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| **Name of Sponsor/Company:**<br>Mundipharma Research Limited | **Individual Study Table Referring to Part of the Dossier**<br><br>**Volume**<br>**Page** | **(For National Authority Use only)** |
| **Name of Finished Product:**<br>Forodesine sterile solution, 10 mg/mL | | |
| **Name of Active Ingredient:**<br>Forodesine hydrochloride | | |
| **Study Centres:**<br>21 sites in Europe (1 site in Austria, 2 sites in Czech Republic, 5 sites in France, 5 sites in Germany, 2 sites in Italy, 1 site in The Netherlands & 5 sites in the United Kingdom) | | |
| **Publication (Reference):**<br>Not yet published | | |
| **Study Period:**<br>First patient screened: 6 May 2009<br>First patient enrolled: 7 May 2009<br>Last patient completed study treatment: 14 September 2010 | **Phase of Development:**<br>Phase I/II | |

**Objectives:**

Primary:

1. To evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) parameters of the proposed intravenous and oral forodesine doses in children with relapsed or refractory T-cell or B-cell precursor (BCP) acute lymphoblastic leukaemia (T-ALL or BCP-ALL) or T-cell Non-Hodgkin's Lymphoma (T-NHL)
2. To attempt to assess the oral bioavailability of forodesine and the level of accumulation after repeated oral and intravenous dosing
3. To attempt to assess whether twice daily dosing alters the oral bioavailability of forodesine compared with once daily dosing

Secondary:

1. To evaluate the safety of six different dose schedules of forodesine in paediatric subjects
2. To collect preliminary efficacy data on forodesine in children with relapsed or refractory haematological malignancies at six different dose schedules
3. To collect preliminary data on the penetration and efficacy of forodesine in the cerebrospinal fluid (CSF).

**Methodology:**

A multi-centre, multi-national, open-label study with four distinct phases: a 7 day Pre-Treatment Phase, a 37 day Treatment Phase, an Extension Phase of a maximum of 6 months duration, and a 30 day Observation Phase.

**Number of Subjects (Planned and Analysed):**

Planned: A total of 28 subjects were planned to be recruited into the Treatment Phase to achieve a minimum of 18 evaluable subjects. An evaluable subject is defined as a subject with any PK data available.

Analysed: A total of 11 subjects were screened and 10 subjects were enrolled and treated. The shortfall in the number of subjects enrolled and treated was as a result of a slower than expected recruitment rate and subsequent early termination of the study.

**Diagnosis and Main Criteria for Inclusion:**

- Males and females aged $\geq$ 2 years to $\leq$ 18 years and weighing $\geq$ 13 kg
- Unequivocal histological diagnosis of T-ALL, BCP-ALL or T-NHL (World Health Organisation [WHO] classification) at initial diagnosis
- T-ALL or T-NHL subjects:

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a. 1st relapse after HSCT, or
b. ≥ 2 relapses, or
c. newly diagnosed subjects who were refractory to 1 standard induction chemotherapy regimen, or
d. 1st relapse subjects who were refractory to 1 standard induction chemotherapy regimen

- BCP-ALL subjects:
  a. ≥ 2 relapses, or
  b. newly diagnosed subjects who were refractory to 2 standard induction chemotherapy regimens, or
  c. 1st relapse subjects who were refractory to 2 standard induction chemotherapy regimens
- KPS or LPS (as appropriate for subject's age) scores ≥ 60
- Anticipated life expectancy of at least 6 weeks
- Adequate kidney and liver function in the opinion of the Investigator and the Medical Monitor e.g. creatinine levels ≤ 2.0 times upper limit of normal, liver function tests (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT] ≤ 3 times upper limit of normal and total bilirubin ≤ 5 times upper limit of normal
- Female subjects of childbearing potential (i.e. have reached the age of menarche) had to have a negative urine pregnancy test recorded prior to the first dose of study medication, be non-lactating, and be willing to use adequate and highly effective method of contraception throughout the study and for one month after the last dose of study medication, if sexually active. A highly effective method of birth control is defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as sterilisation, implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs) (hormonal), sexual abstinence or vasectomised partner
- Sexually active male subjects had to be willing and able to use a barrier form of contraception (i.e. condoms) or sexual abstinence throughout the study and for one month after the last dose of study medication
- Signed informed consent form and assent if appropriate according to local laws and regulations prior to start of any study specific procedures

