Analysis of safety and pharmacokinetic data derived from a single ascending dose Phase 1 study involving a promising non-cytotoxic anti-cancer agent Sulforafale®

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Introduction

It is widely documented in the literature that consumption of cruciferous vegetables (family Cruciferae) containing specific compounds is capable of suppressing the initial stages of carcinogenesis or the progression of neoplastic cells to cancer1. Sulforaphane, a derivative of glucoraphanin, was found to be one of such compounds. Several epidemiological studies have demonstrated that intake of cruciferous vegetables containing sulforaphane might reduce the risk of prostate cancer2. It has been established in literature that sulforaphane inhibits histone deacetylase, which is up-regulated in certain types of cancer including prostate cancer3. In human beings, it has been documented that decreases in histone acetylation is associated with increased cancer malignancy and risk of prostate cancer recurrence4.

Although there are many clinical trials in progress with sulforaphane derived from botanical sources5, to date there is no clinical experience with Sulforafale®. In this double-blind, placebo-controlled single ascending dose Phase 1 study, 29 healthy male subjects received single oral doses (50 mg, 100 mg, 300 mg, 500 mg and 700 mg) of Sulforafale® or placebo to assess its safety and PK in healthy male volunteers.

Methods

This was a Phase 1, randomised, double-blind, placebo-controlled study with single ascending doses of Sulforafale® administered to healthy male subjects between 18 to 45 years of age on a normal diet and free from the use of any of the Cohorts in the initial 4 weeks. Three on active [A]; two on placebo [P]; participated in Cohort 1 (50 mg dose level), four healthy subjects (two on A; one on P) participated in Cohort 2 and 3 (100 mg and 300 mg dose level) and eight healthy subjects (six on A; two on P) participated in Cohort 4 and 5 (500 mg and 700 mg dose level) and received Sulforafale® or placebo.

Each healthy male subject received verbal (from a Research Physician) and written information prior to signing of the Informed Consent Form. Subjects were screened within 21 days prior to first dosing and there was one in-house period to the Clinical Pharmacology Unit (CPU). Subjects were admitted to the CPU on Day -1 and remained in-house until discharge on Day 3 with a follow-up visit performed 7-14 days after discharge. Administration of the study drug was on Day 1 with safety monitoring and blood samples for PK evaluation.

Statistical Methods

Adverse events (AEs) were tabulated according to Medical Dictionary for Regulatory Activities (version 15.1), primary system organ class and preferred term. The results of AE reporting, vital signs, 12-lead ECG and standard clinical laboratory safety tests were listed by subject and analysed by descriptive statistics as appropriate.

PK data was listed for each subject, along with univariate statistics including arithmetic and geometric means, standard deviation, range, sample size, maximum, minimum and median with and inter-subject coefficients of variation (CV). Dose proportionality was analysed with a linear regression model using the logarithm of the PK parameters as the dependent variable. The linearity of the dose as the independent variable.

Results

The descriptive statistics for demography parameters for all enrolled subjects is presented in Table A (Table 1).

PK Analysis

Plasma Concentration-Time Profiles

One of the objectives of this study was to study the plasma PK of sulforaphane from Sulforafale® in healthy male volunteers. The mean tmax of sulforaphane was found to occur between 0.63 – 1.0 hours, and the plasma mean t1/2 values ranged from 2.19 hours to 3.24 hours. The distribution phases to elimination phases appeared to be similar. For some dose levels (50 mg, 150 mg, 300 mg and 500 mg) the full complement of results for every parameter could not be achieved because plasma concentrations of sulforaphane were below the lower limit of quantification (LLOQ) which meant that there was insufficient data for the estimation of dose PK parameters.

Pharmacokinetic Parameters

The summary for the plasma PK parameters, Cmax, tmax, AUC0-T, AUC0-T, Kp and t1/2 are presented in Table B (Table 2) for sulforaphane.

Safety Evaluation

Adverse Events

There were no serious adverse events (SAEs) reported during the study and no subject was withdrawn from the study due to adverse events. All of the AEs reported were of moderate intensity. No treatment emergent AEs were reported for the 100 mg and 300 mg Sulforafale® treatment groups. For the placebo group, two treatment emergent AEs were reported. No subjects were reported to have had values outside the normal range in vital signs and 12-lead ECGs. However, the isolated departures from the normal ranges in vital signs and 12-lead ECG recordings were in 2/7 by the placebo subject as not clinically significant and not related to the studied drug.

Discussion

The safety findings from the study demonstrated that there were no SAEs and no subject withdrew due to AEs or any other reasons. In addition, the findings showed that oral doses up to 300 mg Sulforafale® were safe and well tolerated. However, oral doses of 500 mg and 700 mg Sulforafale® were not as tolerated as evidenced by the review of AEs. The majority of reported AEs were of mild intensity and four (vomiting and abdominal pain) were of moderate intensity. Notably, the study has shown that oral doses of 500 mg and 700 mg Sulforafale® were associated with an increasing frequency of vomiting in subjects. The PK data demonstrated that the mean plasma concentrations of sulforaphane following administration of single doses of Sulforafale® (50 mg, 100 mg, 300 mg, 500 mg and 700 mg) in healthy subjects appeared to be dose linear. Cmax and AUC values increased in proportion to the dose given, however the variability in the PK data particularly at the 100 mg and 300 mg dose levels precludes definitive conclusions regarding dose linearity from being made. In addition, dose proportionality was not established for Cmax, AUC0-T and AUC0-T.

Table: Summary of Demographic Data

<table>
<thead>
<tr>
<th>Parameter/Cohort</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
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<tbody>
<tr>
<td>Cohort 1</td>
<td>22</td>
<td>75</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>23</td>
<td>78</td>
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<tr>
<td>Cohort 3</td>
<td>24</td>
<td>80</td>
</tr>
<tr>
<td>Cohort 4</td>
<td>25</td>
<td>82</td>
</tr>
<tr>
<td>Cohort 5</td>
<td>26</td>
<td>84</td>
</tr>
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</table>

Table: Summary of Plasma PK parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>Cohort 4</th>
<th>Cohort 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/ml)</td>
<td>2.5</td>
<td>2.8</td>
<td>3.0</td>
<td>3.2</td>
<td>3.4</td>
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<tr>
<td>tmax (hr)</td>
<td>1.0</td>
<td>0.9</td>
<td>1.0</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>AUC0-T (ng hr/ml)</td>
<td>60</td>
<td>65</td>
<td>70</td>
<td>75</td>
<td>80</td>
</tr>
<tr>
<td>Kp (hr^-1)</td>
<td>0.5</td>
<td>0.6</td>
<td>0.7</td>
<td>0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>t1/2 (hr)</td>
<td>2.5</td>
<td>2.7</td>
<td>2.9</td>
<td>3.1</td>
<td>3.3</td>
</tr>
</tbody>
</table>

References


Clinical Laboratory Safety Parameters

Overall, there were no significant changes in the biochemistry, haematology, and urinalysis parameters. Some subjects were found to have values that were slightly elevated but none were considered to be clinically significant.

Vital Signs and 12-Lead ECGs

Some subjects were noted to have had values outside the normal range in vital signs and 12-lead ECGs. However, the isolated departures from the normal ranges in vital signs and 12-lead ECG recordings were in 2/7 by the placebo subject as not clinically significant and not related to the studied drug.