INTRODUCTION

Cushing’s disease is a rare disorder of chronic hypercortisolism, which is caused by an adrenocorticotrophic hormone (ACTH)-secreting pituitary adenoma. 

Unintreated, Cushing’s disease is associated with significant clinical and metabolic complications, including osteoporosis, hypertension, diabetes, and psychiatric disorders. 

In a randomized, 12-month, Phase III study (IB2305), the multitargeted, small-molecule inhibitor pazopanib (Zelboraf®) led to a rapid and sustained decrease in mean urinary free cortisol (UFC) and provided clinical benefit in patients with persistent, recurrent or de novo Cushing’s disease. 

Based on the results of this study, pazopanib was approved in the US and EU for the treatment of adult patients with Cushing’s disease’s refractory to conventional therapy. 

Here, we report long-term efficacy and safety data from the IB2305 study following an open-ended extension.

METHODS

Study Design

Randomized Phase III study with an open-ended, open-label extension: 12- and 24-month results have been reported previously. 

The extension included patients who continued with the same dose of pazopanib or received a dose decrease to 200 or 100 mg twice daily. 

Patients who had UFC levels up to the upper limit of normal (ULN) or who were achieving clinical benefit at month 12 could enter the extension.

Assessments and Statistical Analyses

Efficacy data were presented for patients who received ≥1 dose of pazopanib (overall population) and for patients who reached month 60. 

All patients who received ≥1 dose of pazopanib were included in the analysis of safety and adverse events (AEs), regardless of whether they entered the extension, unless otherwise stated.

AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3.0. 

Kaplan-Meier estimates of cumulative event rate for first occurrence of AEs of special interest were calculated.

RESULTS

Patient Disposition

Seventy-eight of the 162 patients who received pazopanib completed 12 months of treatment; 56 of these patients continued into the extension. 

In the overall population, 16 patients reached month 60; 15 patients reached month 60 with pazopanib, and one patient reached month 60 without pazopanib.

At baseline, median (range) serum cortisol and ACTH levels were 691 nmol/L (260–729) and 13 pmol/L (11–14), respectively, in the overall population and 488.3 nmol/L (258–591) in the 16 patients who reached month 60. 

For patients who reached month 60, median UFC decreased during the first 3 months of treatment and continued to do so until month 12, after which median UFC increased (Figure 1).

For patients who reached month 60, 10/16 and 11/16 had UFC < ULN at month 12 and month 60, respectively.

At baseline, median (range) serum cortisol and ACTH levels were 691 nmol/L (260–729) and 13 pmol/L (11–14), respectively, in the overall population and 488.3 nmol/L (258–591) in the 16 patients who reached month 60. 

For patients who reached month 60, 10/16 and 11/16 had UFC < ULN at month 12 and month 60, respectively.

Long-term Safety of Pazopanib

In general, there was a minimal increase in the incidence of adverse events (AEs) over time, with the exception of hypertension, diabetes, and psychiatric disorders. 

In patients who received pazopanib, clinical events were reported in 75% of patients at baseline, 70% of patients at month 12, and 62% of patients at month 60. 

Most AEs related to bradyhypertension, hypoglycemia, and psychiatric disorders. 

Most AEs related to bradyhypertension, hypoglycemia, and psychiatric disorders. 

Most AEs related to bradyhypertension, hypoglycemia, and psychiatric disorders. 

CONCLUSIONS

The findings presented here demonstrate that the reductions in UFC and improvements in clinical signs of Cushing’s disease reported after 12 months were maintained for up to 5 years of pazopanib treatment in the 16 patients who remained on treatment. 

Median UFC, serum cortisol, and plasma ACTH levels were lower at baseline in patients who reached month 60 compared with the overall patient population at baseline. 

First-reported AEs related to bradyhypertension and hypoglycemia were the most common AEs reported during the first 12 months of treatment. 

Importantly, most patients with AEs related to bradyhypertension, hypoglycemia, and psychiatric disorders did not experience a worsening of these AEs after first occurrence of pazopanib or beyond. 

RESULTS from this study suggest that pazopanib can be an effective long-term treatment of Cushing’s disease.

ACKNOWLEDGEMENTS

We thank Robert Joan PhD, MUdKoppier Business Limited (funded by Novartis Pharmaceuticals Corporation) for providing medical editorial assistance.

REFERENCES


Table 1: Cumulative Event Probabilities for Time to First Occurrence of AEs Related to Hypoglycemia, the Gallbladder/Biliary Tract, the Liver, or by Bradyhypertension

<table>
<thead>
<tr>
<th>Month</th>
<th>Hypoglycemia-related AEs</th>
<th>Gallbladder/biliary-related AEs</th>
<th>Liver-related AEs</th>
<th>Bradyhypertension-related AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>8</td>
<td>19</td>
<td>19</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>9</td>
<td>21</td>
<td>21</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>10</td>
<td>23</td>
<td>23</td>
<td>23</td>
<td>23</td>
</tr>
</tbody>
</table>

Table 2: CTCAE Grade of AEs Related to Hypoglycemia, the Gallbladder/Biliary Tract, the Liver, or by Bradyhypertension at First Occurrence and Worst Value

<table>
<thead>
<tr>
<th>Time</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-reported AEs</td>
<td>10 (0.0)</td>
<td>20 (0.0)</td>
<td>30 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worst reported AEs</td>
<td>10 (0.0)</td>
<td>20 (0.0)</td>
<td>30 (0.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Median (Ala) and FPG from Baseline to Month 60

<table>
<thead>
<tr>
<th>Time</th>
<th>Median (Ala)</th>
<th>FPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>100 (50.0)</td>
<td>100</td>
</tr>
<tr>
<td>Month 60</td>
<td>100 (50.0)</td>
<td>100</td>
</tr>
</tbody>
</table>

Figure 1: Median (A) UFC, Serum Cortisol and (C) ACTH Levels from Baseline to Month 60

Figure 2: Median (A) Systolic Blood Pressure, (B) Diastolic Blood Pressure, (C) Weight, and (D) BMI from Baseline to Up to Month 60

Figure 3: Median (A) HbA1c and (B) FPG from Baseline Up to Month 60

Note: Error bars show 95% distribution free cortisol limits for median values; numbers of patients with available measurements are shown beneath each point in the overall population. Concentration treatment with antithrombotic medication was permitted at the discretion of the investigator.