STUDY No. FUS 9602 UK

Evaluation of the bioavailability of a new oral suspension of Fusidic Acid versus a dry granulated, film coated tablet of Sodium Fusidate in healthy volunteers

STUDY REPORT

CLINICAL INVESTIGATOR: Dr. [Redacted]

SPONSOR
LEO PHARMA TECHNICAL PRODUCTS Ltd. A/S (LEO)
(Løwens kemiske Fabrik Produktionsaktieselskab)
Industrparken 55
DK-2750 Ballerup
Denmark

STUDY CENTRE

[Redacted]
United Kingdom

The clinical study report has been redacted using the following principles: Where necessary, information is anonymised to protect the privacy of study subjects and named persons associated with the trial as well as to retain commercial confidential information. Summary data are included but data on individual study subjects, including data listings, are removed. This may result in page numbers not being consecutively numbered. Access to anonymised data on individual study subjects may be obtained upon approval of a research proposal by the Patient and Scientific Review Board. Appendices to the clinical study report are omitted. Further details and principles for anonymisation are available in the document LEO PHARMA PRINCIPLES FOR ANONIMISATION OF CLINICAL TRIAL DATA.
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AUTHENTICATION

We, the undersigned, hereby declare that this work was performed by ourselves or under our supervision according to the procedure herein described and that this report represents a true and accurate record of the work performed. The clinical phase of the study was performed by [redacted], UK.

Dr [redacted]
Clinical Investigator

Date 5-3-97
QUALITY ASSURANCE STATEMENT

Inspections were made by the Quality Assurance Unit (QAU) of the various phases of the study described in this report. The dates on which the inspections were made and the dates on which the findings were reported to the Clinical Investigator and to the Facility Management are given below:

<table>
<thead>
<tr>
<th>Date of Inspection/Audit</th>
<th>Date of report to Clinical Investigator and Management</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

This report has been audited by the QAU and was found to be an accurate description of such methods and procedures as were used during the conduct of the study and an accurate reflection of the raw data:

Date of Final Report audit: 05.03.1997
## STU Dy SYNOPSIS

### STUDY TITLE
Evaluation of the bioavailability of a new oral suspension of Fusidic Acid versus a dry granulated, film coated tablet of Sodium Fusidate in healthy volunteers.

**PROTOCOL NO. FUS 9602 UK.**

### INVESTIGATOR
Dr. [Redacted]

### STUDY CENTRE
[Redacted] U.K.

### SPONSOR
Leo Pharmaceutical Products Ltd.
A/S (Loven's kermiske Fabrik Produktionsaktieselskab),
Industriparken 55,
DK-2750 Ballerup Denmark.

### PUBLICATION
None

### STUDY PERIOD
Clinical phase started on 29 July, 1996 and concluded on 5 September, 1996. Fusidic acid serum assay and pharmacokinetic analysis were performed in September-October 1996.

### OBJECTIVE
Evaluate the bioavailability after a single oral 500mg dose of two formulations, Fusidic Acid and Sodium Fusidate, respectively, in healthy fasting volunteers.

### METHODOLOGY
Study design: single centre, open label, two-periods two-treatments cross-over study

### VOLUNTEERS
Eighteen healthy volunteers, 9 male, 9 female, 19 to 52 years old.

### DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION
Healthy volunteers

### TEST PRODUCT:
**Name, Dosage Form, Strength, Route of Admin., Regimen and Duration**
- **Test Formulation (A):** Fusidic acid suspension 5% (Leo) containing 50 mg/mL.
  - Batch No.: [Redacted] Expiry date: May 1999.
  - Single oral dose of 500 mg (10 mL of suspension).

### REFERENCE PRODUCT:
**Name, Dosage Form, Strength, Route of Admin., Regimen and Duration**
- **Reference Formulation (B):** Dry granulated, film coated tablet (Leo) containing 250 mg of sodium fusidate.
  - Batch No.: [Redacted] Expiry date: May 1999.
  - Single oral dose of 500 mg (2 tablets).

### CRITERIA FOR EVALUATION
Pharmacokinetic bioequivalence. Safety was assessed by physical examinations, clinical laboratory evaluation and adverse event monitoring.

### RESULTS AND STATISTICAL SIGNIFICANCE

<table>
<thead>
<tr>
<th></th>
<th>Formulation (A)</th>
<th>Formulation (B)</th>
<th>Significance</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>mean ± s.d.</td>
<td>mean ± s.d.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(range)</td>
<td>(range)</td>
<td></td>
</tr>
<tr>
<td>Cmax (µg/ml)</td>
<td>8.3±2.8</td>
<td>24.4±9.8</td>
<td>NS&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>(μg/ml)</td>
<td>(4-13)</td>
<td>(11.4-50)</td>
<td></td>
</tr>
<tr>
<td>tmax (h)</td>
<td>4</td>
<td>2.5</td>
<td>(p&gt;0.05)&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>(1.5-4)</td>
<td>(1-6)</td>
<td></td>
</tr>
<tr>
<td>AUCz (h·µg/ml)</td>
<td>111±56.5</td>
<td>278±82.6</td>
<td>NS&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>(34.8-190.7)</td>
<td>(149.9-461.4)</td>
<td></td>
</tr>
<tr>
<td>AUC (h·µg/ml)</td>
<td>174.4±82.7</td>
<td>329.4±87.6</td>
<td>NS&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>(77.9-368.8)</td>
<td>(192.1-524.7)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> (90% C.I. = 0.28-0.40) 90% C.I. after log transformation

<sup>2</sup>(Wilcoxon matched-pairs rank)

<sup>3</sup>(90% C.I. =0.28-0.42) 90% C.I. after log transformation

<sup>4</sup>(90% C.I. =0.40-0.56) 90% C.I. after log transformation

1 page 6 of 36
| ADVERSE EVENTS | Thirteen adverse events were reported by 11 volunteers. The most frequently reported adverse events were headaches (6 out of 13). The adverse events considered possibly or probably related to the study drug were similarly distributed between the 2 study formulations (5 after formulation A and 3 after formulation B). |
| CONCLUSIONS | The clinical phase of the study ran well and was incident free. The 18 healthy volunteers enrolled, completed the study and no serious, severe or unexpected A.E. occurred. No drug-related, clinically significant modifications of the laboratory safety tests were observed. The result of the pharmacokinetic parameters and comparison of bioavailability for evaluation of bioequivalence (AUC, C\text{max}, and T\text{max}) showed that the test formulation (10 ml of the 50 mg/ml fusidic acid suspension) did not have a compatible bioavailability to the reference formulation (2 x 250 mg sodium fusidate dry granulated film coated tablet). |
LIST OF ABBREVIATIONS

Note: Numbers are considered before latin alphabet characters. Greek alphabet characters are considered after latin alphabet characters. Symbols are not considered.

