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1. TITLE PAGE

Short term safety and tolerance study for a formulation of humic acid and trace minerals

Sponsor : *HUMET Co.*

Protocol identification: *HUMET 101/2000*
Development phase of study: *Phase I*
Study initiation date: 2001 APR 18
Study completion date: 2001 JUN 01

Principal investigator:

- Béla Gachályi MD PhD DSc

Co-Investigators:

- Géza Lakner MD
- Mészáros Zsolt MD

Study site:

***Department of Clinical Pharmacology and Therapeutics, Hungarian Railways Hospital,
Budapest***

2. SYNOPSIS

Name of Sponsor/Company:	HUMET Co.
Name of Finished Product:	HUMET® capsules
Title of Study:	Short term safety and tolerance study for a formulation of humic acid and trace minerals HUMET 101/2000
Investigators:	<ul style="list-style-type: none"> • Béla Gachályi MD PhD DSc • Géza Lakner MD, • Zsolt Mészáros MD
Study centre(s):	Department of Clinical Pharmacology and Therapeutics, Hungarian Railways Hospital, Budapest
Phase of development:	Phase I
Studied period	initiation: 2001 APR 18 finish: 2001 JUN 01
Objectives:	The objective of this study was to show the short term safety of Humet® administered in solid, capsular formulation per os in healthy male volunteers over a period of three weeks on an outpatient basis. The specific goal is to evaluate routine laboratory parameters, trace metal levels, changes in serum endothelin levels, qualitative assessment of myeloperoxidase activity and physical status during the treatment period.
Methodology:	Per os, single blinded, randomized, outpatient safety-tolerance study.
Number of volunteers (planned and analyzed):	40 healthy male volunteers
Test product: dose: mode of administration: batch number (expiry date):	HUMET® capsules (HUMET Co.) <i>equivalent dose of 10 ml HUMET® syrup (registered product) ;</i> Group "A": - Week #1 : 1 HUMET capsule (equivalent in dose to 10 ml HUMET®-R syrup) + 2 capsules placebo - Week #2 : 2 HUMET capsules + 1 placebo - Week #3 : 3 capsules HUMET ; per os – once daily after the main meal; K0010101 (Manufacturing date: 20 JAN 2001 , expiry period: 6 months)
Duration of treatment:	3 weeks, once daily dose administration according to the randomization schedule.
Reference product: dose: mode of administration: batch number (expiry date):	Placebo capsules (HUMET Co.) --- ; Group "B"; per os – once daily after the main meal ; K0020101; (Manufacturing date: 20 JAN 2001 , expiry period: 6 months)

Criteria for evaluation:	Significant changes in vital parameters; various laboratory parameters; adverse event profile of the study drugs. Exploratory analysis of trace metal levels.
Statistical methods:	Descriptive statistics of <i>safety parameters</i> - numeric instrumental and laboratory test results: average, standard deviation, minimum and maximum values. Trace metal levels: <ul style="list-style-type: none"> • area under the micronutrient level versus time curve; mean AUCs of the two treatment groups compared by a two-sample, two sided t-test, assuming equal group variances • individual changes from baseline (end of treatment – baseline) were computed: treatment group means were compared by a two-sample, two sided t-test, assuming equal group variances • correlation between whole blood - serum and blood - RBC and serum-RBC micronutrient levels was characterized by Kendal's τ_b correlation coefficient
Summary - Conclusions:	Based on clinical observations no difference can be shown between the active and the control group respective to the study drug's effect or side effect profile. The statistical analysis of trace metal levels revealed a significant difference - with the mean greater in the HUMET-treated group: <ul style="list-style-type: none"> • Mean AUCs (serum levels as a function of treatment weeks) at level 5% in case of <ul style="list-style-type: none"> • blood: Co, Se, Si, V • serum: Co, Mg, V • The changes from baseline in <ul style="list-style-type: none"> • blood: Ti, V • serum: Se, V
Date of the report:	10 DEC 2001

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Addenda

**"A" Authorization Certificates of the NIP and the
Regional / Central Ethical Committees**

"B" Statistical Evaluation

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Vol.	volunteer
DOA	drugs of abuse
CRF	case report form
WBC	white blood cell count
NEU	segmented leukocyte
EOS	eosinophile leukocyte
MONO	monocyte
HCT	hematocrite
HGB	hemoglobin
se bi	serum bilirubine
rel.	relative
PLT	platelet count

5. ETHICS

Document 2840/40/2001 and 5000/40/2001 (2001.03.28) of the National Institute of Pharmacy (OGYI), authorized study completion (Appendix 16.1.3).

5.1. Independent Ethics Committee, Institutional Review Board

The study documentation has been reviewed and approved by both the Central Ethics Committee (ETT 6030-47/ETT/2001 (2001.04.02)) and Regional Ethical Committee of the Semmelweis University Faculty of Health Sciences (TEB 44/2000 (2000.11.21)).
Appendix 16.1.3 contains the list of the committee members.

5.2. Ethical Conduct of the Study

The study has been conducted in accordance with the Declaration of Helsinki, the ICH Good Clinical Practices Directives and the regulations of the Protocol.

5.3. Volunteer Information and Consent

Informed consent has been obtained at the time of enrollment, preceding any study-related activity. The forms have been countersigned by an investigator, too.
One copy of the signed forms was handed to the volunteers while another original copy was kept in the Study Master File.
The volunteer information and informed consent form in Hungarian language can be found in the Protocol (in Appendix 2).

6. INVESTIGATORS

Appendix 16.1.4 of this report contains the list and curriculum vitae of relevant study personnel.
Appendix 16.1.5 contains the corresponding signatures.

7. INTRODUCTION

The objective of this study was to show the short term safety of Humet® administered in solid, capsular formulation per os in healthy male volunteers over a period of three weeks on an outpatient basis.

The specific goal was to evaluate routine laboratory parameters, trace metal levels, changes in serum endothelin levels, qualitative assessment of myeloperoxidase activity and physical status during the treatment period.

8. STUDY OBJECTIVES

The aim of this outpatient, repeated dose, once daily dose administration, 3 weeks long randomized placebo-controlled single-blind safety-tolerance study was to show the short term safety of Humet® administered in solid, capsular formulation per os in healthy male volunteers. The specific goal was to evaluate routine laboratory parameters, trace metal levels, changes in serum endothelin levels, qualitative assessment of myeloperoxidase activity and physical status during the treatment period.

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design and Plan: Description

This was a single-blind, an outpatient, repeated dose, once daily dose administration, 3 weeks long randomized placebo-controlled safety-tolerance study study in one centre (Protocol Chapter 9).

9.2. Study Design

Chapter 9 of the Protocol details the study plan.

9.3. Selection of Study Population

Forty healthy male volunteers participated in the study. The healthy state of the volunteers has been assessed by routine physical examination, medical history, routine laboratory examination (including hepatitis B, C, HIV virus testing and screening for drugs of abuse), chest X-ray and ECG.

