Clinical Study Report Synopsis

LP0058-1005 - A Phase 1, Open-Label, Four-Way Crossover and Food-Effect Study of LEO 32731 in Healthy Subjects when Administered as an Immediate and Modified Release Formulation

LEO Pharma A/S
Clinical Development and Safety
Report Date 28-Oct-2015
EudraCT Number: 2013-004346-41
Clinical Study Report Synopsis Statements

Approval Statement, Sponsor

The following persons have approved this Clinical Study Report synopsis on behalf of LEO Pharma A/S using electronic signatures:

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<tr>
<td>Biostatistics</td>
<td></td>
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<tr>
<td>Medical Department</td>
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</table>

Approval Statement, Investigator

The Principal Investigator approves the Clinical Study Report synopsis by manually signing the Investigator Clinical Study Report Approval Form, which is a separate document adjoined to this Clinical Study Report Synopsis.

The following person has approved this Clinical Study Report synopsis:

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<tr>
<td>Principal Investigator</td>
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**SYNOPSIS**

<table>
<thead>
<tr>
<th>Trial Registration Number</th>
<th>EudraCT Number</th>
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<tbody>
<tr>
<td>NCT02126371</td>
<td>2013-004346-41</td>
</tr>
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</table>

**Title of Trial**
LP0058-1005 - A Phase 1, Open-Label, Four-Way Crossover and Food-Effect Study of LEO 32731 in Healthy Subjects when Administered as an Immediate and Modified Release Formulation

**Investigator**
This was a single centre trial. **[Redacted]** MBChB was the Principal Investigator.

**Trial Centre**
Covance Clinical Research Unit (CRU) Ltd., Springfield House, Hyde Street, Leeds, LS2 9LH, UK.

**Publications**
None at the time of the final clinical trial report.

<table>
<thead>
<tr>
<th>Trial Period</th>
<th>Development Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of first subject enrolment (informed consent signed): 15-May-2014</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Date of last subject completed: 28-Jan-2015</td>
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**Objectives**
- To determine the relative bioavailability of three modified release formulations compared to an immediate release (capsule) formulation.
- To determine the effect of food on the single oral dose pharmacokinetics (PK) of LEO 32731 in healthy male subjects, when administered as a modified release formulation.

**Methodology**
This was an open-label, randomised, relative bioavailability and food-effect study conducted in two parts.

**Part 1 (Relative Bioavailability)**
Part 1 comprised an open-label, randomised, four-way crossover design. LEO 32731 was administered to healthy male subjects in four treatment periods in the fasted state, with each subject receiving four single doses of 30 mg LEO 32731, as four different formulations; three modified release tablets (A, B and C) and one immediate release capsule. Subjects resided at the CRU from Day -1 to Day 3 (48 hours post-dose) in each treatment period, returning for a non-residential visit on Day 4 of each period.

**Part 2 (Effect of Food)**
Part 2 comprised an open-label, randomised, 2- and 3-period crossover design. The effect of food on three modified release tablets was investigated in four groups (Group B1 to Group B4), with subjects in Groups B1 and B4 participating in two treatment periods and subjects in Groups B2 and B3 participating in three treatment periods, as follows:
- Group B1: modified release tablet formulation A (high fat meal/fasted)
- Group B2: modified release tablet formulation B (high fat meal/standard meal/fasted)
- Group B3: modified release tablet formulation C (high fat meal/standard meal/fasted)
- Group B4: modified release tablet formulation A (high fat meal/standard meal)

Subjects resided at the CRU from Day -1 to Day 3 (48 hours post-dose) in each treatment period, returning for a non-residential visit on Day 4 of each period.

**Number of Subjects Planned and Analysed**
In Part 1, 16 subjects were planned and studied as a single group (Group A).
In Part 2, it was originally planned to study only 8 subjects in one group (Group B1). However, the results from Group B1 instigated the addition of 3 extra groups (Groups B2 to B4). It was planned to enrol a further 9 subjects each for Groups B2 and B3, and a further 8 subjects for Group B4. In Part 2, 8 subjects each were studied in Groups B1, B3, and B4, and 9 subjects were studied in Group B2.

