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# Osilodrostat Is Effective and Well Tolerated in Patients of Asian and Non-Asian Origin With Cushing's Disease: A Pooled Analysis From LINC 3 and LINC 4

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*Potential conflict of interest may exist. Refer to the Meeting App; †AMP was an employee of Recordati at time of abstract/poster development

## Plain language summary

### Why was this analysis carried out?

- People with Cushing's disease have higher-than-normal levels of the hormone cortisol, caused by a tumor within the pituitary gland. Osilodrostat is a medicine that reduces cortisol and maintains normal levels in people with Cushing's disease
- In people of Asian origin, the amount of exposure to osilodrostat from a tablet of the same dose is higher than in people of non-Asian origin. We wanted to examine if osilodrostat would have similar beneficial effects in Asian and non-Asian people and if any side effects would be different between groups

### How was this analysis carried out?

- The results of two previous studies were combined to allow a larger number of people of Asian and non-Asian origin to be included in this analysis
- The beneficial effects of osilodrostat and any side effects caused by the drug were analyzed in people of Asian and non-Asian origin

### What were the overall results?

- Cortisol rapidly dropped to normal levels in Asian and non-Asian people and remained at a normal level after osilodrostat had been taken for a long period of time
- Asian people showed benefit from their treatment with a lower dose of osilodrostat than non-Asian people
- The symptoms of Cushing's disease and a person's quality of life were improved with osilodrostat in Asian and non-Asian people
- Osilodrostat was well tolerated, with a few differences in side effects between groups. Asian people experienced more side effects related to low cortisol levels, or to their existing pituitary tumor, than non-Asian people

### What do the results mean?

- Osilodrostat had similar benefits and was well tolerated in people of Asian and non-Asian origin; Asian people achieved control of cortisol at a lower dose than that in non-Asian people

### Where can I access more information?

- LINC 3 primary publication: https://www.thelancet.com/article/S2213-8587(20)30240-0/fulltext
- LINC 4 primary publication: https://academic.oup.com/jcem/article/107/7/e2882/6553201?login=false

## Conclusions

- The beneficial effects of osilodrostat were similar in patients of Asian and non-Asian origin in terms of biochemical control and clinical improvement
  - The median dose to achieve beneficial effects was lower in Asian than in non-Asian patients
- Mean mUFC rapidly decreased from high baseline values to within the normal range in both Asian and non-Asian patients; reductions were sustained during long-term treatment
- Improvements from baseline in cardiovascular and metabolic-related parameters and CushingQoL score were observed during the core phase and maintained during long-term treatment in both Asian and non-Asian patients
- Osilodrostat was well tolerated in both patient subgroups
  - AEs related to hypocortisolism and pituitary tumor enlargement were reported more frequently in Asian patients than in non-Asian patients. The frequency of AEs related to pituitary tumor enlargement could potentially be affected by the higher frequency of macroadenomas observed at baseline in Asian patients than in non-Asian patients in these studies
- These exploratory analyses have several limitations: differences in study design between LINC 3 and LINC 4, missing time points across studies and the Asian patients being a heterogeneous population

### Acknowledgments

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### Disclosures

The LINC clinical program was sponsored by Novartis Pharma AG; however, as of July 12, 2019, osilodrostat is an asset of Recordati AG.

### Abbreviations

ACTH, adrenocorticotropic hormone; AE, adverse event; BMI, body mass index; CushingQoL, Cushing's Quality of Life Questionnaire; DBP, diastolic blood pressure; FPG, fasting plasma glucose; $HbA_{1c}$, glycated hemoglobin; mUFC, mean urinary free cortisol; SBP, systolic blood pressure; SD, standard deviation; ULN, upper limit of normal

### References

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## Introduction

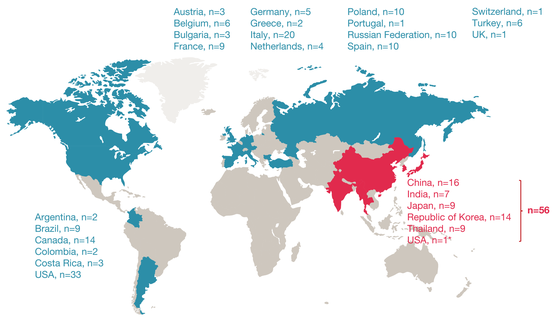
- Osilodrostat, a potent oral 11β-hydroxylase inhibitor, rapidly reduced to and sustained normal levels of cortisol in Phase III studies (LINC 3, NCT02180217; LINC 4, NCT02697734) in patients with Cushing's disease[1–4]
- Relative osilodrostat bioavailability is estimated to be 20% higher in patients of Asian origin than for other ethnicities; body weight is not a major determinant of this difference[5]
- The efficacy and safety of long-term osilodrostat treatment in patients of Asian and non-Asian origin with Cushing's disease were evaluated through pooled analysis of LINC 3 and LINC 4