A.E.- Adverse Event
A/G- Albumin/Globulin
ALT- Alanine aminotransferase
AST- Aspartate aminotransferase
AUC- Area under the serum concentration versus time curve
AUC(0-inf)- Area under the serum concentration versus time curve from the administration time to infinite time
%AUCext- Percentage of extrapolated area under the serum concentration time curve
AUCz- Area under the serum concentration versus time curve up to the last sampling time at which a quantifiable concentration is found
b.i.d.- Twice a day
BP- Blood Pressure
bpm- Beats per minute
BQL- Below Quantitation Limits
BW- Body Weight
cn.- circa
C.I.- Confidence Interval
cm- Centimetres
Cmax- Highest concentration value found in serum
Conc.- Concentration
CPU- Clinical Pharmacology Unit
CRF- Case Report Form
Cz- Concentration value obtained at the last sampling time at which a quantifiable concentration is found in serum
dl- Decilitre
D.O.B.- Date Of Birth
EEC- European Economic Community
F(test/ref)- Index of relative bioavailability of the test treatment versus the reference treatment
fl.- Femtolitre
g- Grams
Gamma-GT- Gamma-Glutamyl Transpeptidase
GCP- Good Clinical Practice
h- Hours
H- Height (in the text of the report and in the tables detailing the demographic characteristics of the volunteers)
H- Flag for any value above the reference range (in the tables detailing the laboratory results)
HB- Haemoglobin
hh:mm- hours:minutes
HIV- Human Immunodeficiency Virus
inf- infinite time
I.U.- International Units
Kel- Elimination rate constant
kg- Kilograms
L- Litre (in the text of the report)
L- Flag for any value below the reference range (in the tables detailing the laboratory results)
Leo- Leo Pharmaceutical Products Ltd. A/S
ln- natural logarithm
mg- milligrams
mL- Millilitres
mm Hg- Millimetres of mercury
mmol- Millimols
n/av- Not available
NEG- Negative
No.- Number
N.S.- Not significant
p- Probability of the type I error
pg- picogram
pH- minus common logarithm of the concentration of hydrogen ions measured in moles per cubic decimetre
POS- Positive
POST- Post-study examination
PRE- Pre-study examination
QAU- Quality Assurance Unit
ref- reference formulation
s.d.- Standard Deviation
SOP- Standard Operating Procedure
s.e.m- Standard Error Mean
t1/2- Elimination half-life
tlin- First time point considered for the determination of half-life
tmax- The time from administration at which the highest concentration value is found in serum
tz- Last sampling time at which a quantifiable concentration is found in serum
U.K.- United Kingdom
Vol.- Volunteer
vs.- Versus
μg- Micrograms
μmol- Micromols
1. ETHICAL ASPECTS

The study protocol was reviewed and approved by the Local Research Ethics Committee of Cambridge Health Authority on 21 June 1996 (Appendix 1). Some minor editorial changes were approved by the Local Research Ethics Committee of Cambridge Health Authority through a Chairman's Action on 26 July 1996.

The study was performed in accordance with the guidelines of the Declaration of Helsinki (Hong Kong revision 1989) on biomedical research involving human subjects and according to the general principles of: "GCP for trials on medicinal products in the EEC (July 1990)" in "The Rules Governing Medicinal Products in the European Community Vol. III, Add 1 (III/9148/90-EN)".

Each subject gave written informed consent after a full explanation of the protocol, including the purposes of the study and the potential risks involved.

A Volunteer Information Leaflet and Informed Consent Form is enclosed in Appendix 1.

1.1 Investigator and study administrative structure

Clinical Investigator
Dr. [redacted]
(CV enclosed in Appendix 1)

Clinical phase

Pharmacokinetic analytical determinations, pharmacokinetic and statistical data analysis

* Companies within [redacted]
2. INTRODUCTION

Fusidic acid and its salts are potent antistaphylococcal agents with unusual ability to penetrate tissue. Bactericidal levels have been found in bone and necrotic tissue. Fusidic acid is active against Staphylococcus (aureus and epidermidis), including methicillin resistant staphylococci.

Fusidic acid for oral administration is available either as tablets (containing sodium fusidate) or as suspension (containing fusidic acid). It is used in the treatment of staphylococcal infections such as: cutaneous and wound infections, osteomyelitis, pneumonia, septicemia, endocarditis and superinfected cystic fibrosis.

The standard oral dose for the treatment of cutaneous staphylococcal infections in adults is 250 mg of sodium fusidate (equivalent to 240 mg fusidic acid) twice daily for 5-10 days. For the treatment of more severe staphylococcal infections such as osteomyelitis, pneumonia, septicemia, wound infections, endocarditis or superinfected cystic fibrosis, the standard dose is 500 mg sodium fusidate (equivalent to 480 mg fusidic acid) three times daily.

Pharmacokinetics: Fusidic acid has been commercially available since 1962. However, pharmacokinetic studies published over the years have yielded widely different results, reporting half-lives ranging from 2.77 to 11 hours. This variability may be explained partly by their use of a microbiological assay, and partly by a non-linear mechanism of elimination. Several single increasing dose studies have confirmed reductions in apparent clearance with increasing dose. Most multiple dose studies tended to indicate that fusidic acid pharmacokinetics shows some degree of non-linearity, although others have not.