**Diagnosis and Main Criteria for Inclusion**
Both parts of the study consisted of healthy males aged between 18 and 55 years, inclusive, with a body mass index between 18.0 and 30.0 kg/m², inclusive.

**Investigational Products, Doses and Modes of Administration, Batch Numbers**
Modified release tablet formulations differed in their rates of dissolution; 65% release within 4 hours for tablet A, 65% release within 8 hours for tablet B, and 65% release within 12 hours for tablet C.
In Part 1, subjects were administered four 30 mg oral doses of LEO 32731 in the fasted state, as either an immediate release capsule or as a modified release tablet.
In Part 2, subjects in Group B1 received two single 30 mg doses of LEO 32731 modified release tablet formulation A in the fasted state and following a high fat breakfast. Subjects in Groups B2 and B3 received three single 30 mg doses of modified release tablet formulations B and C, respectively, in the fasted state and following high fat and standard breakfasts. Subjects in Group B4 received two single 30 mg doses of LEO 32731 modified release tablet formulation A following high fat and standard breakfasts.

The batch numbers were W021841, W021842, and W021843 for modified release tablet formulations A, B, and C, respectively, and G042677 for the immediate release capsule.

### Duration of Treatment

In Parts 1 and 2, single oral doses were administered in each treatment period for each group. Subjects in Group A participated in four treatment periods, subjects in Groups B1 and B4 participated in two treatment periods, and subjects in Groups B2 and B3 participated in three treatment periods. There was a minimum of 7 days between each dose administration.

### Criteria for Evaluation

**Pharmacokinetics:**

Blood samples were collected for the analysis of plasma concentrations of LEO 32731 and its metabolites LEO 32728 and LEO 40815.

**Safety:**

Adverse events (AEs), vital signs (blood pressure [supine and standing], pulse rate, and oral body temperature), 12-lead electrocardiograms (ECGs), clinical laboratory evaluations, faecal occult blood (FOB) test, body weight assessment, and physical examination.

### Statistical Methods

The effects of formulation (Part 1) and food (Part 2) for selected PK parameters (area under the plasma concentration-time curve from time zero up to the last quantifiable concentration \([AUC_{0-t_{last}}]\), area under the plasma concentration-time curve from time zero to infinity \([AUC_{0-\infty}]\), and maximum observed plasma concentration \([C_{max}]\)) was assessed using a mixed model analysis of variance (ANOVA) for LEO 32731 and its metabolites, LEO 32728 and LEO 40815.

### Summary

**Trial Population**

In Part 1, 16 healthy subjects were enrolled and 15 subjects completed the study. One subject was withdrawn after the first treatment period due to a positive FOB test confirmed by a repeat assessment.

In Part 2, 33 healthy subjects were enrolled and 32 subjects completed the study. One subject withdrew their consent after experiencing a panic attack on Day 1 of Period 1.
Pharmacokinetic Results - Part 1

Effect of Formulation on the Pharmacokinetics of LEO 32731

The PK parameters of LEO 32731 following single oral doses of LEO 32731 (modified and immediate release formulations) in the fasted state are summarised in the following table:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LEO 32731 formulation</th>
<th>MR tablet A (N=15)</th>
<th>MR tablet B (N=15)</th>
<th>MR tablet C (N=15)</th>
<th>IR capsule (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀⁻𝑡last (ng h/mL)</td>
<td>274 (46.7)</td>
<td>216 (37.2)</td>
<td>178 (60.6)</td>
<td>420 (41.7)</td>
<td></td>
</tr>
<tr>
<td>AUC₀⁻∞ (ng h/mL)</td>
<td>304d (42.9)</td>
<td>277c (24.9)</td>
<td>246b (48.5)</td>
<td>426d (43.8)</td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>30.9 (54.6)</td>
<td>22.3 (42.7)</td>
<td>16.9 (53.8)</td>
<td>82.8 (33.3)</td>
<td></td>
</tr>
<tr>
<td>tmax (h)</td>
<td>4.00 (1.50, 6.00)</td>
<td>4.00 (1.50, 6.00)</td>
<td>4.00 (2.00, 6.00)</td>
<td>3.00 (1.50, 4.00)</td>
<td></td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>8.47d (37.6)</td>
<td>9.93c (40.4)</td>
<td>11.5c (41.0)</td>
<td>6.31d (75.1)</td>
<td></td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>98.6d (34.8)</td>
<td>108b (31.6)</td>
<td>125c (68.9)</td>
<td>70.5d (43.1)</td>
<td></td>
</tr>
<tr>
<td>Vz/F (L)</td>
<td>1200d (57.0)</td>
<td>1550c (54.0)</td>
<td>2080c (61.8)</td>
<td>642d (86.8)</td>
<td></td>
</tr>
</tbody>
</table>