9.3.1. Inclusion Criteria

- Age 18-45 years
- Their body build is : $18 \text{ kg/m}^2 < \text{BMI} < 28 \text{ kg/m}^2$
- Hungarian citizenship
- Signed informed consent
- Negative physical examination
- Absence of any exclusion criterion

9.3.2. Exclusion Criteria

- According to state ruling (CLIV /1997 161 . §) no person may participate in human clinical studies who is
 - foreign citizen
 - prisoner
 - enlisted soldier
- Further exclusion criteria
 - medication within 14 days before the start of the study
 - participation in human drug studies within 3 month
 - blood donation within 6 weeks
 - pursuing sports by professional standards
 - known hypersensitivity to the study preparation
 - heavy smoking (i.e. in excess of 10 cigarettes/day), alcoholism, drug dependence

- dietary restriction resulting in a deviation from normal protein, carbohydrate and fat intake (e.g. vegetarianism)
- any pathologic finding in the screening examination panel that precludes enrollment of the particular volunteer. N.B. deviations of $\pm 20\%$ from normal range limits may be acceptable at the discretion of the investigators
- any disease state in the medical history which may significantly affect the volunteer's safety or the evaluability of the study parameters
- any acute and chronic pathological condition
- pursuing sports
- foreseen noncompliance

Throughout the study period the volunteers were not allowed to consume

- excessive amounts of alcoholic drinks and nicotine (more than 5 cigarettes per day)
- excessive amounts of alkaloids-containing beverages: tea, coffee, energy drinks
- excessive amounts of nutritional fibers: e.g. bran or corn flakes
- excessive amounts of micronutrient-rich (trace metal-rich) foods: seashells, oyster, crabs, meat (chicken, beef, calf), liver, huskies, beans, nut, almond, wheat/bran flakes, broccoli, tomatoes, mustard, milk, cheese, chocolates, cocoa, banana

9.3.3. Removal of Volunteers From Therapy or Assessment

The volunteer were assigned to prematurely finish the study and be regarded as drop-out in case of:

- development of an adverse event warranting withdrawal of therapy
- volunteer was wishing to withdraw.
- non-compliance with study procedures or blood sampling schedule
- trial termination (by the Regulatory Authorities, Ethical Committee, Sponsor or Investigators)

If a subject is withdrawn prior to completion of the study, the reason for this decision will be recorded in the case report forms. The remaining follow-up evaluations will be conducted if subject consent is maintained.

9.4. Treatments

9.4.1. Treatments Administered

Group "A":

- Week #1 : 1 HUMET capsule (equivalent in dose to 10 ml HUMET®-R syrup) + 2 capsules placebo
- Week #2 : 2 HUMET capsules + 1 placebo
- Week #3 : 3 capsules HUMET

Group "B" : 3 capsules placebo for 3 weeks.

9.4.2. Identity of Investigational Product(s)

9.4.2.1. Test drug

Preparation:	HUMET® capsules
Manufacturer:	HUMET Co.
Active ingredient:	equivalent dose of 10 ml HUMET® syrup (registered product)
Expiry date:	Manufacturing date: 20 JAN 2001 , expiry period: 6 months
Batch number:	K0010101

9.4.2.2. Reference drug

Preparation:	Placebo capsules
Manufacturer:	HUMET Co.
Active ingredients:	---
Expiry date:	Manufacturing date: 20 JAN 2001 , expiry period: 6 months
Batch number:	K0020101

9.4.3. Method of Assigning Volunteers to Treatment Groups

The volunteers received the treatments in the order set by the randomization table (see below). Treatment numbers were assigned in the order of enrollment in the study.

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- Group "A" - 20 volunteers, Humet® group
- Group "B" - 20 volunteers, placebo-group

9.4.4. Selection of Doses in the Study

Treatment Group	Week #1	Week #2	Week #3
"A" (HUMET®)	1 capsule HUMET® + 2 capsules placebo	2 capsules HUMET® + 1 capsule placebo	3 capsules HUMET®
"B" (Placebo)	3 capsules placebo	3 capsules placebo	3 capsules placebo

9.4.5. Selection and Timing of Dose for Each Volunteer

See Section 9.4.1 of this report.

9.4.6. Blinding

The study was single-blind.

9.4.7. Prior and Concomitant Therapy

No prior chronic drug treatment was allowed by the Protocol.

9.4.8. Treatment Compliance

The treatment was based on self-administration in outpatient form. In the lack of personal supervision of the investigators during study preparation administration, ensuring the treatment compliance was a principal issue.

The timely self-administration of the study preparations has been assured :

- by packaging (two bottles with indication of taking 1+2 capsules from each, daily) and
- by the Treatment Diary, with a daily sign of the volunteer and the return of the used, empty preparation-containers certifying the self-administration.

9.5. Efficacy and Safety Variables

9.5.1. Efficacy and Safety Measurements Assessed and Flow Chart

The following table indicates the test panels applied during the study. For easier reading the short panel code will be referenced in the text further.

Panel code	Procedures
HIST0	<ul style="list-style-type: none"> • initial medical history, recording of demography data including chronic medication • body height and weight (calculation of BMI).
HIST	Supplementary medical history aimed at the recent changes of medical history: <ul style="list-style-type: none"> • tolerance will be assessed by the review of the appropriate fields of the diary • recording of adverse events upon interview • intercurrent medication issues
BASIC0	<ul style="list-style-type: none"> • body temperature • routine physical examination
BASIC	<ul style="list-style-type: none"> • changes in physical state
END-PX	<ul style="list-style-type: none"> • measurement of serum endothelin levels and qualitative assessment of myeloperoxidase activity
CARDIO	<ul style="list-style-type: none"> • pulse rate, blood pressure in sitting position • ECG (12 lead)

X-RAY0	<ul style="list-style-type: none"> chest X-ray (previous screening results from within 1 year will be accepted)
LAB	<ul style="list-style-type: none"> haematology: hemoglobin, hematocrit, RBC, WBC, platelet count, differential blood count, erythrocyte sedimentation rate (ESR), prothrombin chemistry: Na, K, Cl, Ca, P, serum iron, BUN, Se-creatinine, Se bi, blood glucose, SGOT, SGPT, GGT, LDH, ALP, cholesterol, triglycerides, uric acid, total protein, albumin urinalysis: specific gravity, pH, glucose, albumin, ketones, microscopic evaluation (RBC, WBC, casts, crystals, other cells)
VIR_DOA0	<ul style="list-style-type: none"> virus serology testing : HBsAg, anti HCV, HIV 1-2 urine test for drugs of abuse (amphetamine, cocaine, metamphetamine, morphine, THC)
CPL	<p>Assessment of compliance:</p> <ul style="list-style-type: none"> revision of the volunteer diary and the returned preparation containers
METAL	<p>Trace metal analysis by <i>Inductively Coupled Plasma Emission Spectroscopy</i> (executed in a certified specialized laboratory):</p> <ul style="list-style-type: none"> Aluminium, Antimony, Arsenic, Barium, Beryllium, Cadmium, Chromium, Cobalt, Copper, Gallium, Germanium, Lead, Magnesium, Manganese, Mercury, Molybdenum, Nickel, Palladium, Platinum, Rubidium, Selenium, Silver, Strontium, Thallium, Tin, Umalum, Vanadium, Zinc, Zirconium

Activity	Screening	Treatment period (daily)	Follow-up visits (weekly)	Post-study (final) visit
HIST0	✓			
BASIC0	✓			
DOA_VIRO	✓			
X-RAY0	✓			
HIST			✓	✓
END-PX	✓			✓
BASIC			✓	✓
CARDIO	✓		✓	✓
LAB	✓		✓	✓
METAL	✓		✓	✓
Study preparation administration (by the volunteer himself)		✓		
Diary logging (by the volunteer himself)		✓		
CPL			✓	

9.5.2. Appropriateness of Measurements

9.5.2.1. Blood pressure and pulse rate determination

Determination of these noninvasive cardiologic parameters has been carried out using OMRON 705-CP automatic blood pressure meters.