Fusidic acid is extensively metabolised in the liver, and excreted primarily by bile. Only 2% is eliminated unchanged in the bile and renal elimination is negligible. Although 7 metabolites of fusidic acid have been found on thin-layer chromatography only 4 have been identified. The metabolites identified in bile include 3-ketofusidic acid (small quantities), 27-carboxyfusidic acid (10%) fusidic acid 21-glucuronide (15%) and a hydroxy derivative called metabolite E (3%). The only fusidic acid metabolite quantifiable in serum is 3-ketofusidic acid. The mean serum concentration of 3-ketofusidic acid ranges from 12 to 18% of the corresponding fusidic acid concentration.

Fusidic acid is highly bound to albumin (95-97%). Fusidic acid is considered an extensively metabolised, low clearance drug whose hepatic elimination is dependent on its free fraction and intrinsic clearance.

MacGowan et al. documented that bioavailability was not affected when taken with food, although the time to achieve the peak concentration was delayed and the peak concentration was reduced. Following single oral doses of fusidic acid, most studies show peak concentrations of approximately 10-15 mg/L for every 250 mg of fusidic acid ingested that are reached 2-3 hours after dose. The concentrations found...
hours after dosing are in the range of 1.5 to 2.0 mg/L when normalised to a 250 mg
dose (assuming linear kinetics)\textsuperscript{5,7}. Blood levels are cumulative, reaching
concentrations of 20-35 mg/L after oral administration of 250 mg twice daily for
seven days and 50-100 mg/L after oral administration of 1.5 g daily for 3-4 days.

\textbf{Adverse Effects and Precautions}: apart from mild gastrointestinal upsets, fusidic acid
or sodium fusidate appear to be well tolerated when given by mouth. Treatment with
fusidates, by mouth or specifically by the intravenous route, has been associated with
jaundice and changes in liver function. Normal liver function is usually restored when
treatment is discontinued. They should be given with caution to patients with impaired
liver function. Hypersensitivity reactions such as rashes and irritation may occur after
the topical administration of fusidates; rash is rare after systemic administration.
There have been occasional reports of granulocytopenia and thrombocytopenia
following systemic doses of fusidic acid\textsuperscript{15}.

\section{3. OBJECTIVE OF THE STUDY}
The aim of the present study was to evaluate the bioavailability after a single oral 500
mg dose of two fusidic acid formulations in healthy fasting volunteers.

Two oral formulations were compared in this study: a solution containing 50 mg/mL
of fusidic acid and a dry granulated, film coated tablet containing 250 mg of sodium
fusidate. Both were manufactured and certified by Leo Pharmaceutical Products A/S.

\section{4. STUDY DESIGN}
Open, randomised, single dose, two treatment two-period cross-over design in
healthy, fasting volunteers.

\section{5. DRUG SUPPLIES}
Both formulations (including an appropriate number of countersamples) produced and
certified by Leo, were provided by the Sponsor to the Clinical Investigator, along with
the certificates of analysis and of qualitative and quantitative composition.

\begin{itemize}
\item \textbf{Formulation A}: Fusidic acid suspension 5% containing 50 mg/mL.
\item \textbf{Formulation B}: Dry granulated, film coated tablet containing 250 mg of sodium
\end{itemize}
\begin{itemize}
\item fusidate.
\end{itemize}
6. METHODS

6.1 Clinical Methods

The study was conducted at the UK.

Clinical haematology, biochemistry, and urinalysis were carried out at the UK.

The inclusion criteria were the following:

Race: caucasian

Sex: males and females

Age: 18-55 years old.

Body weight: within ± 15% of ideal body weight, according to sex and height, as calculated by the following Lorenz formulas:

males: \[ BW^* = H - 100 - (H - 150) / 4 \]

females: \[ BW^* = H - 100 - (H - 150) / 2 \]

where: \[ BW^* = \text{ideal body weight (kg)} \]
\[ H = \text{height (cm)} \]

Physical examination: normal findings at physical examination.

Physical examination included review of the following: eyes, ears, nose, throat, neck (including thyroid), heart, lungs, abdomen (including liver and spleen), skin, lymph nodes, urogenital, muscular-skeletal and nervous systems.

Blood pressure, heart rate: normal values of blood pressure (100-140 mm Hg systolic and 60-90 mm Hg diastolic) and heart rate (50-90 bpm), measured after 5 minutes of rest in the sitting position.

Electrocardiographic examination: normal findings.

Full comprehension: ability to comprehend the full nature and purpose of the study, including possible risks and side effects, ability to cooperate with the Investigator and to comply with the requirements of the entire study.

Written informed consent: provision of consent to participate in the study as shown by the signature of the Volunteer Consent Form.

Clinical laboratory analyses: clinical laboratory values within the reference range (unless the Investigator considered the deviations not clinically significant).
The following clinical laboratory parameters were tested:

- Haematology: erythrocytes, haemoglobin, mean cell volume, mean cell haemoglobin, mean cell haemoglobin concentration, packed cell volume (haematocrit), thrombocyte count, leucocytes total and differential count: neutrophils, eosinophils, basophils, monocytes, lymphocytes.

- Blood chemistry: total protein, total bilirubin (direct and indirect bilirubin were performed only if total bilirubin was outside the normal range), alkaline phosphatase, serum glutamic oxalacetic transaminase and serum glutamic pyruvic transaminase, gamma glutamyl transpeptidase, urea, creatinine, uric acid, sodium, potassium, calcium, inorganic phosphorus, glucose, total cholesterol, albumin, globulin, albumin/globulin ratio, pregnancy test (females only).

- Virology: Hepatitis B and C, HIV.

- Urinalysis: pH, colour, leucocytes, nitrite, glucose, protein, red cells and ketones, drug of abuse (amphetamines, cannabis, methadone, opiates, benzodiazepines, cocaine, barbiturates, ecstasy, phencyclidine).

The exclusion criteria included the following:

**Allergy**: history of serious adverse reactions or hypersensitivity to any drug and antibiotic and fusidic acid in particular. History or presence of allergy requiring treatment (e.g., seasonal hay fever).