Formulation A: 30 mg LEO 32731 modified release tablet (65% release within 4 hours)
Formulation B: 30 mg LEO 32731 modified release tablet (65% release within 8 hours)
Formulation C: 30 mg LEO 32731 modified release tablet (65% release within 12 hours)
IR capsule: 30 mg LEO 32731 immediate release capsule

Geometric mean (CV%) data are presented

Abbreviations: AUC₀⁻𝑡last = area under the plasma concentration-time curve from time zero up to the last quantifiable concentration; AUC₀⁻∞ = area under the plasma concentration-time curve from time zero to infinity; CL/F = apparent total plasma clearance; Cmax = maximum observed plasma concentration; CV = coefficient of variation; N = number of subjects studied; t½ = apparent plasma terminal elimination half-life; tmax = time of the maximum observed plasma concentration; Vz/F = apparent volume of distribution during the terminal phase

Systemic exposure to LEO 32731, as assessed by AUC₀⁻𝑡last, AUC₀⁻∞, and Cmax, was significantly less for all modified release tablet formulations compared to the immediate release capsule. As AUC₀⁻∞ could not be determined for all subjects, AUC₀⁻𝑡last, was considered as the more reliable measure of systemic exposure. Exposure to LEO 32731 decreased as the rate of dissolution decreased, with AUC₀⁻𝑡last being approximately 35%, 49%, and 58% lower for modified release tablet formulations A, B, and C, respectively, compared to the immediate release capsule. The largest difference was observed for Cmax, with values approximately 62%, 73%, and 80% lower for the modified release tablet formulations A, B, and C, respectively, compared to the immediate release capsule. Administration of LEO 32731 as modified release tablet formulations delayed the rate of absorption by approximately 1 hour compared to that of the immediate release capsule, with median tmax for all three modified release formulations occurring at 4.0 hours post-dose (range of 1.5 to 6.0 hours).

Effect of Formulation on the Pharmacokinetics of LEO 32728

The systemic exposure to metabolite LEO 32728, as assessed by AUC₀⁻𝑡last, was significantly higher for all modified release tablet formulations compared to the immediate release capsule. This increased exposure to LEO 32728 decreased as the rate of dissolution of the modified tablets decreased, with AUC₀⁻𝑡last being approximately 1.8-, 1.7- and 1.5-fold higher for modified release tablet formulations A, B and C, respectively, compared to the immediate release capsule. There was no statistically significant difference between the modified release tablets A and B and the immediate release capsule for Cmax, while Cmax was approximately 16% lower for modified release tablet formulation C compared to the IR capsule. A median tmax of 6.0 hours (range of 4.0 to 12.0 hours) was observed for the immediate release capsule and 6.0 to 16.0 hours (range of 6.0 to 36.0 hours) for the modified release tablet formulations, with median tmax increasing as the rate of dissolution of the modified tablets decreased.
The metabolite ratio was similar for the three modified release tablets (ranging from 0.050 to 0.066), an increase from that observed following dosing with the immediate release capsule (0.019).

**Effect of formulation on the Pharmacokinetics of LEO 40815**

In common with the parent compound, AUC\(_{0-t}\) and C\(_{\text{max}}\) for LEO 40815 were significantly lower for all of the modified release tablet formulations compared to the immediate release capsule. Exposure to LEO 40815 also decreased as the rate of dissolution of the modified tablet decreased, with AUC\(_{0-t}\) being approximately 37%, 51%, and 60% lower, and C\(_{\text{max}}\) being approximately 57%, 71%, and 77% lower for the modified release tablet formulations A, B, and C, respectively, compared to the immediate release capsule. The time of maximum plasma concentrations of LEO 40815 was comparable for all formulations at approximately 4 hours post-dose.