The instrument (applying the Doppler principle) shows on its display the systolic and diastolic BP values as well as the pulse rate. Blood pressure and pulse rate were determined in supine position at the time of screening, at each follow-up visit and on the day of post-study checkup visit.

14.5.2.2. ECG-recording

12 lead ECG was recorded by an Innomed CardioPC, computer-based ECG recorder. This instrument displays on the ECG sheet the heart rate, PQ, QRS and QTc time intervals. The ECG was recorded during the screening, at each follow-up visit and on the day of post-study checkup visit.

9.5.3. Primary Efficacy Variables

Not applicable.

9.5.4. Drug Concentration Measurements

No pharmacokinetic assessment had taken place during this human study.

9.6. Data Quality Assurance

9.6.1. Monitoring

The Sponsor's Monitor visited the study site on days as follows:

Type of the visit	Date
Study initiation visit	2001 APR 17
Monitoring visit	###
Closing visit	###

9.6.2. Auditing

No audit has taken placen during the human study.

9.6.3. Official Inspection

The National Institution of Pharmacy (OGYI) has not inspected the clinical study site in connection with the actual human study.

9.7. Statistical Methods

9.7.1. Statistical and Analytical Plans

The parametric safety clinical study data were analysed as follows:

- tabular representation of average values, standard deviation, minimum and maximum values of the appropriate data sets

Appendix 16.1.9 lists the parameters included in the statistical analysis.

All trace metal data were included in the statistical analysis. Data below the detection limit were considered to be 0. Missing data (the RBC micronutrient levels of the volunteer nr. 13 in period 2) were considered to be equal to the levels measured in the previous period ("last observation carried forward" method).

The extent of the absorption during the three-week treatment was primarily characterised by the area under the micronutrient level versus time curve. The area under the curve (AUC) was computed applying trapezoidal interpolation, for each volunteer separately. The mean AUCs of the two treatment groups were then compared by a two-sample, two sided t-test, assuming equal group variances.

Individual changes from baseline (end of treatment - baseline) were computed. Treatment group means were compared by a two-sample, two sided t-test, assuming equal group variances

Correlation between whole blood - serum and blood - RBC and serum-RBC micronutrient levels was characterized by Kendal's τ_b correlation coefficient¹, computed for each time point and each treatment group separately. This coefficient was computed only for the pair of parameters where the number of values below the detection limit was less than 5. For $n=5$ the threshold value of τ_b for a 5% significance is 0.4¹. Thus values above 0.4 and below -0.4 were considered to be significant

Descriptive statistics (tables containing the mean, standard deviation, median, minimum, maximum) was made for each parameter, each period and both treatment groups.

9.7.2. Determination of Sample Size

The Protocol has defined the study population to 40 healthy male volunteers

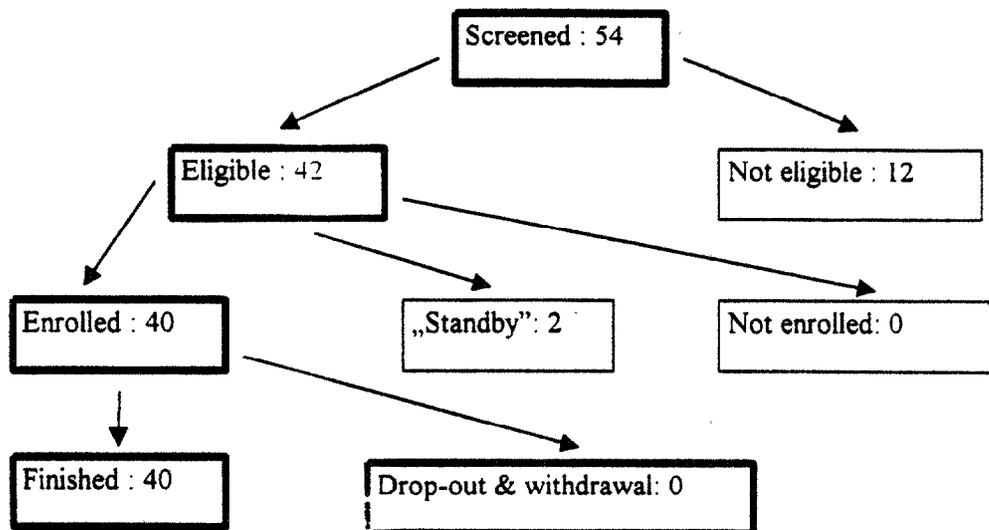
9.8. Changes in the Conduct of the Study or Planned Analyses

See Section 10.2, *Protocol Deviations*.

¹ Hollander M, Wolfe DA: Nonparametric Statistical Methods, New York, Wiley, 1972

10. STUDY VOLUNTEERS

10.1. Disposition of Volunteers



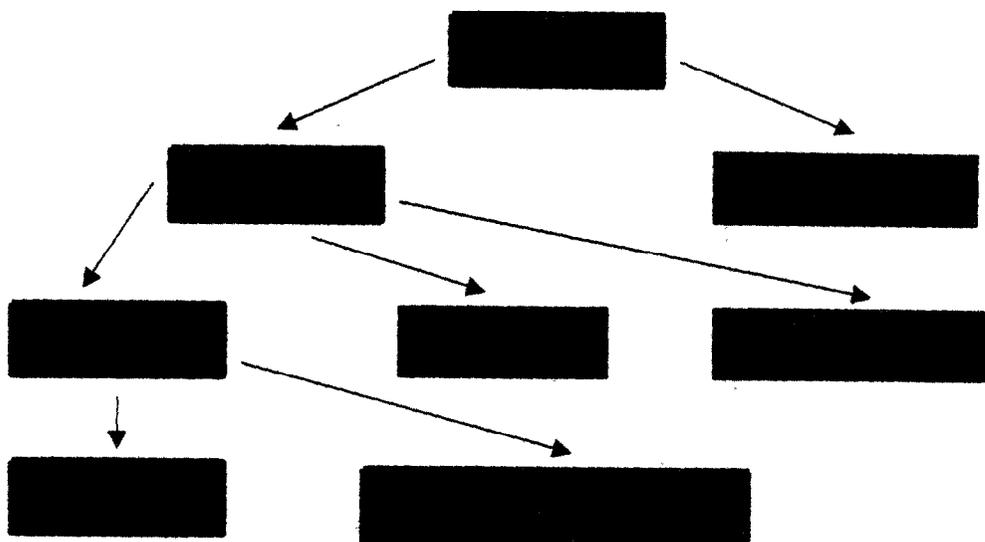
See Appendix 16.2.4 for an enrollment log of the volunteers.