**Diseases**: history or presence of renal, hepatic, gastrointestinal, cardiovascular, haematological, respiratory, endocrine or central nervous system diseases. In particular history or presence of peptic ulcer.

**Medication**: any medication during 2 weeks before the start of the study, which (the Investigator considered) might affect the validity of the study (e.g. interaction with test drug).

Subjects were informed not to take drugs during this pre-study period, including cold preparations, aspirin, vitamins and antacids.

**Investigational drug trials**: participation in the evaluation of any drug during the 3 months before the start of the study.

**Clinical laboratory analyses**: positivity to hepatitis B (not due to immunisation) or C or HIV tests. Positivity to drugs of abuse test.

**Blood loss or donations**: blood loss or donations greater than 400 mL during the 3 months before the start of the study.

**Pregnancy or breast-feeding conditions**

**Child bearing potential**: (without satisfactory contraception)

**Drug, Alcohol, Caffeine, Tobacco abuse**: history of drug or alcohol (> 75 g of ethanol/day) or caffeine (more than 5 cups of tea or coffee/day) or tobacco (> 10 cigarettes/day) abuse.
6.2 Drugs

The study drugs were received, checked and stored in the pharmacy by the Pharmacist, who also maintained accountability of the study drug.

The following formulations were used in the study:

Formulation A: Fusidic acid suspension 5% containing 50 mg/mL.
- Batch No.: 
- Manufacturer date: May 1996
- Expiry date: May 1999

Formulation B: Dry granulated, film coated tablet containing 250 mg of sodium fusidate.
- Batch No.: 
- Manufacturer date: May 1996
- Expiry date: May 1999

6.3 Study Procedure

6.3.1 Pre-Study

Volunteer screening took place not earlier than 30 days before the start of the study. The volunteers were informed of the study objectives and requirements. Written informed consents were obtained. Clinical and laboratory evaluation of each volunteer was undertaken to ensure compliance with the entry (inclusion and exclusion) criteria defined in the Study Protocol.

6.3.2 Clinical Phase

The volunteers were admitted to in the evening (around 21:00-22:00) before dosing. Their general health was assessed by inquiry and the measurement of vital signs (blood pressure, heart rate, body temperature). The volunteers had to fast for 8 hours before dosing. Water was allowed ad libitum up to 1 hour pre-dose. Volunteers were randomly assigned an identification number (1 to 18) and allocated to their respective wards and beds. The volunteers were dosed at five minutes intervals starting at approximately 07:45. Each volunteer received the study drug orally with 200 mL of tap water, according to the predefined randomisation list (Table 1, section 7.1).

The following doses were administered under the supervision of the Clinical Investigator or Assistant:

Formulation A: Single oral dose of 10 mL suspension containing fusidic acid 50 mg/mL. (Total dose 500 mg)
- Administered with 200 mL of tap water.

Formulation B: Single oral dose of two dry granulated, film coated tablets containing each 250 mg of sodium fusidate. (Total dose 500 mg)
- Administered with 200 mL of tap water.
A dose of 500 mg was chosen as the most appropriate for this study because it is the usual therapeutic dose for moderately severe infections, as detailed in Section 2.

A plastic cannula was inserted in a forearm vein and venous blood samples (about 7 mL) were collected. The cannula was rinsed, after each sampling, with about 2 mL of heparin solution in sterile saline (5 I.U./mL). The blood samples were collected into plain tubes, at the following 13 times:

0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 and 36 hours after administration.

The actual times of each blood sampling were recorded in the corresponding individual Case Report Form (CRF). Actual sampling times were recorded in the CRF as equivalent to the scheduled ones if deviations were lower than 2 minutes. After 30 minutes, the blood samples were centrifuged at 3,000 revolutions per minute for 20 minutes, the cells were discarded and serum was obtained. Each sample was equally divided into 2 tubes and immediately stored at -20°C.

The volunteers were under medical supervision during the study sessions.

The volunteers had to remain fasting after dosing up to the 4 hour's blood sampling, after which they received a standardised light lunch. A standardised light dinner was given to each volunteer between the 9 hours and 12 hours sampling. No other food was allowed up to 12 hours after dosing. The volunteers did not smoke or consume alcohol, caffeine or xanthine-containing products (chocolate, tea, coffee, cola, etc.) for 48 hours before and during each study session.

Fluid intake was standardised from 1 hour before dosing up to the 4 hour's blood sampling as follows: drug was given with 200 mL of tap water, 200 mL of soft drink containing no caffeine or xanthine were provided after the 2 hour sampling. Water was allowed ad libitum after 4 hour sampling.

On the days of the study (from 1 hour before dosing to 12 hours after dosing) the physical activity of the subjects was reduced to a minimum. The supine position was not allowed from the time of drug administration up to 4 hours after dosing. The volunteers were allowed to leave 12 hours after dosing. Volunteers returned to as “out-patients” for the subsequent post-dose samples, according to the predefined schedule.

Each volunteer repeated the above procedure two times with a wash-out interval between both study sessions of at least 1 week.

### 6.3.3 Post-Study Examination

Within 10 days after the completion of the clinical procedure, a post-study medical examination took place. During this examination, the laboratory tests required for admission to the study were repeated, except for the screening for hepatitis B and C, HIV and drugs of abuse.
7. RESULTS

7.1 Clinical Data
The clinical phase of the study started on 29 July 1996 (first pre study examination) and ended on 5 September 1996 (last post study examination). The study dosing sessions were held on 8 August 1996 (Period 1) and 15 August 1996 (Period 2). Eighteen healthy volunteers (9 males and 9 females) were enrolled into and completed the study.

Table 1 details the study session dates, the pre and post study medical examination dates and the randomisation of the formulations for each volunteer.

Table 1: Study Schedule And Randomisation list

<table>
<thead>
<tr>
<th>Vol. No.</th>
<th>Pre-study Examination Date</th>
<th>Dosing Period 1 Date</th>
<th>Randomised Formulation</th>
<th>Dosing Period 2 Date</th>
<th>Randomised Formulation</th>
<th>Post study Examination Date</th>
</tr>
</thead>
</table>

Formulation A: Single oral dose of 10 mL suspension containing fusidic acid 50 mg/mL.