The metabolic ratio for all three modified release tablets (approximately 0.35) was similar to that of the immediate release capsule (0.37).

**Pharmacokinetic Results - Part 2**

**Effect of Food on the Pharmacokinetics of LEO 32731**

The PK parameters of LEO 32731 following single oral doses of LEO 32731 in the fasted state, following a standard meal and following a high fat meal for modified release tablet formulation A are summarised in the following table:

<table>
<thead>
<tr>
<th>LEO 32731 formulation/dietary state</th>
<th>MR tablet A (fasted) (N=7)</th>
<th>MR tablet A (high fat meal, Group B1) (N=7)</th>
<th>MR tablet A (high fat meal, Group B4) (N=8)</th>
<th>MR tablet A (standard meal) (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>AUC(_{0-t}) (ng h/mL)</td>
<td>C(_{\text{max}}) (ng/mL)</td>
<td>CL/F (L/h)</td>
<td>V(_F) (L)</td>
</tr>
<tr>
<td>Formulation A: 30 mg LEO 32731 modified release tablet (65% release within 4 hours)</td>
<td>327 (18.4)</td>
<td>342 (17.0)</td>
<td>37.7</td>
<td>970 (30.1)</td>
</tr>
<tr>
<td>Formulation B: 30 mg LEO 32731 modified release tablet (65% release within 8 hours)</td>
<td>783 (14.6)</td>
<td>790 (14.2)</td>
<td>140</td>
<td>122 (24.7)</td>
</tr>
<tr>
<td>Formulation C: 30 mg LEO 32731 modified release tablet (65% release within 12 hours)</td>
<td>671 (27.0)</td>
<td>657(^b) (29.0)</td>
<td>125</td>
<td>135(^b) (40.5)</td>
</tr>
</tbody>
</table>

Formulation A: 30 mg LEO 32731 modified release tablet (65% release within 4 hours)
Formulation B: 30 mg LEO 32731 modified release tablet (65% release within 8 hours)
Formulation C: 30 mg LEO 32731 modified release tablet (65% release within 12 hours)

Geometric mean (CV%) data are presented

Abbreviations: AUC\(_{0-t}\) = area under the plasma concentration-time curve from time zero up to the last quantifiable concentration; AUC\(_{0-t}\)= area under the plasma concentration-time curve from time zero to infinity; CL/F = apparent total plasma clearance; C\(_{\text{max}}\) = maximum observed plasma concentration; CV = coefficient of variation; N = number of subjects studied; t\(_{1/2}\) = apparent plasma terminal elimination half-life; t\(_{\text{max}}\) = time of the maximum observed plasma concentration; V\(_F\) = apparent volume of distribution during the terminal phase

\(^a\) Median (min, max); \(^b\) N = 7
The PK parameters of LEO 32731 following single oral doses of LEO 32731 in the fasted state, following a standard meal, and following a high fat meal for modified release tablet formulations B and C are summarised in the following table:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MR tablet B (fasted) (N=9)</th>
<th>MR tablet B (high fat meal) (N=9)</th>
<th>MR tablet B (standard meal) (N=9)</th>
<th>MR tablet C (fasted) (N=8)</th>
<th>MR tablet C (high fat meal) (N=8)</th>
<th>MR tablet C (standard meal) (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{AUC}_{0-\infty} ) (ng h/mL)</td>
<td>195 (45.7)</td>
<td>654 (20.3)</td>
<td>257 (68.0)</td>
<td>158 (56.9)</td>
<td>498 (35.2)</td>
<td>235 (111.4)</td>
</tr>
<tr>
<td>( \text{AUC}<em>{0-t</em>{\text{max}}} ) (ng h/mL)</td>
<td>204 (46.4)</td>
<td>659 (20.2)</td>
<td>268 (65.5)</td>
<td>211 (43.7)</td>
<td>519 (32.9)</td>
<td>230 (104.4)</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/mL)</td>
<td>15.5 (41.3)</td>
<td>133 (11.2)</td>
<td>41.7 (72.2)</td>
<td>14.0 (83.1)</td>
<td>85.1 (37.2)</td>
<td>25.1 (132.1)</td>
</tr>
<tr>
<td>( t_{\text{max}} ) (h)</td>
<td>4.00 (6.00)</td>
<td>6.00 (6.02)</td>
<td>3.00 (2.00)</td>
<td>3.00 (1.50)</td>
<td>6.03 (3.00)</td>
<td>3.00 (2.00)</td>
</tr>
<tr>
<td>( t_{1/2} ) (h)</td>
<td>7.24 (59.7)</td>
<td>2.27 (101.2)</td>
<td>5.25 (40.2)</td>
<td>9.73 (11.6)</td>
<td>5.31 (77.1)</td>
<td>6.62 (50.3)</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>147 (37.6)</td>
<td>45.5 (22.2)</td>
<td>112 (64.0)</td>
<td>142 (45.9)</td>
<td>57.8 (35.4)</td>
<td>131 (56.2)</td>
</tr>
<tr>
<td>( V_{Z/F} ) (L)</td>
<td>1540 (50.0)</td>
<td>149 (85.1)</td>
<td>847 (57.3)</td>
<td>2000 (55.1)</td>
<td>443 (81.3)</td>
<td>1250 (59.7)</td>
</tr>
</tbody>
</table>