## Methods

- Individual data from the LINC 3 and LINC 4 studies were pooled (scan QR code for LINC 3 and LINC 4 study designs)
  - LINC 3 comprised a 48-week core phase, including an 8-week randomized withdrawal for eligible patients
  - LINC 4 included an upfront 12-week, double-blind, placebo-controlled period followed by 36 weeks of open-label osilodrostat
  - Both studies had an optional extension
- These analyses were exploratory; outcomes were evaluated separately in Asian and non-Asian patients, and numerical comparisons were made between groups
- Periods during which patients received placebo were excluded

## Results

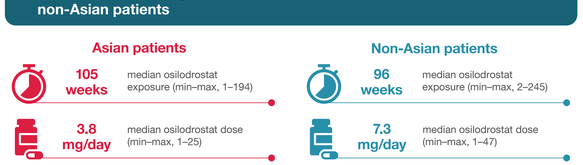
### 1. From a total of 210 patients, 56 patients from LINC 3 and LINC 4 were from a heterogeneous population of Asian origin – most non-Asian patients were Caucasian (n=138/154; 90%); Asian patients had higher mUFC at baseline




*One patient of Asian origin enrolled in the USA

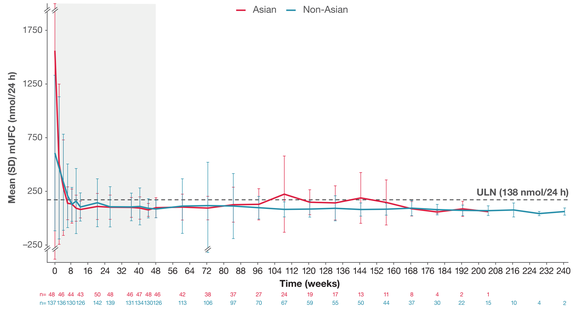
| Patient characteristics | Asian patients, N=56 | Non-Asian patients, N=154 |
|---|---|---|
| Median **age**, years (min–max) | 38.5 (19–70) | 41.0 (19–70) |
| **Female**, n (%) | 44 (78.6) | 123 (79.9) |
| Mean **weight**, kg (SD) | 69.5 (16.0) | 83.7 (21.0) |
| Mean **height**, cm (SD) | 157.7 (7.1) | 164.3 (8.9) |
| Mean **BMI**, kg/m$^2$ (SD) | 27.9 (5.8) | 31.0 (7.6) |
| Median **time** to first osilodrostat dose since diagnosis, months (min–max) | 62.2 (3–216) | 52.5 (2–287) |
| **Disease status**, n (%)<br>*De novo*<br>Persistant/recurrent | 7 (12.5)<br>49 (87.5) | 13 (8.4)<br>141 (91.6) |
| Proportion of patients with **previous surgery**, n (%) | 46 (82.1) | 138 (89.6) |
| Proportion of patients who received **prior medical therapy**, n (%) | 46 (82.1) | 130 (84.4) |
| Mean **mUFC**, nmol/24 h (SD) | 1412.0 (2210.9) | 586.1 (693.1) |
| Patients, n (%), with:<br>**Macroadenoma**<br>**Microadenoma**<br>**Missing** | 19 (33.9)<br>36 (64.3)<br>1 (1.8) | 29 (18.8)<br>122 (79.2)<br>3 (1.9) |

### 2. Patients of Asian origin received lower doses of osilodrostat than non-Asian patients



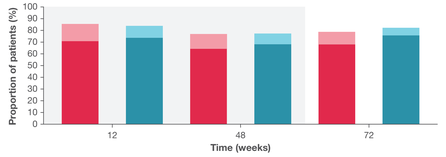

- Evaluation of dose received by kilogram of body weight showed that patients of Asian origin received lower doses of osilodrostat than patients of non-Asian origin (scan QR code)

### 3. Mean mUFC decreased from high baseline values to within the normal range during the first 8 weeks of treatment and stabilized during long-term treatment in Asian and non-Asian patients