10.2. Protocol Deviations

No deviation occurred in the study performance from the Study Protocol.

10. STUDY VOLUNTEERS

10.1. Disposition of Volunteers



See Appendix 16.2.4 for an enrollment log of the volunteers.

10.2. Protocol Deviations

No deviation occurred in the study performance from the Study Protocol.

11. EFFICACY EVALUATION

11.1. Data Sets Analyzed

All volunteers' clinical data have been included for descriptive statistical analysis.

11.2. Demographic and Other Baseline Characteristics

Individual demographic data of the volunteers (identification, age, body height and weight) are presented in the data listing of Appendix 16.4 .

This table shows the descriptive statistical parameters of these data, too.

11.3. Measurements of Treatment Compliance

Treatment compliance was complete: 100% of the predefined treatments have been realized.

11.4. Efficacy Results and Tabulations of Individual Volunteer Data

11.4.1. Analysis of Efficacy

Mean AUCs showed a significant difference (with the mean greater in the HUMET-treated group) at level 5% :

a/ in blood: Co (p=0.026), Se (p<0.001), Si (p=0.038), V (p<0.001)

b/ in serum: Co (p=0.007), Mg (p=0.024), V (p=0.033)

Borderline significance (p<0.1) was observed:

a/ in blood: Li (p=0.058)

b/ in serum: K (p=0.057)

For RBC neither significance nor borderline significance was found.

The changes from baseline showed a significant difference between the two treatment groups (with greater increases in the HUMET-treated groups):

a/ in blood: Ti (p=0.034), V (p<0.001)

b/ in serum: Se (p=0.039), V (p=0.006)

For RBC no significant difference was observed.

Borderline significance (p<0.1) was observed:

a/ in blood: Al (p=0.096), Cr (p=0.091)

b/ in serum: Ca (p=0.067), Li (p=0.093)

c/ RBC: Mn (p=0.081)

The correlation coefficients did not reveal any systematic relationship in spite of the fact that some of them were significant (some of them showed positive correlation, while some of them showed negative correlation or no correlation at all).

Note: Detailed statistical report is included in Addendum "B" ("*Statistical Evaluation*") of this Clinical Report.

11.4.2. Statistical / Analytical Issues

Appendix 16.1.9 lists the parameters included in the statistical analysis. Statistical analysis of these clinical safety data is represented in tabular form of average values, standard deviation, minimum and maximum values of the appropriate data sets.

Serum metal levels were assessed by exploratory hypothesis testing. All calculations were performed with SAS® version 6.12 (SAS Institute, Cary, NC).

11.4.3. Tabulation of Individual Response Data

Appendix 16.4 lists the individual numeric clinical data.

11.4.4. Drug Dose, Drug Concentration, and Relationships to Response

Section 11.4.1 covers the relationship between the drug administration and the efficacy parameters.

11.4.5. Drug-Drug and Drug-Disease Interactions

No concomitant treatments and no concurrent diseases were allowed in this study.

11.4.6. By-Volunteer Displays

Appendix 16.4 lists the individual numeric clinical data of each volunteer in a tabular arrangement.

11.4.7. Efficacy Conclusions

The statistical analysis of trace metal levels revealed a significant difference - with the mean greater in the HUMET-treated group:

- Mean AUCs (serum levels as a function of treatment weeks) at level 5% in case of
 - blood: Co, Se, Si, V
 - serum: Co, Mg, V
- The changes from baseline in
 - blood: Ti, V
 - serum: Se, V

Missing data:

- RBC micronutrient levels of the volunteer #13 in study period 2

12. SAFETY EVALUATION

12.1. Extent of Exposure

Section 9.4 details the treatment arrangement.

12.2. Adverse Events

12.2.1. Brief Summary of Adverse Events

Beyond minor and rare gastrointestinal problems a considerable amount of "positive", beneficial adverse events, i.e. increase of appetite, increase of mental vigility and physical performance occurred in several cases.

In one case (Volunteer 26 at the 2nd follow-up visit) we observed transient increase of liver enzymes but this deviation was not dependent on study drug exposure: the volunteer had a considerable fitness training prior to blood sampling.

12.2.2. Display of Adverse Events

See Appendix 16.2.7.

12.2.3. Analysis of Adverse Events

In a total of 23 adverse events occurred, 15 in the active compound group, 8 in the placebo control group. The AEs included:

The occurrence of the AEs in each treatment group was as follows:

AE description	Active group	Control group
better digestion		1
diarrhoea	1	2
general discomfort		1
higher liver enzymes (SGOT, SGPT, LDH)	1	
increase of vigility / appetite / performance	6	3
nausea	1	1
stool, darker	3	
stool, less	1	
stool, softer	1	
vomitus	1	
weight loss	1	

Notable is the increase of liver enzymes in case Volunteer 26 at the 2nd follow-up visit: the enzymes returned to normal in 4 days. The volunteer reported that he forgot and neglected the lifestyle recommendations found in the volunteer information and he had a quite strenuous session of fitness training just prior to that laboratory sampling. He has been randomized into the active compound group but the facts suggest it is not likely that the study drug may have happened to cause this transient laboratory deviation (in the light of the normalization of the values even during the study drug exposure).

The "beneficial adverse events" - i.e. increase of physical and mental performance occurred more frequently in the active compound group, although no firm conclusion could be drawn regarding the relationship between their frequency and the increase of the HUMET doses.

12.2.4. Listing of Adverse Events by Volunteer

The accompanying table in Appendix 16.2.7 lists the individual adverse events.

12.3. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No serious adverse events occurred during the study.

12.4. Clinical Laboratory Evaluation

12.4.1. Listing of Individual Laboratory Measurements by Volunteer (Appendix 16.2.8, Appendix 16.4) and Each Abnormal Laboratory Value (see section 14.3.4)

A full listing of the clinical parameters included in the statistical analysis is featured in Appendix 16.1.9 of this clinical report.

Appendix 16.4 contains a table of the individual clinical data which comprises the display of abnormal laboratory parameters, too: the out-of-range values are highlighted (engraved border and bold typeface applied).

