INTRODUCTION

Cushing’s disease (CD) is an endocrine disorder characterised by chronic hypercortisolism that results from excess adrenocorticotropic hormone (ACTH) secretion from a pituitary corticotroph adenoma. The treatment options for CD includes pituitary surgery, pituitary irradiation, medical therapy, and bilateral adrenalectomy. Several medications are currently available for the treatment of CD. However, for most medications safety and efficacy is supported by a low level of evidence and/or are not widely approved for this indication except pasireotide and mitotane. AOs.

Osilodrostat (LCI699) is a potent, oral inhibitor of the 11β-hydroxylase enzyme (CYP11B1) (Figure 1).

Figure 1. Mechanism of Action of Osilodrostat in Cushing’s Disease

ACTH, adrenocorticotropic hormone.

STUDY RATIONALE

There is a need for new medications to treat the patients with CD who may not achieve normalization of mean daily cortisol (mUFC) or may not tolerate available medications. Results from the phase II LINCY and LINCY2 study showed that osilodrostat normalised UFC in 86% (111/129) and 78.9% (15/19) of patients at week 10 and week 22, respectively. Osilodrostat treatment was generally well tolerated. Thus, LINCY3 (LCI699C3051), a 48-week confirmatory phase III study in 8-week randomly withdrawn period design is evaluated to long-term safety and efficacy of osilodrostat in a large population of patients with CD (Table 1).

A randomised withdrawn study is appropriate in rare and serious diseases because long term placebo control in patients with CD might lead to chronic uncontrolled hypercortisolism. The short (8-88) week withdrawn withdrawal period and rescue treatment in this study design will allow a placebo-controlled comparison while minimising the duration of placebo exposure in patients with untreated CD.

Table 1. Objective and Related Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>To compare the complete response rate at the end of the randomised withdrawal period (week 24) between patients randomised to continue osilodrostat therapy in placebo.</td>
</tr>
<tr>
<td>Key Secondary</td>
<td>To assess the complete response rate at the end of week 24.</td>
</tr>
</tbody>
</table>

Table 2. Methods

Table 2. Methods

Patients

- Adults (aged 18-75 years) with persistent or recurrent CD after primary pituitary surgery and/or irradiation as evidenced by the following:
  - mUFC > 15 μU/L
  - morning plasma ACTH > lower limit of normal (ULN)
  - confirmed pituitary source of excess ACTH

- de novo CD who are not considered as surgical candidates and refuse to undergo surgery

- Patients receiving other medical treatment for CD are eligible after appropriate drug washout.

- Patients with tumour causing compression of the optic chiasm, uncontrolled diabetes (glycosylated haemoglobin [HbA1c] > 9%), and/or hypertension (BP > 150/100) are excluded.

Study Design

Phase III, multicentre study with 4 treatment periods and an optional extension period (Figure 2).

Figure 2. Study Design

METHODS

Patients

- Adults (aged 18-75 years) with persistent or recurrent CD after primary pituitary surgery and/or irradiation as evidenced by the following:
  - mUFC > 15 μU/L
  - morning plasma ACTH > lower limit of normal (ULN)
  - confirmed pituitary source of excess ACTH

- de novo CD who are not considered as surgical candidates and refuse to undergo surgery

- Patients receiving other medical treatment for CD are eligible after appropriate drug washout.

- Patients with tumour causing compression of the optic chiasm, uncontrolled diabetes (glycosylated haemoglobin [HbA1c] > 9%), and/or hypertension (BP > 150/100) are excluded.

Study Design

Phase III, multicentre study with 4 treatment periods and an optional extension period (Figure 2).