**Test Product, Dose and Mode of Administration, Batch Number:**

Forodesine sterile solution, 10 mg/mL contained in 10 mL clear glass vials or 5mL clear glass ampoules (as per Substantial Protocol Amendment No.1 of 04 Nov 2008 [Refer to Appendix 16.1.1]). Forodesine sterile solution, 10 mg/mL administered intravenously once a day (o.d.) to all subjects on Days 1-5 at either 40 mg/m$^2$ (Cohorts 1, 2 and 3) or 80 mg/m$^2$ (Cohorts 4, 5 and 6). After two days without treatment, subjects resumed treatment on Days 8-36 with the forodesine sterile solution, 10 mg/mL given orally at 4 dose regimens: 80 mg/m$^2$ o.d. (Cohort 1), 80 mg/m$^2$ every 12 hours (q12h) (Cohorts 2 and 4), 160 mg/m$^2$ o.d. (Cohorts 3 and 5) and 160 mg/m$^2$ q12h (Cohort 6). Study drug administration via a naso-gastric tube or gastrostomy tube was permitted. Oral forodesine was to be taken at approximately the same time each day, preferably in the morning for those subjects on a daily dosing regimen.

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| | Days 1-5 (IV) | Days 8-36 (Oral) |
|---|---|---|
| **Cohort 1** | 40 mg/m$^2$ o.d. | 80 mg/m$^2$ o.d. |
| **Cohort 2** | 40 mg/m$^2$ o.d. | 80 mg/m$^2$ q12h |
| **Cohort 3** | 40 mg/m$^2$ o.d. | 160 mg/m$^2$ o.d. |
| **Cohort 4** | 80 mg/m$^2$ o.d. | 80 mg/m$^2$ q12h |
| **Cohort 5** | 80 mg/m$^2$ o.d. | 160 mg/m$^2$ o.d. |
| **Cohort 6** | 80 mg/m$^2$ o.d. | 160 mg/m$^2$ q12h |

Subjects who responded to therapy had the option to continue oral forodesine treatment after Day 37 until disease progression, HSCT, intolerable toxicity or removal from study for any other cause. The dose a subject received in the Extension Phase was to be the same as the oral dose they received on Days 8-36.

Batch numbers:

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| Ampoules (10 mg/mL) | PN3274 & PN3548 |
| Vials (10 mg/mL) | PN3378 |

**Duration of Treatment:**

Duration of the Treatment Phase was scheduled for 37 days. Subjects who showed an objective response (Complete Response [CR], Complete Response with incomplete blood count recovery [CRi], Partial Response [PR], or Stable Disease [SD]) to therapy or subjects who showed clinical benefit (at the Investigator's discretion) at the end of the Treatment Phase had the option to continue oral forodesine treatment in an Extension Phase until disease progression, HSCT, intolerable toxicity, or removal from study for any other cause. The Extension Phase was planned for up to 6 months duration

**Reference Therapy, Dose and Mode of Administration, Batch Number:**

No reference treatment.