Formulation B: Single oral dose of two dry granulated, film coated tablets containing each 250 mg of sodium fusidate.
Table 2 reports the demographic data and physical characteristics of the subjects.

**Table 2: Volunteers Demographic Data and Physical Characteristics**

<table>
<thead>
<tr>
<th>Vol. No.</th>
<th>Initials</th>
<th>D.O.B.</th>
<th>Sex</th>
<th>Age</th>
<th>Height (cm)</th>
<th>Body Weight (kg)</th>
<th>BW*</th>
<th>Body Weight vs. BW* (%)</th>
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<tbody>
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</tr>
</tbody>
</table>

**Mean**
- 30.6
- 172.1
- 64.5

**s.d.**
- 9.5
- 9.9
- 9.3

**Range**
- 19-52
- 155-193
- 48-92

**Females**
- Mean: 36.9
- s.d.: 9.0
- Range: 25-52

**Males**
- Mean: 24.4
- s.d.: 5.1
- Range: 19-30

- Ideal Body weight as calculated by the Lorenz Formula
- s.d.: Standard Deviation

D.O.B. - Date of birth

BW = Body weight

BW* = Ideal Body weight as calculated by the Lorenz Formula
The vital signs recorded at pre study and post study physical examinations are detailed in Table 3.

Table 3: Volunteers Vital Signs At Pre Study And Post Study Physical Examinations

<table>
<thead>
<tr>
<th>Vol. No.</th>
<th>BP systolic (mm Hg)</th>
<th>BP diastolic (mm Hg)</th>
<th>Heart rate (bpm)</th>
<th>BP systolic $^*$ (mm Hg)</th>
<th>BP diastolic $^*$ (mm Hg)</th>
<th>Heart rate $^*$ (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>124.39*</td>
<td>69.39</td>
<td>71.83</td>
<td>117.67*</td>
<td>68.89</td>
<td>70.28</td>
</tr>
<tr>
<td>s.d.</td>
<td>8.46</td>
<td>7.16</td>
<td>9.98</td>
<td>10.35</td>
<td>7.36</td>
<td>7.69</td>
</tr>
<tr>
<td>Range</td>
<td>108-140</td>
<td>60-88</td>
<td>56-88</td>
<td>103-140</td>
<td>54-85</td>
<td>59-84</td>
</tr>
</tbody>
</table>

BP- Blood Pressure
bpm- Beats Per Minute
$^*$ Post study examination. * t-Test Paired Two Samples for Means $p=0.017$ (Post study vs. Pre study)

As shown in Table 2 and 3 the volunteers fulfilled the criteria defined in the protocol regarding age, body weight, findings at physical examination including vital signs.

At pre study examination all the volunteers were screened by clinical laboratory analysis, and the results were negative for hepatitis B and C, HIV and drugs of abuse.

None of the volunteers were under chronic drug treatment.

No clinically significant variations were observed. The statistically significant decrease of the mean systolic blood pressure at post-study examination compared to the pre-study values was not clinically relevant. The difference is more likely to be related to the adaptation of the volunteers to the study settings.
7.2 Adverse Events
All the adverse events (A.E.) reported during the study are detailed in Table 4.

A total of 13 A. E. were reported by 11 out of 18 volunteers during the study.

After the administration of Formulation A Fusidic acid suspension, 8 A.E. were reported by 8 out of 18 volunteers.

After the administration of Formulation B Sodium fusidate tablet, 5 A.E. were reported by 5 out of 18 volunteers.

Four of the 13 AEs occurred after first dose and before second dose. Eight AEs occurred after second dose, and the last AE was reported/took place during the pre-dose period.

The 8 out of 13 reported A.E.’s considered possibly related to the study drugs are detailed in Table 5. For subject nos and no A. E. were considered probably related to the study drug.

### Table 5: Adverse Events Considered Possibly Related To The Study Drug

<table>
<thead>
<tr>
<th>Description</th>
<th>Formulation A</th>
<th>Formulation B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

Formulation A: Single dose of 10 mL suspension containing fusidic acid 50 mg/mL. (Total dose 500 mg)

Formulation B: Single dose of two dry granulated, film coated tablets containing each 250 mg of sodium fusidate. (Total dose 500 mg)

The remaining five out of the 13 A.E.’s were considered not related to the study drugs because of the temporal relationship between drug administration and their onset or because of their clear relationship with non study-related factors. (see Table 4 for subjects nos and )
Table 4: Adverse Events

<table>
<thead>
<tr>
<th>Vol. No.</th>
<th>A.E. Description</th>
<th>Reported by</th>
<th>Onset</th>
<th>Study drug period</th>
<th>Drug Admin.</th>
<th>Duration (h:mm)</th>
<th>Severity</th>
<th>Action Taken (see Table 6, page 22)</th>
<th>Outcome</th>
<th>Relationship to study drug</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Headache</td>
<td>Subject</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Moderate</td>
<td>Pharmacological Treatment</td>
<td>Recovered</td>
<td>Unlikely</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Diarrhoea</td>
<td>Subject</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Moderate</td>
<td>Pharmacological Treatment</td>
<td>Recovered</td>
<td>Possibly</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Headache</td>
<td>Subject</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mild</td>
<td>None</td>
<td>Recovered</td>
<td>Possibly</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Lump in right inguinal site</td>
<td>Subject</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mild</td>
<td>None</td>
<td>Unknown</td>
<td>Unlikely</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Headache</td>
<td>Subject</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Moderate</td>
<td>None</td>
<td>Recovered</td>
<td>Possibly</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Headache</td>
<td>Subject</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Moderate</td>
<td>Pharmacological Treatment</td>
<td>Recovered</td>
<td>Possibly</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Backache</td>
<td>Subject</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Moderate</td>
<td>Pharmacological Treatment</td>
<td>Recovered</td>
<td>Unlikely</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Headache</td>
<td>Subject</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mild</td>
<td>None</td>
<td>Recovered</td>
<td>Unlikely</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Headache</td>
<td>Subject</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mild</td>
<td>None</td>
<td>Recovered</td>
<td>Possibly</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Dyspepsia</td>
<td>Subject</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mild</td>
<td>None</td>
<td>Recovered</td>
<td>Possibly</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Dyspepsia</td>
<td>Subject</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mild</td>
<td>None</td>
<td>Recovered</td>
<td>Possibly</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Lower urinary tract infection</td>
<td>Investigator</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Moderate</td>
<td>Pharmacological Treatment</td>
<td>Recovered</td>
<td>Unlikely</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Dyspepsia</td>
<td>Subject</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Moderate</td>
<td>None</td>
<td>Recovered</td>
<td>Possibly</td>
<td></td>
</tr>
</tbody>
</table>

c.a. - circa  n/a - Not available  b.i.d. - twice a day  N/A - Not Applicable
The concomitant medications are detailed in Table 6.