12.4.2. Evaluation of Each Laboratory Parameter

Except for the transient liver enzyme increase of Volunteer 26 registered as an AE, no abnormal laboratory finding could be attributed as clinically significant, these include:

- several minor changes in qualitative blood count
- several minor increase in serum albumin levels
- minor elevation of serum Ca level

Clinically notable solitary deviations included:

- consistently higher serum cholesterol levels of Volunteer #22 - N.B. even the screening result was higher
- higher serum iron levels in case of Volunteer #9
- high starting serum endothelin levels in some cases
- in 19 cases (10 in Group "A", 9 in Group "B") serum endothelin levels increased during the treatment
- in 20 cases the serum endothelin levels decreased and in one case the parameter was unchanged

The individual data table in Appendix 16.4 contains the descriptive statistics of the study parameters.

12.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

Appendix 16.4 contains data regarding ECG recording and blood pressure measurements. No clinically relevant changes occurred in these parameters, however.

12.6. Safety Conclusions

The HUMET treatment proved to be safe and well tolerated.

13. DISCUSSION AND OVERALL CONCLUSIONS

The objective of this study was to show the short term safety of Humet® administered in solid, capsular formulation per os in healthy male volunteers over a period of three weeks on an outpatient basis.

The specific goal was to evaluate routine laboratory parameters, trace metal levels, changes in serum endothelin levels, qualitative assessment of myeloperoxidase activity and physical status during the treatment period.

No drop-out occurred during the study.

Beyond minor and rare gastrointestinal problems a considerable amount of "positive", beneficial adverse events, i.e. increase of appetite, increase of mental vigility and physical performance occurred in several cases.

In one case (Volunteer 26 at the 2nd follow-up visit) we observed transient increase of liver enzymes but this deviation was not dependent on study drug exposure: the volunteer had a considerable fitness training prior to blood sampling.

Based on clinical observations the HUMET treatment proved to be safe and well-tolerable.

14. TABLES, FIGURES, AND GRAPHS

14.1. Demographic Data Summary figures and tables

Individual demographic data of the volunteers (identification, age, body height and weight, BMI) and their descriptive statistical parameters are presented in the data listing of Appendix 16.4 .

14.2. Efficacy Data Summary figures and tables

Not applicable.

14.3. Safety Data Summary figures and tables

14.3.1. Displays of Adverse Events

Beyond minor and rare gastrointestinal problems a considerable amount of "positive", beneficial adverse events, i.e. increase of appetite, increase of mental vigility and physical performance occurred in several cases.

In one case (Volunteer 26 at the 2nd follow-up visit) we observed transient increase of liver enzymes but this deviation was not dependent on study drug exposure: the volunteer had a considerable fitness training prior to blood sampling.

14.3.2. Listings of Deaths, Other Serious and Significant Adverse Events

Not applicable.

14.3.3. Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

Not applicable.

14.3.4. Abnormal Laboratory Value Listing (each volunteer)

The individual study data table in Section 16.4 comprises the display of abnormal laboratory parameters, too: the out-of-range values are highlighted.

15. REFERENCES

1. International Conference on Harmonisation; Good Clinical Practice: Consolidated Guideline – Step 5 consolidated Guideline 1.5.96
2. Expert Working Group of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (November 30, 1995): Note for Guidance on Structure and Content of Clinical Study Reports (CPMP/ICH/137/95)
3. Gyógyszervizsgálatok helyes klinikai gyakorlata (Good Clinical Practice - GCP)
OGYI-P-50-1992

16. APPENDICES

16.1. Study Information

16.1.1. Protocol and protocol amendments.

[Photocopy of the Protocol and its amendments – appended separately to this report]

16.1.2. Sample case report form (unique pages only)

[Photocopy of the CRF – appended separately to this report]

16.1.3. List of the members of the Ethics Committees

16.1.3.1. Regional Ethics Committee

Name
Dr. Egyed, Jenő (chairman)
Dr. Berentey, Ernő
Dr. Dékány, Miklós
Dr. Endrőczy, Elemér
Dr. Ferencz, Antal
Dr. Róna, Kálmán
Dr. Vályi-Nagy, István
Mrs. Kanizsai, Tibor

16.1.3.2. Central Ethics Committee

Name
Dr. Papp, Gyula (chairman)
Dr. Fenyvesi, Tamás (secretary)
Dr. Bartkó, György
Dr. Dömök, István
Dr. Farsang, Csaba
Dr. Gyurkovits, Kálmán
Dr. Hernádi, Ferenc
Dr. Hunyadi, János
Dr. Javor, Tibor
Dr. Julesz, János
Dr. Kádár, András
Dr. Mózsik, Gyula
Dr. Rákóczi, István
Rozsos, Erzsébet
Dr. Sas, Géza
Dr. Szántó, János
Dr. Mrs. Artúr Vasvári
Dr. Vizkelety, Tibor

16.1.4. List and description of investigators and other important participants in the study

Name	Position	Assignment during study
Dr. Gachályi, Béla	senior supervising doctor	principal investigator research physician
Dr. Lakner, Géza	senior lecturer	project manager research physician
Dr. Mészáros, Zsolt	doctor	research physician
Dr. Tóth, Agnes	senior lecturer	independent physician
Mrs. Kosztolányi, Edit	supervising nurse	supervising study nurse
Ms. Balog, Orsolya	nurse	study nurse

The curriculum vitae of the listed personnel follows right below.

Professional Biographies

Name	Béla Gachályi M.D.
Birth place and date	Szatmárnémeti, 1944 AUG 25
Marital status	married, two sons
Qualification	M.D. (Semmelweis University of Medicine; Faculty of Medicine, Budapest, Hungary, 1969)
Specification	<ul style="list-style-type: none"> • internal medicine (1974) • clinical pharmacology (1980) • geriatrics (2000)
Scientific degree	<ul style="list-style-type: none"> • Ph.D. (1979) • D.Sc. (1989) • Med. habil. (2000)
Publications	160
Employments	<ul style="list-style-type: none"> • EGIS Pharmaceutical Works (Budapest, Hungary; 1969-1971) • Semmelweis University of Medicine, 2nd Dept. of Medicine (Budapest, Hungary; 1971-1977) • St. John Municipal Hospital, 1st Dept. of Medicine (Budapest, Hungary; 1977-1982) • Haynal Imre University of Health Sciences, 1st Department of Medicine (Budapest, Hungary; 1982-1999) • Hungarian Railways Hospital, 1st Department of Medicine - Division of Clinical Pharmacology (from 2000, ongoing) •
Conference participation	<ul style="list-style-type: none"> • XV. Congress of the European Society of Cardiology (1993, Nice) • 1st Congress of EACPT (1995, Paris) • VI. World Congress on Clinical Pharmacology and Therapeutics (1996, Buenos Aires) • 2nd Congress of the European Association for Clinical Pharmacology and Therapeutics (EACPT) (1997, Berlin) • 16th European Workshop on Drug Metabolism (1998, Kopenhagen) • 7th European ISSX Meeting (1999, Budapest)