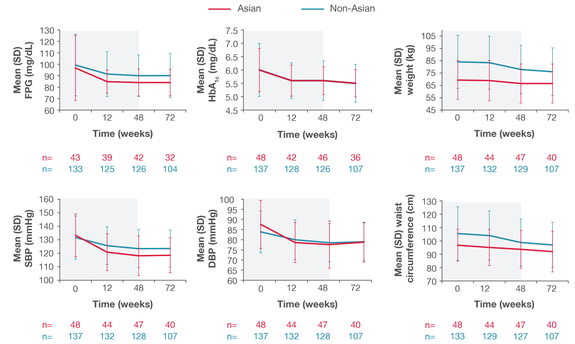

Shaded area indicates core phase of the studies, n indicates the number of patients with an evaluable assessment at baseline and the given visit

### 4. Response rates to osilodrostat were similar in both Asian and non-Asian patients and maintained during the extension studies



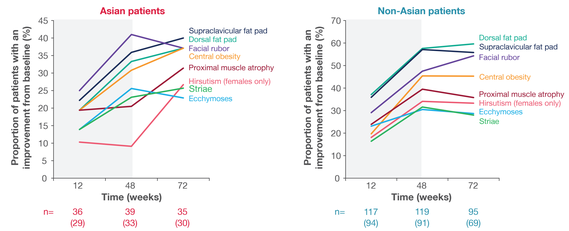

Shaded area indicates core phase of the studies. The denominator is the full analysis set for all visits up to week 48. Beyond week 48, patients who entered the extension were included in the denominator until their individual end of treatment. If included in the analysis for calculating the proportion of responders at a given time point, patients who discontinued before this time point were counted as non-responders. Patients with missing mUFC at a visit were counted as non-responders

### 5. Early improvements in cardiovascular and metabolic-related parameters were observed during osilodrostat treatment in Asian and non-Asian patients; improvements were maintained during long-term treatment




Shaded area indicates core phase, n indicates the number of patients with an evaluable assessment at baseline and the given visit (scan QR code for data on BMI, cholesterol and triglycerides)

### 6. Improvements in physical manifestations of hypercortisolism were observed as early as week 12 of osilodrostat treatment in both Asian and non-Asian patients

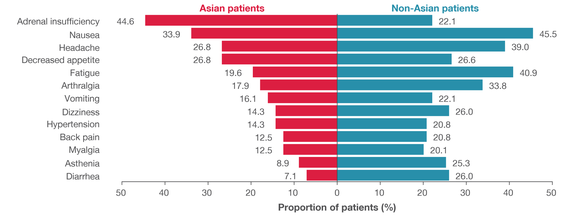



Shaded area indicates core phase. Improvement was defined as the symptom score being lower (ie less severe) than at baseline. The denominator for the percentage includes all enrolled patients who received at least one dose of osilodrostat with an evaluable assessment at baseline and the given visit (n). Numbers in brackets indicate n for female patients assessed for hirsutism. In the non-Asian patient population, n varied across parameters: at week 12, 116 patients were assessed for striae and dorsal fat pad; at week 48, 117 were assessed for striae and 118 for facial rubor, dorsal fat pad and ecchymoses improvement; and at week 72, 93 were assessed for striae and 94 for facial rubor, dorsal fat pad and ecchymoses improvement

- Quality of life improved in both Asian and non-Asian patients during osilodrostat treatment (scan QR code)

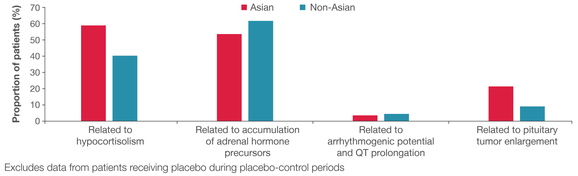
### 7. Osilodrostat was generally well tolerated in both Asian and non-Asian patients

Most common AEs (≥20% of patients in either group) regardless of relationship to study drug




### 8. Adverse events related to hypocortisolism and pituitary enlargement were reported more frequently in Asian than in non-Asian patients

Adverse events of special interest




Excludes data from patients receiving placebo during placebo-control periods

- There was no change in median tumor volume over time in Asian and non-Asian patients (scan QR code)
  - The proportion of patients with macroadenomas at baseline was higher in Asian patients (33.9%) than in non-Asian patients (18.8%; see table in first column)
- ACTH levels increased over time to a numerically greater extent in Asian than in non-Asian patients (scan QR code)
- There were no trends observed in ACTH levels in patients who experienced a pituitary-related AE (scan QR code)
- AEs related to the pituitary tumor led to osilodrostat discontinuation in 8/56 (14.3%) Asian and 6/154 (3.9%) non-Asian patients