The majority of these medications were self administered for pain relief.

**Table 6: Concomitant Medications**

<table>
<thead>
<tr>
<th>Vol. No.</th>
<th>Medication</th>
<th>Daily Dose</th>
<th>Start Date</th>
<th>End Date</th>
<th>Reason For Use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Administered from 2 weeks before screening to the first study session
2. Co-Proxamol 2 tablets
3. Administered during a study session
4. Single dose taken at an unknown date within 2 weeks prior to the screening examination

Overall the clinical phase of the study ran well and was incident free. No serious, severe or unexpected A.E. were observed. Most A.E. resolved spontaneously or with symptomatic treatment during the observation period: Exceptions were:

- was noticed in the post-study examination of Vol. No. 1.

No further follow-up was deemed as necessary for the purposes of the study due to the nature and mild intensity of the finding.

A urinary tract infection was detected in the post-study examination of Vol. No. that resolved after trimethoprim treatment.
7.3 Laboratory Results

All the pre and post-study individual laboratory results: haematology, biochemistry, and urinalysis are detailed in Appendix 2.

Table 7 details all the haematology and biochemistry results out of the reference range.

Table 7: Biochemistry And Haematology Out Of Range Results

<table>
<thead>
<tr>
<th>Vol. No.</th>
<th>Occasion</th>
<th>Test</th>
<th>Result</th>
<th>Units</th>
<th>Reference Range - Lower Limit</th>
<th>Reference Range - Upper Limit</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Overall the haematology and biochemistry results did not show variations clinically significant for volunteer safety or interfere with study end point.

The individual data for the urinalysis are detailed in Appendix 2. Minor and clinically non significant abnormalities have been observed. The only exception was Vol. No. 1, who had 25 erythrocytes and 500 leucocytes per µL, 0.3 g/L of protein and positive nitrites in the post-study examination. A diagnosis of urine infection was made and she was treated with trimethoprim 200 mg b.i.d. for one week. A repeat urine examination at the third day of treatment was normal.

Overall, the deviations from the reference ranges observed were considered not clinically significant and not related to the study drugs.

Protocol deviations are summarised in section 12.
8. FUSIDIC ACID ASSAY

The assay of fusidic acid in plasma was performed at the [REDACTED], ITALY) by the [REDACTED].

The determination was performed according to a published validated HPLC method with ultraviolet detection supplied by the Sponsor. The analytical method was validated [REDACTED] before the start of the analyses of the unknown samples (see Report [REDACTED]).

The performance of the analytical method during the before-study validation is summarized below:

- Range of nominal concentrations (serum calibration curves): 2 - 100 µg/ml

- Limit of Quantitation (LOQ): 2 µg/ml
- Accuracy at LOQ: 90.3 - 102.1 %
- Precision at LOQ: 2.4 - 8.9 %

- Overall accuracy at concentrations higher than LOQ: 97.6 - 101.2 %
- Overall precision at concentrations higher than LOQ: 3.6 - 6.8 %

- No degradation of sampling in autosampler vials (solubilized in injection solvent) after 24 h at room temperature.

- It was concluded that the HPLC method for the determination of fusidic acid was usable for proving accuracy, precision and stability for the present study.

The performance of the analytical method was also checked and evaluated during the period of analyses of unknown samples (within-study validation).

The detailed descriptions of the analytical method used and of the procedures and the results of the within-study validation are reported in Appendix 3.
9. DATA ANALYSIS

9.1 Pharmacokinetic Parameters

9.1.1 Non compartmental analysis

A non compartmental pharmacokinetic data analysis of the individual serum concentrations of FUSIDIC ACID (as μg/ml) vs time (as hours) after administration of formulations A and B was performed using Pharm-NCA program version 1.31e (SIMED, Paris-Creteil, France).

The following pharmacokinetic parameters were obtained directly by observation of the individual concentration vs time profiles:

- **Cmax**: The highest concentration value found in serum.
- **tmax**: The time from administration at which the Cmax value is found.
- **tz**: The last sampling time at which a quantifiable concentration is found.
- **Cz**: The concentration value obtained at sampling time tz.

The following pharmacokinetic parameters were obtained by the Pharm-NCA program from the individual concentration vs time profiles:

- **AUCz**: The area under the serum concentration vs time curve up to sampling time tz, calculated by the linear-linear trapezoidal rule.
- **tlin**: The first point considered for the determination of the elimination half-life.
- **Kel**: The elimination rate constant, calculated by the slope of the linear regression curve obtained by fitting the natural logarithms of the terminal concentration values vs time (from tlin to tz).
- **t½**: The elimination half-life, calculated by the equation:

\[ t \frac{1}{2} = \frac{\ln 2}{Kel} \]

- **AUC**: The area under the serum concentration vs time curve, calculated by the following equation:

\[ AUC = AUCz + Cz/Kel \]
The following pharmacokinetic parameters were obtained by calculation, from the above described parameters, using Microsoft Excel® 4.00 spreadsheet:

- **%AUC<sub>ext</sub>:** The percentage of extrapolated AUC (i.e. obtained by extrapolation), calculated by the following equation:
  \[
  \%AUC_{\text{ext}} = \left[ \frac{(AUC - AUC_z)}{AUC} \right] \cdot 100
  \]

- **F(test/ref):** The index of relative bioavailability of the test treatment vs the reference treatment, calculated by the following equation:
  \[
  F = \frac{AUC \text{ (test)} \times \text{Dose (ref)}}{AUC \text{ (ref)} \times \text{Dose (test)}}
  \]

The printouts of the Pharm-NCA program are enclosed in Appendix 5. AUCz, AUC and Kel are reported as AUC (0-last), AUC (0-inf) and Ke respectively by Pharm-NCA.

