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Dosing And Titration Of Osilodrostat In A Real-world Cohort Of US Patients With Endogenous Cushing's Disease: Analysis Of The ILLUSTRATE Study

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*Potential conflict of interest may exist. Refer to the Meeting App.

Background

- Cushing's disease (CD), the most common form of endogenous Cushing's syndrome (CS), results when a pituitary corticotroph adenoma produces excess adrenocorticotropic hormone (ACTH).
- Medical therapy is indicated when a patient has failed first-line surgery, surgery is not feasible, while awaiting onset of radiation, or when there is recurrent hypercortisolism.
- Osilodrostat is a potent oral inhibitor of 11β- hydroxylase with demonstrated efficacy in normalizing urinary free cortisol (UFC) in Cushing's disease (CD) patients and was well tolerated in clinical trials.
- Information describing osilodrostat's use in clinical practice is limited.
- We present osilodrostat dosing and titration information from a real-world study in U.S. patients with endogenous Cushing's syndrome (CS), focused on CD.

Methods

- ILLUSTRATE, a retrospective chart review study analyzed confirmed endogenous CS patients in the U.S. who initiated osilodrostat treatment between May 1, 2020 and October 29, 2021.
- The study was approved by WIRB on October 29, 2021.
- U.S. sites with patients prescribed osilodrostat were approached to participate, a sub-set of sites agreed and entered patient data.
- Forty-two adult patients from 26 U.S. clinics with endogenous CS and a prescription for osilodrostat were included in this real-world study.
- We collected patients' medical history, laboratory results, concomitant medications, and signs and symptoms.
- We describe patients' experience with initial osilodrostat dose, dose titration, and persistence in the CD subset (n=34, 81%). (Table 1)

Table 1. Patient Characteristics

	CD Patients
Number of patients, n (%)	34 (81)
Age (years), mean, SD	40.8 (13.9)
Age at diagnosis (years), mean, SD	34.9 (12.7)
Female, n (%)	27 (79.4)
Race n (%)	
White	17 (50.0)
Black	8 (23.5)
Asian	1 (2.9)
More than one race	1 (2.9)
Unknown	7 (20.6)
Disease duration prior to osilodrostat, months, mean (SD)	57.3 (82.0)
Prior pituitary or adrenal surgery for CS, n (%)	32 (94.1)
Prior medical therapy for CS, n (%)	21 (61.8)

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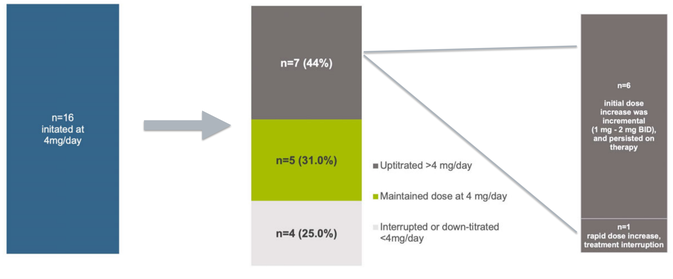
Table 2. Starting Doses in Cushing's Disease Patients

	Patients, n (%)
Total	34 (81)
1 mg QD	1 (2.9)
2 mg QD	1 (2.9)
1 mg BID	9 (26.5)
4 mg QD	1 (2.9)
2 mg BID	21 (61.8)
3 mg BID	1 (2.9)

Results

- In patients with CD (n=34), the mean total daily starting dose was 3.4 mg (SD 1.1; median 4 mg; range 1-6 mg/day).
- Starting doses varied (Table 2). 8 patients had a singe encounter.
- In CD patients with multiple documented clinical encounters (n=26), mean days on therapy was 292.1 (median 298; range 15-547).
- 16 of 26 started at 4 mg/day
  - 4 patients (25%) had the dose interrupted or down-titrated within 71 days of treatment initiation; 2/4 of these patients experienced hypocortisolism-related symptoms and permanently discontinued
  - 5 patients (31%) were maintained on 4 mg/day throughout the observation period, with a mean (SD) treatment duration of 273 (median 278 days; SD 92) days
  - 7 patients (44%) had a dose up-titration; in 6/7 patients, initial dose increase was incremental (1-2 mg BID), and the mean (SD) time to up-titration was 78 (SD 25; median 83; range 40-108) days. (Figure 1)
- 10 of 26 started at <4 mg/day
  - 6 (60%) did not require dose reduction or interruption, all of which had up-titration in small increments (1-2 mg/day) and/or first titration at ≥80 days