**Criteria for Evaluation:**

Primary efficacy variable

The (exploratory) primary efficacy endpoint was treatment response assessed as CR, CRi, PR, SD or Progressive Disease. Treatment response criteria were defined in the protocol as follows:

Treatment response criteria for subjects with Acute Lymphoblastic Leukaemia (ALL):

- A CR is defined as:
  - An M1 bone marrow (≤ 5% blasts)
  - Recovery of peripheral counts (platelets ≥ 100 × $10^9$/L and absolute neutrophil count [ANC] ≥ 1000 × $10^6$/L)
  - No evidence of leukaemia elsewhere
- A CR with incomplete blood count recovery
  - A CR with incomplete blood count recovery (ANC < 1000 x $10^6$/L and/or platelets < 100 x $10^9$/L independent of platelet transfusion) is defined as a CRi
- A PR is defined as:

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- Complete disappearance of circulating blasts
- An M2 bone marrow (>5% to ≤ 25% blasts)

• SD is defined as:
- Bone marrow not meeting criteria for a CR/PR or progressive disease

• Progressive Disease is defined as:
- Increase in blast cells in marrow, peripheral blood, or extramedullary site

• Relapse is defined as:
- The reappearance of unequivocal leukaemia blast cells in the blood, the bone marrow (>5%), the CNS, or in any other extramedullary site after a CR or CRi
- Progression to >25% leukaemia blasts cells in the bone marrow after a PR

Treatment Response criteria for subjects with Non-Hodgkin's Lymphoma (NHL) are defined as follows:

• A CR is defined as:
- Disappearance of all evidence of disease
- Disappearance of all signs, symptoms and biochemical changes related to the tumour and no new lesions

• A PR is defined as:
- ≥50% decrease in sum of the products of the perpendicular diameters (SPD) of up to 6 largest dominant masses
- No increase in size of other nodes
- No increase in size of liver or spleen

• Progressive disease is defined as:
- ≥50% increase in SPD of previous lesions
- Any new lesions

• SD is defined as:
- Failure to attain CR/PR/PD

For the summaries, three different dichotomous responses are defined:

• Complete response is a treatment response of CR or CRi
• Complete/partial response is a treatment response of CR, CRi or PR
• Response (no progression) is a treatment response of CR, CRi, PR or SD

The response variable with 4 levels (Progressive disease, SD, PR, CR/CRi) was also presented.

Efficacy was also assessed by:

• Peripheral blood flow cytometry
• Bone marrow morphology and cytometry
• Radiological evaluation
• Chest X-ray

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Safety variables

Safety was evaluated by the following parameters:

- Adverse events (AEs)
- Laboratory parameters including CD4/CD8 lymphocyte ratio
- Vital signs
- Physical examination
- Lansky/Karnofsky performance status (LPS/KPS)
- Electrocardiogram (ECG)
- Blood serology (virology)

Pharmacokinetic variables

The following single dose parameters were calculated at Day 1 and Day 8:

- Area under the plasma concentration-time curve calculated from the time of dosing to the last measurable concentration ($AUC_t$),
- Area under the plasma concentration-time curve calculated from the time of dosing to infinity ($AUC_{inf}$),
- Maximum observed plasma concentration ($C_{max}$),
- Time from dosing to the maximum observed plasma concentration ($t_{max}$),
- Terminal phase rate constant (LambdaZ),
- Terminal phase half life ($t_{1/2Z}$)

And the following steady state parameters were calculated at Day 5 and Day 36:

- Area under the plasma concentration-time curve calculated over one dosing interval at steady state ($AUC_{tau}$),
- Maximum observed plasma concentration over one dosing interval at steady state ($C_{max}ss$),
- Time from dosing to the maximum observed plasma concentration over one dosing interval at steady state ($t_{max}ss$),
- Minimum observed plasma concentration over one dosing interval at steady state ($C_{min}ss$),
- Fluctuation Index (FI),
- Accumulation ratio (RA)

Pharmacodynamic variables

Plasma levels of dGuo, PNP and dGTP were assessed.

Cerebrospinal Fluid Cytology

CSF samples were collected for cytology, as well as analysis of forodesine and dGuo concentration levels.

Subjects' ratings of palatability and taste were collected.