Formulations A and B are reported as administrations nos 1 and 2 respectively by Pharm-NCA.

### 9.2 Statistical Analysis (21-25)

#### 9.2.1 Descriptive statistics of the serum concentrations

The mean, standard deviation, coefficient of variation and range (min and max) values of the serum concentrations at each sampling time after administration of each formulation were calculated using Microsoft Excel® 4.00 spreadsheet.

Concentrations Below the Quantitation Limit (BQL) were considered as 0 for descriptive statistics.

- **Concentrations Below the Quantitation Limit**

  Mean concentration values Below the Quantitation Limit (BQL) were reported as BQL in tables and were not reported in graphs. The corresponding standard deviations and coefficients of variations were not reported in tables (only range values are reported).

#### 9.2.2 Descriptive statistics of the pharmacokinetic parameters

The mean, standard deviation, coefficient of variation and range (min and max) values of each pharmacokinetic parameter obtained for each formulation (median and range values for tmax and tz) were calculated using Microsoft Excel® 4.00 spreadsheet.

#### 9.2.3 Statistical comparisons of the pharmacokinetic parameters

The following statistical comparisons of the significant pharmacokinetic parameters obtained for test vs reference treatment were made using Pharm-STAT program version 1.3 (SIMED, Paris-Creteil, France):
- The values of AUCz calculated for FUSIDIC ACID after formulation A vs B were compared by the analysis of variance (Anova) test (logarithmically transformed data). The value of residual variance, calculated by the Anova test, was used to compare the values of AUCz according to the 90% confidence interval test (test vs reference formulation).

The acceptance criterium for bioequivalence is the following: the 90% confidence interval of the ratio of the mean test to reference value must be included within the range 0.80-1.25.

- The values of AUC calculated for FUSIDIC ACID after formulation A vs B were compared by the analysis of variance (Anova) test (logarithmically transformed data). The value of residual variance, calculated by the Anova test, was used to compare the values of AUC according to the 90% confidence interval test (test vs reference formulation).

The acceptance criterium for bioequivalence is the following: the 90% confidence interval of the ratio of the mean test to reference value must be included within the range 0.80-1.25.

- The values of Cmax obtained for FUSIDIC ACID after formulation A vs B were compared by the analysis of variance (Anova) test (logarithmically transformed data). The value of residual variance, calculated by the Anova test, was used to compare the values of Cmax according to the 90% confidence interval test (test vs reference formulation).

The acceptance criterium for bioequivalence is the following: the 90% confidence interval of the ratio of the mean test to reference value must be included within the range 0.70-1.43.

- The values of tmax obtained for FUSIDIC ACID after formulation A vs B were compared by the non parametric Wilcoxon matched-pairs signed-rank test (at the level of significance p=0.05).

Cmax, AUCz and AUC measured after reference formulation B were corrected for the different dose administered (500 mg of Sodium fusidate, corresponding to 480 mg of Fusidic acid).

The printouts of Pharm-STAT program are enclosed in Appendix 5.
10. PHARMACOKINETIC RESULTS

The individual results of serum fusidic acid concentration are reported in Appendix 3.

The individual results of pharmacokinetic parameters are reported in Appendix 4.

Statistical calculations and computer printouts are enclosed in Appendix 5.

Figure 1 represents the mean ± s.e.m. fusidic acid serum concentrations determined for both formulations at each time point.

After oral single dose administration of 2 dry granulated, film coated tablets containing 250 mg each of sodium fusidate to fasting subjects (formulation B, reference), fusidic acid was rapidly absorbed and peaked at 2.5 h, (median value, range: 1 - 6 h), the Cmax being (mean ± s.d., range) 24.4 ± 9.8 (11.4-50) µg/ml .

After this time, concentrations declined with an apparent terminal half-life (mean ± s.d., range) of 11.9 ± 3.0 (6.4-18.6) h.

Quantifiable serum concentrations were still found at 36 h, the last sampling time, in 13 of the 18 subjects, being quantifiable up to 24 h only in the other 5 volunteers.

The Cz (mean ± s.d., range) was 2.9 ± 0.7 (2.1-4.5) µg/ml.

The value of area under the serum concentration vs time curve calculated up to time tz by the trapezoidal rule, AUCz (mean ± s.d., range) was 278.0 ± 82.6 (149.9-461.4) h·µg/ml.
The value of area under the serum concentration vs time extrapolated to infinity (mean ± s.d., range) was 329.4 ± 87.6 (192.1-524.7) h·µg/ml, the percent of AUC extrapolated being 16.2 ± 6.5%.

After oral single dose administration of 10 ml of suspension containing 50 mg/ml of fusidic acid to fasting subjects (formulation A, test), fusidic acid was rapidly absorbed and peaked at 4 h, (median value, range: 1.5 - 4 h), the Cmax (mean ± s.d., range) of 8.3 ± 2.8 (4-13) µg/ml, i.e. 3 times lower than after the reference formulation.

After this time, concentrations declined with an apparent terminal half-life (mean ± s.d., range) of 17.6 ± 12.0 (5-58.9) h, a value similar to that observed for the reference formulation. Quantifiable serum concentrations were found up to 12 h in 6 subjects, up to 24 h in 5 subjects and up to 36 h, the last sampling time, in the remaining 7 volunteers.

The Cz (mean ± s.d., range) was 2.5 ± 0.4 (2.1-3.3) µg/ml.

The value of area under the serum concentration vs time curve calculated up to time tz by the trapezoidal rule, AUCz (mean ± s.d., range) was 111.0 ± 56.5 (34.8-190.7) h·µg/ml.

The value of area under the serum concentration vs time extrapolated to infinity (mean ± s.d., range) was 174.4 ± 82.7 (77.9-368.8) h·µg/ml.

