and using

During Clinical Investigation there was verified the whole instructions mentioned in „Instructions for Using" are understandable and Electrotherapeutic Device MDM-2000/1 – Set realized operation duly and none data from database or from patient´s card have been lost.

Control elements of device are placed logically and digestedly.

Clinical Investigation was started up with device containing software program MDM-2000/1 ver. 3.0. Within Clinical Investigation the correction of Czech „Instructions for Using" has been finished and related correction of communication reports for English and Russian language software too. After breaking in to „Clinical Investigation Plan revision 02" and its approving by Ethics Committee the installation of version 3.1 has been made for medical devices and the Clinical Investigation was finished under this software version, vide enclosure No. 9.4. The one part of installation contained training for Investigators and their meeting with the change 02 of the „Clinical Investigation Plan", related documentation a program. No-one of mentioned changes has got impact to realization of „Clinical Investigation" from the patient's viewpoint.

Controlling, placing and description of control elements for each components of Electrotherapeutical Device including program report are understandable and logical. During Clinical Investigation there was found-out no defects in applying of Electrotherapeutical Device autodiagnostics. Device has been working according to „Instruction for Using" and it signalized simulated defect in expected way.

Data insertion into the program is intuitive and practicable without problems. This declaration is valid for each one investigated language version (Czech, English, Russian).

Other detailed information concerning evaluated Electrotherapeutical Device are mentioned in Questionnaire for Investigator stated in Enclosure No. 9.9.

6.2.2 Operation

Investigating doctor has been worked with device after unambiguous and adequate training for using. Device operation was not hard and there was found-out no undesirable effects during its using. It is possible to suppose that trained aid-man who absolved Secondary school can work with device.

6.2.3 Application

It is more than suitable to use single room during device application so the patients cannot be disturbed during treatment procedure. It is possible to realize treatment for 4 patients together by using of one MDM device.

During application in some patients insufficient wetting in the area of inset of the electrode placing on patient's nape came out this has been evoke by insufficient hair wetting cause that was not possible to start up the procedure or cause that was stopped its realization. It has been removed by using of hand-water-spray (on base of airbrush) thanks to which the nape was wetted by water and repeated insets wetting before their placing between electrode and patient skin again.

During study there was registered no one negative patient feeling caused by Medical Device application.

6.3 Conclusion

Study proved significant improvement of algic diabetic polyneuropathy symptoms by MDM using. There were registered no undesirable effects of MDM during study.

This is demonstrated in following graphs:

Graph 1 – Degree of improvement of complaints – stimulation vs. placebo: patient after patient individually (median). The graph shows the median obtained from 13 MDM procedures in individual patients in comparison with placebo (fictive modulation). It is evident from the graph that in all patients the effect of MDM was markedly higher than the effect of fictive modulation. In patient No. 13 only MDM and in patient No. 21 only fictive modulation were performed. However, even in these patients it is clear that only MDM exerted an effect on painful manifestations of diabetic polyneuropathy. Differences between the groups were evaluated by means of non-parametric tests (Mann-Whitney and Kolmogorov-Smirnov). In all patients there was a significant difference between placebo modulation and MDM.

Graph 2 – Degree of improvement of complaints – stimulation vs. placebo: patient after patient individually (maximal effect).

The maximal effect of MDM in individual patients in comparison with placebo (fictive modulations). The graph clearly shows that in all patients the effect of MDM was markedly higher than the effect of fictive modulation. In patient No. 13 only MDM and in patient No. 21 only fictive modulation were performed. However, even in these patients it is clear that only MDM exerted an effect on painful manifestations of diabetic polyneuropathy.

Graph 3 – Degree of improvement of complaints – stimulation vs. placebo: for the sequence number of the procedure (median).

The graph represents the effect of MDM in the whole group of patients. It is clear from the graph that commencing with the very first day of stimulation (after the second stimulation) a significant improvement of the feeling of relief occurred. Differences between the groups were evaluated by means of non-parametric tests (Mann-Whitney and Kolmogorov-Smirnov). Already after the second procedure a significant difference between placebo modulation and MDM was observed.

Graphs 4 – Blood pressure, stimulation with MDM, examinations in individual patients.
No significant difference was observed between individual groups of patients beginning with placebo or mesodiencephalic modulation.