Memberships	<ul style="list-style-type: none"> • Hungarian Pharmacological Society (Presently Secretary of the Clinical Pharmacology Section) • Hungarian Society of Internal Medicine • Hungarian Society of Gerontology • Deutsche Gesellschaft für Klinische Pharmakologie • European Association of Clinical Pharmacology
Fellowships, postgraduate educations	<ul style="list-style-type: none"> • University of Oulu, Clinical Research Unit; Oulu, Finland (6 months; 1984-1985) • 8 oral presentation on GCP in the United Kingdom and Sweden (October 1993; Liverpool, Dundee, Aberdeen, Edinburgh, Cardiff, Stockholm, Uppsala) • Visiting two clinical pharmacology lab facilities in Sweden and five CF research facilities in England (1994) • Rostrum course on Quality Assurance (Dec. 1995)
Foreign languages	<ul style="list-style-type: none"> • English (Ph.D. examination) • Russian (Ph.D. examination) • German
Note	-

Name	Géza Lakner M.D.
Birth place and date	Budapest, 1967 DEC 24
Marital status	single
Qualification	M.D. (Semmelweis University of Medicine; Faculty of Medicine, Budapest, Hungary, 1991)
Specification	<ul style="list-style-type: none"> • internal medicine (1997) • clinical pharmacology (1999)
Scientific degree	• -
Publications	13
Employments	<ul style="list-style-type: none"> • Institute of Pathology , Postgraduate Medical University (1991-93) • 1st Dept. of Medicine, Div. of Clin. Pharmacol. Haynal Imre University of Health Sciences (1993-2000) • Hungarian Railways Hospital, 1st Department of Medicine - Division of Clinical Pharmacology (from 2000, ongoing)
Conference participation	<ul style="list-style-type: none"> • "Arbeitskreis für medizinische Informatik" (1992, Austria, Graz) • Medical Informatics in Europe (1997: Porto Carras, 1999: Ljubljana) • MEDINFO 1998 (Seoul) • Congress of Hungarian Clinical Pharmacologists (2000 NOV; Debrecen, Hungary)
Memberships	<ul style="list-style-type: none"> • Hungarian Society for Medical Informatics (Secraetary from 1997, Secretary General from 1999) • Hungarian Society for Pharmacology and Clinical Pharmacology • European Association of Clinical Pharmacology and Therapeutics
Fellowships, postgradual education	<ul style="list-style-type: none"> • 2 week short fellowship : Graz, Karl Franzens University , Department of Medical Informatics (1992) • Continuing Education in Clinical Pharmacology (1997, 1999 - oral presentation also) • Clinical Trials 1998 - Richter Gedeon CRA Training (invited oral presentation) • Vienna School of Clinical Research : Introduction to Clinical Drug Research - postgraduate course (2001 JAN 22-26; successful examination)
Foreign languages	<ul style="list-style-type: none"> • English (negotiation level) • German (negotiation level) • French (basic level)
Note	-

Name	Zsolt Mészáros M.D.
Birth place and date	Budapest, 1967 SEP 23
Marital status	single
Qualification	Szent-Györgyi Albert Medical University Faculty of Medicine; 1993
Specification	<ul style="list-style-type: none"> • internal medicine (1998) • acupuncture (1998)
Scientific degree	•
Publications	-
Employments	<ul style="list-style-type: none"> • Markusovszky Hospital, 3rd Department of Medicine (Szombathely) (1993-1995) • HIETE 1st Department of Medicine (1996-1998) • "Varázsvölgy" Medical Centre, Budapest (1998-1999) • Kardirex Medical Centre ; general practice , Győr (1999-2000) • Hungarian Railways Hospital, 1st Department of Medicine - Division of Clinical Pharmacology (from 2001, ongoing)
Conference participation	• -
Memberships	• Hungarian Society of Cardiology
Fellowships, postgradual educations	• course on intensive care (2000)
Foreign languages	• English (basic)
Note	-

Name	Agnes Tóth M.D.
Birth place and date	Budapest, 1953.06.23
Marital status	married
Qualification	M.D. (Semmelweis University of Medicine; Faculty of Medicine, Budapest, Hungary, 1977)
Specification	<ul style="list-style-type: none"> • internal medicine (1985) • endocrinology (1994)
Scientific degree	• -
Publications	-
Conference participation	<ul style="list-style-type: none"> • Conferences of the Hungarian Diabetes Mellitus Society • Conferences of the Hungarian Endocrinology and Metabolic Disorders Society • EFES Postgraduate Clinical Endocrinology Course (1999) • Crossroads of Medicine - Complications of diabetes mellitus (1999)
Memberships	<ul style="list-style-type: none"> • Hungarian Diabetes Mellitus Society • Hungarian Endocrinology and Metabolic Disorders Society
Fellowships, postgradual educations	•
Foreign languages	<ul style="list-style-type: none"> • English (basic level) • German (basic level)

Name	Mrs. Edit Kosztolányi
Birthplace and date	Mezőkovácsháza, 1955 FEB 26
Marital status	married, one daughter
Qualification	highschool graduation specification in transport
Specification	<ul style="list-style-type: none"> • transport administration • general nursing qualification
Scientific degree	• -
Publications	-
Conference participation	• -
Memberships	• -
Fellowships, postgradual educations	• -
Foreign languages	• -

Name	Balog Orsolya
Birthplace and date	Gyöngyös, 1975.04.03
Marital status	single
Qualification	health college graduation (1993)
Specification	<ul style="list-style-type: none"> • adult nursing qualification (1995)
Scientific degree	•
Publications	
Employments	<ul style="list-style-type: none"> • Gyöngyös, Bugát Pál Hospital - Central Anaesthesiology and Intensive Care Unit (1993-1996) • Budapest Military Hospital - Traumatology Intensive Care Unit (1996) • Haynal Imre Universit of Health Sciences, 1st Department of Medicine (1996-2000) • Hungarian Railways Hospital 1st Department of Medicine, Divison of Clinical Pharmacology (from 2001, ongoing)
Conference participation	•
Memberships	•
Fellowships, postgradual educations	•
Foreign languages	•
Note	-

16.1.5. Signatures of principal or coordinating investigator(s)

Name	Position/assignment during study process	Signature	Date
Dr. Géza Lakner	senior lecturer project manager study physician		
Dr. Zsolt Mészáros	doctor study physician		
Dr. Agnes Tóth	senior lecturer independent physician		

Study title	Short term safety and tolerance study for a formulation of humic acid and trace minerals
Study report authors	<ul style="list-style-type: none"> • Béla Gachályi MD PhD DSc • Géza Lakner MD

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Name	Position/assignment during study process	Signature	Date
Dr. Béla Gachályi	study site executive principal investigator study physician		

Affiliation	Department of Clinical Pharmacology and Therapeutics, Hungarian Railways Hospital, Budapest
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Date	10 DEC 2001
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16.1.6. Listing of volunteers receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used

[Not applicable]

16.1.7. Randomization scheme and codes (volunteer identification and treatment assigned)

[Not applicable]

16.1.8. Audit certificates

No official inspection (OGYI) have occurred during the study. Reports of Sponsor's audit are not included in the study report.