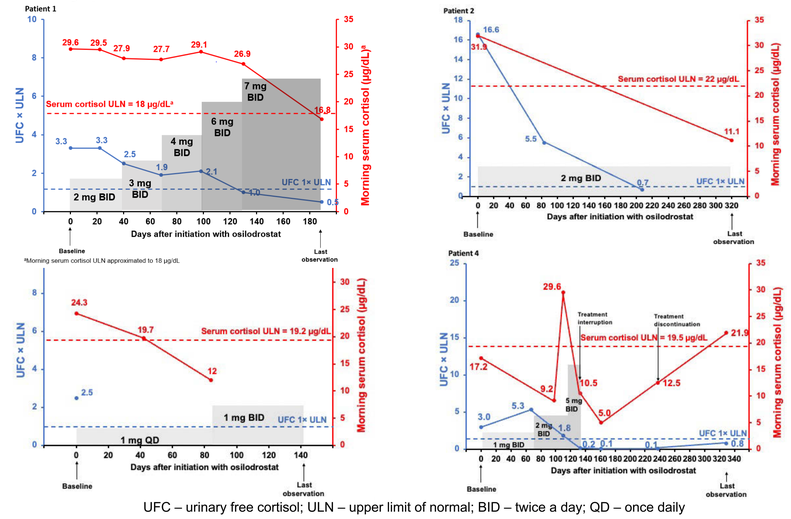
Figure 1. Dose titrations in patients initiated on 4 mg/day with multiple clinical encounters



Osilodrostat Tolerance

- Osilodrostat was generally well tolerated.
- Symptoms related to decreased cortisol levels were reported in 10/26 patients (38%), including 3 patients with adrenal insufficiency based on physician characterization of patient symptoms and biochemistry and 7 patients with glucocorticoid withdrawal symptoms (e.g., dizziness, fatigue, headache, and nausea).

Figure 2. Osilodrostat dosing in representative patients during the study period



UFC – urinary free cortisol; ULN – upper limit of normal; BID – twice a day; QD – once daily

- Sample of patients showing various trends in response to osilodrostat treatment.
- Patient 1 was started on 2 mg BID with slow up-titration and had cortisol normalization with treatment persistence.
- Patient 2 was started on 2 mg BID with no up-titration and had cortisol normalization with treatment persistence.
- Patient 3 started at 1 mg QD with dose up-titration to 1 mg BID and had treatment persistence.
- Patient 4 was started on 1 mg BID with up-titration to 2 mg BID on D67. On D110 the dose was more than doubled which led to over-treatment; the patient subsequently experienced a rapid decrease in serum cortisol and required treatment interruption with ultimate discontinuation.

Conclusions

- ILLUSTRATE captures real-world U.S. data describing the experience of a subset of CD patients treated with osilodrostat.
- Of the 16 patients who started at 4 mg/day, 4 (25%) required interruption or down-titration and 5 (31%) remained on the initial dose throughout the observation period.
- One-third (11/34) of patients were started on lower than the indicated dose of 4 mg/day.
- Overall, patients with a gradual dose up-titration (i.e., prolonged titration interval) tended to have greater persistence with therapy.
- There were no new safety findings.

Limitations

- This chart review was limited by the small number of sites that participated.
- Patient abstractions were conducted by physicians via voluntary response sampling.
- Length of observation window during the index period varied across patients.
- Similar to other retrospective studies, this chart review was limited by what was documented in patient medical records, including labs, concomitant medications, and physician notes.