Graphs 5 – Blood pressure, placebo (fictive) modulation, examination in individual patients.
No significant difference was observed between individual groups of patients beginning with placebo or mesodiencephalic modulation.

Graphs 6 – Blood pressure, modulation with MDM, examination of all patients after procedures.
No significant difference between individual groups of patients beginning with placebo or mesodiencephalic modulation was observed.

Graphs 7 – Blood pressure, placebo modulation, before/after procedures.The graphs represent the mean and standard deviation of the mean from thirteen measurements carried out in each patient.

Graphs 8 - Heart rate in individual patients. No significant difference between the individual groups of patients beginning with placebo or mesodiencephalic modulation was observed.

Table 1 – Individual data of pain's spectrum for fictitious modulation (placebo)

Table 2 – Individual data of pain's spectrum for MDM

Tables 1 and 2 are supplemented by statistic evaluation and mutual comparison in files:
A_patient: Patients registered into group A
B_patient: Patients registered into group B
A_B comparison: Mutual comparisons of patients registered to group A and B
A_1-13_day_Placebo_versus_modulation: Characteristics of patients registered to group A in terms of each one procedure.
B_1-13_day_Placebo_versus_modulation: Characteristics of patients registered to group B in terms of each one procedure.
A_p_B_1-13_day_Placebo_versus_modulation: Comparison of patient's characteristics registered to group A and B in terms of each one procedure.

Table 3 – 5 – Biochemical parameters before and after a 10-day period of MDM or placebo modulation

Table 6 – Hematological parameters before and after a 10-day period of MDM or placebo modulation.

6.3.1 Generalization of results

On the base of our Clinical Investigation it is possible to state that MDM led to modulation even to complete relieffrom painful diabetic polyneuropathy symptoms for each monitored patient (100 % success of the treatment).

The shortest time of effect was monitored in one woman-patient and it was for 6 weeks after MDM . Other patients are monitored by Diabetic Consulting Room of our Department and MDM effect will be monitored for one-year period.

After evaluation it will be possible to say at what time-interval it would be proper to repeat the treatment.

6.3.2 Recommendation

6.3.2.1 Doctor´s specialization

I recommend to use method of mesodiencephalic modulation applied by Electrotherapeutic Device MDM-2000/1 – Set for diabetic neuropathy diagnose to doctors specialized on diabelogy, physiatry and internal medicine.

6.3.2.2 Territory for application

The proper place for using of mesodiencephalic modulation method is Ambulatory institution on condition of proper room in which will be possible to realized method in quiet and noise-free atmosphere.

6.3.2.3 Records

During using of Electrotherapeutic Device I recommend to pursue records about adjusted treatment current for each procedure into the patient's clinical record, simplified form of daily record from „Protocol of Participant in Clinical Study", vide enclosure No. 9.8.

6.4 Publications made on the base of Clinical Investigation

There was made no publications on the base of „Clinical Investigation" yet.

7 Discussion

Clinical monitoring proves effectivity and safeness of MDM using for treatment of painful diabetic polyneuropathy symptoms. Patients will be further monitored for one year time period so that will be possible to determine the period of treatment effect duration. In case the treatment effect will be shorter

than 6 months it is right to check up if possible to combine MDM with other treatment method of algic diabetic polyneuropathy symptoms (especially pharmacotherapy).

With regard to very stimulative study results it will be right to extend the study for algic polyneuropathy different from diabetic aetiology (uremic polyneuropathy, polyneuropathy after cytostatic treatment). Advantageous will be monitoring of MDM impact to peripheral vascular perfusion and finally to healing of skin defects.

For the next study probably it is not necessary to monitor ECG before and after MDM. That cause the fact during our study have been made 52 ECG records without evident pathological changes for each patient.

Our results show surprising and very well MDM effect to algic diabetic polyneuropathy symptoms. We recommend long-time monitoring of patients and determinate optimum period between each treatment.