Formulation A: 30 mg LEO 32731 modified release tablet (65% release within 4 hours)
Formulation B: 30 mg LEO 32731 modified release tablet (65% release within 8 hours)
Formulation C: 30 mg LEO 32731 modified release tablet (65% release within 12 hours)
Geometric mean (CV%) data are presented

Abbreviation: \( \text{AUC}_{0-\infty} \) = area under the plasma concentration-time curve from time zero to infinity; \( \text{AUC}_{0-t_{\text{max}}} \) = area under the plasma concentration-time curve from time zero to the last quantifiable concentration; \( C_{\text{max}} \) = maximum observed plasma concentration; CV = coefficient of variation; N = number of subjects studied; \( t_{1/2} \) = apparent plasma terminal elimination half-life; \( t_{\text{max}} \) = time of the maximum observed plasma concentration; \( V_{Z/F} \) = apparent volume of distribution during the terminal phase

Administration of modified release tablets following a high fat meal significantly increased exposure to LEO 32731 (as assessed by \( \text{AUC}_{0-\infty} \)) compared to administration in the fasted state, with 2.4-, 3.3-, and 3.3-fold increases observed for modified release tablet formulations A, B, and C, respectively. The increased lipid content of the high fat meal was pivotal to this elevated exposure as there were no significant differences in \( \text{AUC}_{0-\infty} \) between administration in the fasted state and following a standard meal for modified release tablets B and C (this comparison was not performed for modified release tablet A), whereas \( \text{AUC}_{0-\infty} \) was significantly higher following a high fat meal compared to a standard meal for all tablet formulations. Maximum exposure, as assessed by \( C_{\text{max}} \), was significantly higher following a high fat meal compared to administration in the fasted state for all tablet formulations. Absorption was delayed by approximately 3 hours following a high fat meal compared to administration in the fasted state or following a standard meal.

For each modified release tablet formulation, between-subject variability for \( \text{AUC}_{0-\infty} \), \( C_{\text{max}} \), and \( C_{\text{max}} \) was lower following a high fat meal, than when administered in the fasted state, or following a standard meal.