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**Statistical Methods:**

Sample Size Considerations

The sample size was not based on statistical power calculations. Six subjects each were to be enrolled into Cohorts 1 and 6 and four subjects each were to be enrolled into Cohorts 2, 3, 4 and 5 for a total of 28 subjects to achieve a minimum of 18 evaluable subjects.

Statistical Methods

The following populations were defined:

- Enrolled Population: All subjects who provided written consent to take part in the study.
- Safety Population: All subjects who received any study drug. The Safety Population was used to assess safety.
- PK Full Analysis Population: All subjects who received any study drug and who had any PK measurements. (Since the PK measurements were taken on four separate occasions within each subject a subject could potentially drop in or out of the populations over time.)
- PD Full Analysis Population: All subjects who received any study drug and who had any PD measurements. (Since the PD measurements were taken on four separate occasions within each subject a subject could potentially drop in or out of the populations over time.)
- PK/PD Analysis Population: The PK/PD Analysis Population is the intersection of the PK and PD Full Analysis Populations. It was used to analyse the correlation between PK and PD measures.
- Efficacy Evaluable Population: All subjects whose treatment response was observed, either at the end of the core Treatment Phase or at withdrawal due to disease progression and had received ≥75% of scheduled doses in the intravenous dosing period and ≥75% of scheduled doses in the oral dosing period prior to assessment of treatment response. Days following withdrawal were not included as 'scheduled' for this definition.

In summary and analysis tables of continuous variables, standard descriptive statistics (N, mean, standard deviation (StDev), median, minimum and maximum) are presented. The minimum and maximum statistics are presented in summary tables to the same number of decimal places as the original data. The mean, median and StDev are presented to one more decimal place than the original data.

All statistical analysis was performed using SAS® v9.2 or higher.

Results are presented for the core phase. A single patient, 40301, entered the extension phase but withdrew early. Demographics and disposition are presented together with the main study data. No study specific assessments were performed however for the extension phase (due to the early withdrawal) and thus no such results are presented.

**Summary – Conclusions:**

Due to small sample sizes (N=1 or 2 in each treatment Cohort) statistical comparisons were not possible and results are inconclusive. The (exploratory) primary efficacy endpoint was treatment response and was assessed as CR, CRi, PR, SD or Progressive Disease. At Day 15, a total of 5/9 subjects had stable disease; 2 in each of Cohorts 1 and 6, and 1 in Cohort 2. Both subjects in Cohort 3 were withdrawn on Day 17 and Day 22 respectively due to progressive disease. The remaining 2 subjects withdrew / discontinued prior to Day 15: the subject in Cohort 4 died on Day 11 (SAE of sudden death) and the subject in Cohort 5 withdrew on Day 12. The discontinuation (Day 37/discontinuation) assessment for these 2 subjects was PD. At Day 37/discontinuation, 8

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subjects had progressed and 1 subject in Cohort 1 continued to show stable disease. Safety assessments suggest forodesine dosing was well tolerated and the serious grade 4 or 5 adverse events can be attributed to progression of the malignant disease in this patient population.

Concerning pharmacokinetic data, due to the low number of observations in this study no firm conclusions can be drawn. The conclusions are based on the available data, and are not intended to imply any statistical significance. Based on the limited data available, the IV treatments of 40 mg/m$^2$ and 80 mg/m$^2$ were roughly dose proportional following a single dose and at steady-state. However, this is not reflected in the concentrations following oral administration.

The absolute oral bioavailability of forodesine, based on AUCt values, was similar for both the once and twice daily administrations, at the 80 mg/m$^2$ and 160 mg/m$^2$ dose levels. When comparing the twice daily 80 mg/m$^2$ administration to the once daily 160 mg/m$^2$, based on AUCINF values and limited data, absolute oral bioavailability was slightly greater from the twice daily 80 mg/m$^2$ regimen. Based on the available data, accumulation appears to be minimal for both IV and oral administration.

**Date of the Report:**
09 June 2011