8 Investigator´s opinions to Final Report

Investigators:	Date:	Signature:	Suggestions*:
Prof. MUDr. L. Sobotka, CSc.			No/Yes – reference
MUDr. A. Šmahelová, Ph.D.			No/Yes – reference
MUDr. F. Musil, Ph.D.			No/Yes – reference

* *- delete as appropriate*

9 Enclosures to „Final Report“

9.1 List of using Professional Publication

Enclosure 1 *Publication*

9.2 Tables and Graphs made on the base of „Clinical Investigation“

Graph 1 – Degree of improvement of complaints – stimulation *vs.* placebo: patient after patient individually (median)

Graph 2 – Degree of improvement of complaints – stimulation *vs.* placebo: patient after patient individually (maximal effect)

Graph 3 – Degree of improvement of complaints – modulation *vs.* placebo: for the sequence number of the procedure (median)

Graphs 4 – Blood pressure, modulation with MDM, examinations in individual patients

Graphs 5 – Blood pressure, placebo (fictive) modulation, examination in individual patients

Graphs 6 – Blood pressure, modulation with MDM, examination of all patients after procedures

Graphs 7 – Blood pressure, placebo modulation, before/after procedures

Graphs 8 - Heart rate in individual patients

Table 1 – Individual data of pain's spectrum for fictitious modulation (placebo)

Table 2 – Individual data of pain's spectrum for MDM

Tables 1 and 2 are supplemented by statistic evaluation and mutual comparison in files:

A_patient: Patients registered into group A

B_patient: Patients registered into group B

A_B comparison: Mutual comparisons of patients registered to group A and B

A_1-13_day_Placebo_versus_modulation

B_1-13_day_Placebo_versus_modulation

A_p_B_1-13_day_Placebo_versus_modulation
Table 3 – 5 – Biochemical parameters before and after a 10-day period of MDM or placebo modulation
Table 6 – Hematological parameters before and after a 10-day period of MDM or placebo modulation

9.3 Curriculum Vitae of Principal Investigator*)

9.4 Written agreement of Ethics Committee of University Hospital in Hradec Králové with Clinical Investigation realization
Ethics Committee, University Hospital in Hradec Králové, address: Sokolská 581,
500 05 Hradec Králové
Agreement with Clinical Investigation realization and subsequent documents completion were negotiated by Ethics Committee of University Hospital in Hradec Králové under evidence number: 200507 S09m, 200508 I20m, 200603 I63m

9.5 Copy of Declaration to realize „Clinical Investigation“ of Ethics Committee University Hospital in Hradec Králové
Declaration evidence number 200609 I80m dated 5.10.2006

9.6 Specimen of the document „Information for Patient” *)

9.7 Specimen of the document „Informed Agreement“
The method how to get „Informed Agreement“ is described in „Clinical Investigation Plan“. Signed „Informed Agreement“ makes a part of Medical Documentation.*)

9.8 Specimen of the file „Protocol of Participant in Clinical Study“ *)
- Instructions for using of file
- Protocol of Participant in Clinical Study (LP05027CZR00/x/y)
  Contains randomization scheme how to realized investigations for groups of participants, identification of subject evaluation, specification of used Medical Device / channel
- Envelope of randomized selection

9.9 Questionnaire for Investigator
- Subjective evaluation of „Clinical Investigation Documentation“ and using of Electrotherapeutic Device MDM-2000/1-Set

9.10 Amendments
- Copy of „Contract between Submitter and Provider and Investigators about Investigation of Medical Device, evidence No. 10-0031-05-0137”.
- Copy of „Contract between Submitter and Investigators“ about Management of Clinical Investigation, evidence No. 10-0032-05-0000”.
- Copy of „Contract between Submitter and Submitter’s Assistant“ in applying of Clinical Investigation, evidence No. 10-0069-05-0137”.

9.11 Clinical Investigation Plan *)

9.12 Accompanying documents of Medical Device *)
Following documentation in Czech, Russian and English language version
- Instructions for Using
- Doctor`s Guide
- Instructions for Using – Head-set
- Instructions for Using – Cotton inset

**) enclosure makes a part of file „Clinical Investigation Documentation“*

10 Signatures

Principal Investigator:

Date: Prof. MUDr. Luboš Sobotka, CSc.

Submitter's Assistant:

Date: Prof. MUDr. Zdeněk Zadák, CSc.

Provider:

Doc.MUDr.Leoš Heger, CSc.
Director of University Hospital HK

Submitter:

Eng.Václav Náprstek
Entrusted Person

In Hradec Králové date 20.11.2006