**Effect of Food on the Pharmacokinetics of LEO 32728**

Administration of modified release tablet formulations A and B following a high fat meal significantly decreased exposure to LEO 32728 (as assessed by \( \text{AUC}_{0-\infty} \) and \( C_{\text{max}} \)) compared to administration in the fasted state and following a standard meal. The largest food effect was observed for modified release tablet formulation A, with \( \text{AUC}_{0-\infty} \) and \( C_{\text{max}} \) decreasing by 74.8% and 53.4%, respectively, following a high fat meal compared to administration in the fasted state, while decreases of 67.3% and 31.1%, respectively, were observed for modified release tablet formulation B. The decrease in exposure to LEO 32728 was somewhat less pronounced when administration following a standard meal was compared to a high fat meal (but was still statistically significant); however, there were no statistically significant differences for \( \text{AUC}_{0-\infty} \) and \( C_{\text{max}} \) between administration following a standard meal compared to the fasted state for modified release tablet formulation B. For modified release tablet formulation C, there were no statistically significant differences in exposure to LEO 32728 between dietary states for both \( \text{AUC}_{0-\infty} \) and \( C_{\text{max}} \). For modified release tablet formulations A and B, maximum plasma concentrations occurred at a median \( t_{\text{max}} \) of 6 to 8 hours following a high fat or standard meal. Administration in the fasted state delayed \( t_{\text{max}} \) by approximately 2 hours and 6 hours for modified release formulations A and B, respectively, compared to following a high fat meal. For modified release tablet formulation C the opposite was true, \( t_{\text{max}} \) was delayed following administration in the fed state (12.0 and 14.0 hours following a high fat and standard meal, respectively) compared to the fasted state (7.0 hours).
For all tablet formulations, the metabolic ratio for LEO 32728 decreased upon administration of LEO 32731 following a standard meal, and decreased still further when administered following a high fat meal.

**Effect of Food on the Pharmacokinetics of LEO 40815**

The effects of food on the PK of LEO 40815 mirrored those of the parent compound. Administration of modified release tablets following a high fat meal significantly increased exposure to LEO 40815 (as assessed by AUC\(_{0\text{-t}_{\text{last}}}\)) compared to administration in the fasted state, with 2.4-, 3.3-, and 3.5-fold increases for modified release tablet formulations A, B, and C, respectively. In common with the parent compound, there was no significant difference in AUC\(_{0\text{-t}_{\text{last}}}\) between administration in the fasted state and following a standard meal for modified release tablets B and C, whereas AUC\(_{0\text{-t}_{\text{last}}}\) was significantly higher following a high fat meal compared to a standard meal for all tablet formulations. Maximum exposure (as assessed by C\(_{\text{max}}\)) was significantly higher for all assessed comparisons, with the exception of the comparison between administration in the fasted state compared to following a standard meal for modified release tablet C. Median t\(_{\text{max}}\) for LEO 40815 occurred at 4 to 6 hours post-dose following administration in the fasted state or following a standard meal, with t\(_{\text{max}}\) delayed by approximately 2 to 4 hours following a high fat meal.

There was no food effect on the metabolic ratio of LEO 40815 for all modified release tablet formulations.

**Safety Results**

The majority of AEs reported in Parts 1 and 2 were mild in intensity and resolved without treatment. Only one severe AE was reported (an AE of panic attack in Part 2) and was not considered to be related to LEO 32731. There were no serious AEs reported during the trial.

In Part 1, there was an increase in the incidence and frequency of AEs for the immediate release capsule compared to the modified release tablet formulations of LEO 32731. Eleven (73.3%) out of 15 subjects experienced 34 of the 57 reported AEs following administration of the immediate release capsule. The number of subjects experiencing AEs and the frequency of AEs were comparable between treatment groups receiving the modified release tablet formulations A, B, and C. The most frequently reported treatment-emergent AEs were of the Gastrointestinal Disorders system organ class (SOC) and comprised 28 of the 57 AEs reported in Part 1, with diarrhoea, abdominal pain upper, and nausea the most frequent.

In Part 2, LEO 32731 modified release tablet formulations A and B were well tolerated when administered in the fasted state. The number of subjects experiencing AEs and the frequency of AEs increased when comparing administration in the fasted state against administration with a standard meal and increased again when comparing to administration with a high fat meal for formulations A and B. The number of subjects experiencing AEs and the frequency of AEs reported when LEO 32731 modified release tablet formulation C was administered in the fasted state, with a standard meal, and with a high fat meal were comparable.

As in Part 1, AEs of the Gastrointestinal Disorder SOC were the most frequently reported events, comprising 37 of the 80 AEs reported in Part 2. The majority of gastrointestinal-related AEs were reported after administration of modified release tablet formulation A or B following a high fat meal, with a lower frequency of AEs following a standard meal, and decreasing still further in the fasted state. There was no notable food effect when dosing with LEO 32731 modified release formulation tablet C. Diarrhoea, nausea, and abdominal pain upper were the most common gastrointestinal AEs reported.