Both AUCz and AUC were about 2 - 3 times lower than the corresponding values observed after the reference formulation.

Moreover, due to the lower concentrations found, the percent of AUC (mean ± s.d.) extrapolated was higher, being 37.1 ± 15.1%.

The value of relative bioavailability (mean ± s.d., range) of test formulation A vs reference formulation B (F), was 0.56 ± 0.24 (0.23-1.1).
10.1 Statistical Comparison

The statistical comparison of the logarithmically transformed values of Cmax obtained after the 2 formulations (A vs B), corrected for the different administered dose, showed a 90% confidence interval of the ratio mean Cmax-test / mean Cmax-ref. = 0.28-0.40 vs the 0.70-1.43 threshold interval, being not included in the interval of acceptance for bioequivalence.

The statistical comparison between tmax of formulation A vs B, performed by the non parametric Wilcoxon matched-pairs signed-rank test, did not show any statistically significant difference between the two formulations (p > 0.05).

The statistical comparisons of the logarithmically transformed values of AUCz and AUC, corrected for the different administered dose, showed 90% confidence intervals of the ratio mean AUCz-test / mean AUCz-ref. and mean AUC-test / mean AUC-ref. = 0.28-0.42 and 0.40-0.56 respectively, both not included within the 0.80-1.25 acceptance interval.

Table 8 summarizes the mean ± S.D. values of Cmax, AUCz, AUC and the median and range value of tmax obtained for each formulation and the results of the statistical comparisons (test vs reference formulations) along with the statistical tests used:

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter (Fusidic acid)</th>
<th>A (test)</th>
<th>B (reference)</th>
<th>Significance</th>
<th>Test used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/ml) (µg/ml)</td>
<td>8.3 ± 2.8 (4-13)</td>
<td>24.4 ± 9.8 (11.4-30)</td>
<td>N.S.</td>
<td>90% CI. After log transformation</td>
</tr>
<tr>
<td>tmax (h) (h)</td>
<td>4 (1.5 - 4)</td>
<td>2.5 (1-6)</td>
<td>N.S.</td>
<td>Wilcoxon matched-pairs signed-rank</td>
</tr>
<tr>
<td>AUCz (h · µg/ml)</td>
<td>111.0 ± 56.5 (34.8-190.7)</td>
<td>278.0 ± 82.6 (149.9-461.4)</td>
<td>N.S.</td>
<td>90% CI. After log transformation</td>
</tr>
<tr>
<td>AUC (h · µg/ml)</td>
<td>174.4 ± 82.7 (77.9-368.8)</td>
<td>329.4 ± 87.6 (192.1-524.7)</td>
<td>N.S.</td>
<td>90% CI. After log transformation</td>
</tr>
</tbody>
</table>

NS : not significant  CI : confidence interval
11. CONCLUSIONS

The clinical phase of the study ran well and was incident free. The 18 healthy volunteers enrolled, concluded the study and no serious, severe or unexpected A.E. occurred. No drug-related, clinically significant modifications of the laboratory results were observed.

With regard to the pharmacokinetic results following single doses of 500 mg of the 2 formulations of fusidic acid. Each formulation was rapidly absorbed and peaked at 4 h for fusidic acid suspension (50mg/ml) (Formulation A), vs 2.5 h for sodium fusidate tablet (Formulation B), this was considered not statistically different. The corresponding Cmax (mean ± s.d.) values were 8.3 ± 2.8 µg/ml (A) vs 24.4 ± 9.8 µg/ml (B), being statistically different (90% confidence interval of the ratio mean Cmax-test / mean Cmax-ref = 0.28-0.40 vs the 0.70-1.43 acceptance interval for bioequivalence studies).

The mean AUCz (mean ± s.d.) values were 111.0 ± 56.5 h*µg/ml (A) vs 278.0 ± 82.6 h*µg/ml (B), being statistically different (90% confidence interval of the ratio mean AUCz-test / mean AUCz-ref = 0.28-0.42 vs the 0.80-1.25 acceptance interval for bioequivalence studies).

The terminal half-lives (mean ± s.d.) were 17.6 ± 12.0 h (A) vs 11.9 ± 3.0 h (B).

The AUCs (mean ± s.d.) were 174.4 ± 82.7 h*µg/ml (A) vs 329.4 ± 87.6 h*µg/ml (B), being statistically different (90% confidence interval of the ratio mean AUC-test / mean AUC-ref = 0.40-0.56 vs the 0.80-1.25 acceptance interval for bioequivalence studies).

The mean ( ± s.d.) of relative bioavailability of the test formulation (A) vs the reference formulation (B) was 0.56 ± 0.24.

Therefore, by considering the pharmacokinetic parameters which are requested to be compared for bioequivalence evaluation by the Regulatory Authorities (AUC, Cmax and tmax), is is possible to conclude that the test formulation (10 ml of the 50 mg/ml fusidic acid suspension) cannot be considered to have a comparable bioavailability to the reference formulation (2 x 250 mg sodium fusidate dry granulated, film coated tablets), based on the results of the present study.
12. PROTOCOL DEVIATIONS AND SPECIFICATIONS

Volunteer No. I and Volunteer No. I had their post-study examinations 17 days and 20 days, respectively, after the last blood sample for pharmacokinetics was drawn. The maximum lapse allowed by the Protocol was 10 days. However, this deviation is unlikely to have hindered the volunteers' safety or to have had any influence in the study results.

Volunteer No. I received Loperamide tablets for the treatment of moderate diarrhoea, promptly recovered between period 1 and period 2 of the study. This treatment did not affect the study results.

Volunteer No. I received Paracetamol tablets for the treatment of a headache, between period 1 and period 2 of the study. This treatment did not affect the study results.
13. REFERENCES


14. LIST OF APPENDICES

Appendix 1: Local Ethics Research Committee Approval

Appendix 2: Individual Laboratory Results

Appendix 3: Details of the Analytical Method

Appendix 4: Primary Pharmacokinetic and Statistical Calculations

Appendix 5: Printouts of Pharm-STAT program.