16.1.9. Documentation of statistical methods

Clinical parameters included in the statistical analysis as follows.
 The statistical results are presented in Appendix 16.4

Study period	Parameter	Unit
	Enrollment	
Enrollment	Age	years
Enrollment	Height	m
Enrollment	Weight	kg
Enrollment	BMI	kg/m ²
Enrollment	Temperature	°C
Enrollment	ECG Heart rate	1/min
Enrollment	PQ	msec
Enrollment	QRS	msec
Enrollment	QTc	msec
Enrollment	BP systolic	Hgmm
Enrollment	BP diastolic	Hgmm
Enrollment	Pulse rate	1/min
Enrollment	WBC	G/l
Enrollment	NEU	%
Enrollment	LYM	%
Enrollment	MONO	%
Enrollment	EOS	%
Enrollment	BASO	%
Enrollment	RBC	M/microl
Enrollment	HGB	g/dl
Enrollment	HTC	l/l
Enrollment	PLT	G/l
Enrollment	ESR	mm/h
Enrollment	Prothrombin	INR
Enrollment	Urine / spec. gravity	-
Enrollment	Urine / pH	
Enrollment	Serum bilirubin	µmol/l
Enrollment	BUN	µmol/l
Enrollment	Creatinine	µmol/l
Enrollment	Total protein	g/l
Enrollment	Albumin	g/l
Enrollment	Cholesterol	mmol/l
Enrollment	Triglycerides	mmol/l
Enrollment	Glucose	mmol/l
Enrollment	Na	mmol/l
Enrollment	K	mmol/l
Enrollment	Cl	mmol/l
Enrollment	Ca	mmol/l
Enrollment	P	mmol/l
Enrollment	Uric acid	µmol/l
Enrollment	SGOT	U/l
Enrollment	SGPT	U/l
Enrollment	ALP	U/l
Enrollment	GGT	U/l

Enrollment	LDH	U/l
Enrollment	Se iron	µmol/l
Enrollment	Serum endothelin	fmol/ml
	Follow-up #1	
Follow-up #1	ECG Heart rate	1/min
Follow-up #1	PQ	msec
Follow-up #1	QRS	msec
Follow-up #1	QTc	msec
Follow-up #1	BP systolic	Hgmm
Follow-up #1	BP diastolic	Hgmm
Follow-up #1	Pulse rate	1/min
Follow-up #1	WBC	G/l
Follow-up #1	NEU	%
Follow-up #1	LYM	%
Follow-up #1	MONO	%
Follow-up #1	EOS	%
Follow-up #1	BASO	%
Follow-up #1	RBC	M/microl
Follow-up #1	HGB	g/dl
Follow-up #1	HTC	l/l
Follow-up #1	PLT	G/l
Follow-up #1	ESR	mm/h
Follow-up #1	Prothrombin	INR
Follow-up #1	Urine / spec. gravity	-
Follow-up #1	Urine / pH	
Follow-up #1	Serum bilirubin	µmol/l
Follow-up #1	BUN	µmol/l
Follow-up #1	Creatinine	µmol/l
Follow-up #1	Total protein	g/l
Follow-up #1	Albumin	g/l
Follow-up #1	Cholesterol	mmol/l
Follow-up #1	Triglycerides	mmol/l
Follow-up #1	Glucose	mmol/l
Follow-up #1	Na	mmol/l
Follow-up #1	K	mmol/l
Follow-up #1	Cl	mmol/l
Follow-up #1	Ca	mmol/l
Follow-up #1	P	mmol/l
Follow-up #1	Uric acid	µmol/l
Follow-up #1	SGOT	U/l
Follow-up #1	SGPT	U/l
Follow-up #1	ALP	U/l
Follow-up #1	GGT	U/l
Follow-up #1	LDH	U/l
Follow-up #1	Se iron	µmol/l

	Follow-up #2		
Follow-up #2	ECG	Heart rate	l/min
Follow-up #2	PQ		msec
Follow-up #2	QRS		msec
Follow-up #2	QTc		msec
Follow-up #2	BP systolic		Hgmm
Follow-up #2	BP diastolic		Hgmm
Follow-up #2	Pulse rate		l/min
Follow-up #2	WBC		G/l
Follow-up #2	NEU		%
Follow-up #2	LYM		%
Follow-up #2	MONO		%
Follow-up #2	EOS		%
Follow-up #2	BASO		%
Follow-up #2	RBC		M/microl
Follow-up #2	HGB		g/dl
Follow-up #2	HTC		l/l
Follow-up #2	PLT		G/l
Follow-up #2	ESR		mm/h
Follow-up #2	Prothrombin		INR
Follow-up #2	Urine / spec. gravity		-
Follow-up #2	Urine / pH		
Follow-up #2	Serum bilirubin		µmol/l
Follow-up #2	BUN		µmol/l
Follow-up #2	Creatinine		µmol/l
Follow-up #2	Total protein		g/l
Follow-up #2	Albumin		g/l
Follow-up #2	Cholesterol		mmol/l
Follow-up #2	Triglycerides		mmol/l
Follow-up #2	Glucose		mmol/l
Follow-up #2	Na		mmol/l
Follow-up #2	K		mmol/l
Follow-up #2	Cl		mmol/l
Follow-up #2	Ca		mmol/l
Follow-up #2	P		mmol/l
Follow-up #2	Uric acid		µmol/l
Follow-up #2	SGOT		U/l
Follow-up #2	SGPT		U/l
Follow-up #2	ALP		U/l
Follow-up #2	GGT		U/l
Follow-up #2	LDH		U/l
Follow-up #2	Se iron		µmol/l

	Follow-up #3		
Follow-up #3	ECG	Heart rate	l/min
Follow-up #3	PQ		msec
Follow-up #3	QRS		msec
Follow-up #3	QTc		msec
Follow-up #3	BP systolic		Hgmm
Follow-up #3	BP diastolic		Hgmm
Follow-up #3	Pulse rate		l/min
Follow-up #3	WBC		G/l
Follow-up #3	NEU		%
Follow-up #3	LYM		%
Follow-up #3	MONO		%
Follow-up #3	EOS		%
Follow-up #3	BASO		%
Follow-up #3	RBC		M/microl
Follow-up #3	HGB		g/dl
Follow-up #3	HTC		l/l
Follow-up #3	PLT		G/l
Follow-up #3	ESR		mm/h
Follow-up #3	Prothrombin		INR
Follow-up #3	Urine / spec. gravity		-
Follow-up #3	Urine / pH		
Follow-up #3	Serum bilirubin		µmol/l
Follow-up #3	BUN		µmol/l
Follow-up #3	Creatinine		µmol/l
Follow-up #3	Total protein		g/l
Follow-up #3	Albumin		g/l
Follow-up #3	Cholesterol		mmol/l
Follow-up #3	Triglycerides		mmol/l
Follow-up #3	Glucose		mmol/l
Follow-up #3	Na		mmol/l
Follow-up #3	K		mmol/l
Follow-up #3	Cl		mmol/l
Follow-up #3	Ca		mmol/l
Follow-up #3	P		mmol/l
Follow-up #3	Uric acid		µmol/l
Follow-up #3	SGOT		U/l
Follow-up #3	SGPT		U/l
Follow-up #3	ALP		U/l
Follow-up #3	GGT		U/l
Follow-up #3	LDH		U/l
Follow-up #3	Se iron		µmol/l