There were no apparent trends in clinical laboratory evaluations, 12-lead ECGs, vital signs, or body weight assessments following single doses of LEO 32731 in Parts 1 and 2. One subject in Part 1 (Subject 0102) tested positive for FOB on Day 1 of their first treatment period and at two unscheduled assessments and was subsequently withdrawn from the study.

**Conclusions**

The systemic exposure to LEO 32731 was significantly lower for all modified release tablet formulations compared to the immediate release capsule, with AUC\(_{0\text{-t}_{\text{last}}}\) being approximately 35%, 49%, and 58% lower, and C\(_{\text{max}}\) being 62%, 73%, and 80% lower for modified release tablet formulations A, B, and C, respectively. Administration of LEO 32731 as modified release tablet formulations delayed its rate of absorption by approximately 1 hour compared to that from the immediate release capsule.

Compared to the immediate release capsule, AUC\(_{0\text{-t}_{\text{last}}}\) for the active metabolite LEO 32728 was significantly higher for all modified release tablet formulations compared to the immediate release capsule, being approximately 1.8-, 1.7-, and 1.5-fold higher for modified release tablet formulations A, B, and C, respectively, while C\(_{\text{max}}\) was largely unaffected. The time of maximum concentrations of LEO 32728 was delayed for the modified release tablet formulations compared to the immediate release capsule, most notably for tablet formulations B and C.

The disposition of metabolite LEO 40815 mirrored that of the parent compound, with statistically significant decreases in AUC\(_{0\text{-t}_{\text{last}}}\) and C\(_{\text{max}}\), comparable to those seen for LEO 32731, for the modified release tablet formulations compared to the immediate release capsule.

Administration following a high fat meal significantly increased exposure to LEO 32731 for all modified release tablet formulations compared to administration in the fasted state, with AUC\(_{0\text{-t}_{\text{last}}}\) being approximately 2.4-, 3.3-, and 3.3-fold higher, and C\(_{\text{max}}\) being approximately 3.7-, 8.6-, and 6.5-fold higher for modified release tablet formulations A, B, and C, respectively. Administration of LEO 32731 following a high fat meal delayed absorption by approximately 3 hours compared to the fasted state.
There was no significant difference in AUC0-tlast for LEO 32731 between administration in the fasted state and following a standard meal for modified release tablets B and C, signifying that the greater lipid content of the high fat meal was crucial to increased absorption. There was also no discernible difference in tmax between administration in the fasted state or following a standard meal. The effect of food on the PK of metabolite LEO 40815 mirrored that of the parent compound. Exposure to metabolite LEO 32728 was significantly decreased when modified release tablet formulations A and B were administered following a high fat meal compared to following a standard meal or administration in the fasted state, with the largest decreases observed for the high fat meal versus fasted state dietary comparison. Modified release tablet formulation A displayed the largest food effect, with AUC0-tlast and Cmax decreasing by approximately 75% and 53%, respectively, following a high fat meal compared to administration in the fasted state. In contrast, there was no statistically significant difference in exposure to LEO 32728 between dietary states for modified release tablet formulation C.

LEO 32731 was considered safe and generally well tolerated when administered as 30 mg modified release tablets A (65% release within 4 hours), B (65% release within 8 hours), and C (65% release within 12 hours), and as a 30 mg immediate release capsule in the fasted and fed dietary states. In Part 1, each of the LEO 32731 modified release tablet formulations had an improved tolerability profile compared to the LEO 32731 immediate release capsule. One subject in Part 1 met the withdrawal criteria for FOB which was considered to be possibly related to LEO 32731.

In Part 2, LEO 32731 modified release tablets A and B administered with a high fat meal were less well tolerated than when administered with a standard meal or in the fasted state; however, there was no notable food effect when dosing with LEO 32731 modified release tablet C.

The clinical trial was conducted in compliance with the clinical trial protocol, ICH Good Clinical Practice and the Declaration of Helsinki as adapted by the 18th World Medical Assembly 1964, and subsequent amendments.
Electronic Signatures

Electronic signature made within eDoc LEO by LEO Pharma A/S employees or employees of any LEO Pharma A/S affiliate located anywhere in the world, are to be considered to be legally binding equivalent of traditional handwritten signatures.

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