Post-study	ECG Heart rate	l/min
Post-study	PQ	msec
Post-study	QRS	msec
Post-study	QTc	msec
Post-study	BP systolic	Hgmm
Post-study	BP diastolic	Hgmm
Post-study	Pulse rate	l/min
Post-study	WBC	G/l
Post-study	NEU	%
Post-study	LYM	%
Post-study	MONO	%
Post-study	EOS	%
Post-study	BASO	%
Post-study	RBC	M/microl
Post-study	HGB	g/dl
Post-study	HTC	l/l
Post-study	PLT	G/l
Post-study	ESR	mm/h
Post-study	Prothrombin	INR
Post-study	Urine / spec. gravity	-
Post-study	Urine / pH	
Post-study	Serum bilirubin	μmol/l
Post-study	BUN	μmol/l
Post-study	Creatinine	μmol/l
Post-study	Total protein	g/l
Post-study	Albumin	g/l
Post-study	Cholesterol	mmol/l
Post-study	Triglycerides	mmol/l
Post-study	Glucose	mmol/l
Post-study	Na	mmol/l
Post-study	K	mmol/l
Post-study	Cl	mmol/l
Post-study	Ca	mmol/l
Post-study	P	mmol/l
Post-study	Uric acid	μmol/l
Post-study	SGOT	U/l
Post-study	SGPT	U/l
Post-study	ALP	U/l
Post-study	GGT	U/l
Post-study	LDH	U/l
Post-study	Se iron	μmol/l
Post-study	Serum endothelin	fmol/ml

16.1.10. Documentation of inter-laboratory standardization methods and quality assurance procedures if used

Not applicable.

16.2. Volunteer Data Listings

16.2.1. Discontinued volunteers

No drop-out occurred during the study.

16.2.2. Protocol deviations

See Section 10.2.

16.2.3. Volunteers excluded from the efficacy analysis

All volunteers participated in the analysis.

16.2.4. Demographic data

Individual demographic data of the volunteers (identification, age, body height and weight) are presented in the data listing of Appendix 16.4 .

16.2.5. Compliance and/or drug concentration data

Compliance was 100%.

16.2.6. Individual efficacy response data

See Appendix 16.4.

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Hungarian Railways Hospital - HUMET Co.

HUMET® capsules Phase I HUMET 101/2000

16.2.7. Adverse event listings (each volunteer)

Vol. #	Treat group	Description	Start	End	Classification	Intensity	Type	Relation to study drug	Action	Outcome
03	A	increase of vigily and performance	2001 MAY 03	2001 MAY 06	1	2	3	1	1	1
03	A	increase of vigily and performance	2001 MAY 13	2001 MAY 14	1	2	3	1	1	1
03	A	softer stool	2001 MAY 17	2001 MAY 17	1	1	1	1	1	1
04	A	increase of vigily	2001 MAY 09	2001 MAY 15	1	2	3	1	1	1
12	B	diarrhoea	2001 MAY 03	2001 MAY 04	1	1	1	2	1	1
12	B	better digestion	2001 MAY 16	2001 MAY 16	1	1	1	2	1	1
14	B	nausea	2001 MAY 03	2001 MAY 03	1	1	1	2	1	1
15	A	darker, more solid stool	2001 MAY 10	2001 MAY 10	1	1	2	2	1	1
17	B	increase of vigily and appetite	2001 MAY 03	2001 MAY 08	1	2	3	1	1	1
17	B	general dyscomfort	2001 MAY 12	2001 MAY 12	1	1	1	2	1	1

1: not serious
2: serious

1: mild
2: moderate
3: severe

1: single
2: recurrent
3: continuous

1: likely
2: possible
3: unlikely
4: no relation

1: none (resolved spontaneously)
2: drug therapy
3: withdrawal from trial
4: other

1: resolved completely
2: improved
3: unchanged
4: deteriorated
5: resolved with sequelae

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Hungarian Railways Hospital - HUMET Co.

HUMET® capsules Phase I HUMET 101/2000

Vol. #	Treat. group	Description	Start	End	Classification	Intensity	Type	Relation to study drug	Action	Outcome
17	B	increase of appetite	2001 MAY 18	2001 MAY 18	1	1	1	2	1	1
21	A	increase of vigility and appetite	2001 MAY 05	2001 MAY 10	1	2	3	1	1	1
21	A	less stool	2001 MAY 04	2001 MAY 10	1	1	2	2	1	1
21	A	increase of vigility and appetite	2001 MAY 13	2001 MAY 17	1	2	3	1	1	1
21	A	increase of vigility, concentration, weight loss	2001 MAY 19	2001 MAY 24	1	1	3	2	1	1
22	A	diarrhoea	2001 MAY 05	2001 MAY 07	1	1	2	1	1	1
23	A	vomitus	2001 MAY 17	2001 MAY 17	1	2	2	2	1	1
26	A	higher liver enzymes (SGOT, SGPT, LDH)	2001 MAY 18	2001 MAY 22	1	2	1	3 (strenuous fitness training)	1	1
30	A	darker stool	2001 MAY 04	2001 MAY 10	1	1	2	2	1	1
30	A	darker stool	2001 MAY 11	2001 MAY 17	1	1	2	2	1	1

1 not serious
2 serious

1. mild
2 moderate
3 severe

1: single
2 recurrent
3 continous

1 likely
2 possible
3 unlikely
4 no relation

1 none (resolved spontaneously)
2 drug therapy
3 withdrawal from trial
4. other

1 resolved completely
2 improved
3 unchanged
4 deteriorated
5 resolved with sequelae

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Hungarian Railways Hospital - HUMET Co.

HUMET® capsules Phase I HUMET 101/2000

Vol. #	Treat. group	Description	Start	End	Classifi- cation	Inten- sity	Type	Relation to study drug	Action	Out- come
30	A	darker stool	2001 MAY 18	2001 MAY 24	1	1	2	2	1	1
34	B	increase of vigility	2001 MAY 18	2001 MAY 24	1	2	3	1	1	1
38	B	diarrhoea	2001 MAY 22	2001 MAY 23	1	1	2	2	1	1

1: not serious
2: serious

1. mild
2 moderate
3: severe

1. single
2 recurrent
3. continous

1: likely
2 possible
3. unlikely
4 no relation

1: none
(resolved
spontaneously)
2: drug therapy
3. withdrawal
from trial
4. other

1.resolved
completely
2 improved
3 unchanged
4 deteriorated
5 resolved
with sequelae

**16.2.8. Listing of individual laboratory measurements
by volunteer**

See Appendix 16.4 for a complete data table.

16.3. Case Report Forms (CRF's)

No copies of finished CRFs are included in this report.

16.4. Individual Volunteer Data Listings

The individual study data table comprises the display of abnormal laboratory parameters, too: the out-of-range values are highlighted.