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Management, Safety, And Efficacy Of Osilodrostat Treatment In US Patients With Non-pituitary Cushing's Syndrome: Results From The ILLUSTRATE Study

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

Background

- Cushing's syndrome (CS) results from chronic exposure to excess levels of cortisol, with Cushing's disease (CD) being the most common form of endogenous CS.
- While surgery is first-line treatment, medical therapy is indicated in patients with persistent or recurrent hypercortisolism, or if surgery is not possible.
- Osilodrostat is a potent cortisol synthesis inhibitor with demonstrated efficacy in the treatment of Cushing's disease (CD) with a good safety profile.
- Until now, no information was available describing use of osilodrostat in non-pituitary Cushing's syndrome (CS) in U.S. patients as it is not FDA-approved for non-pituitary CS.
- We present data from a real-world study in U.S. patients with non-pituitary CS from an ectopic or adrenal source.

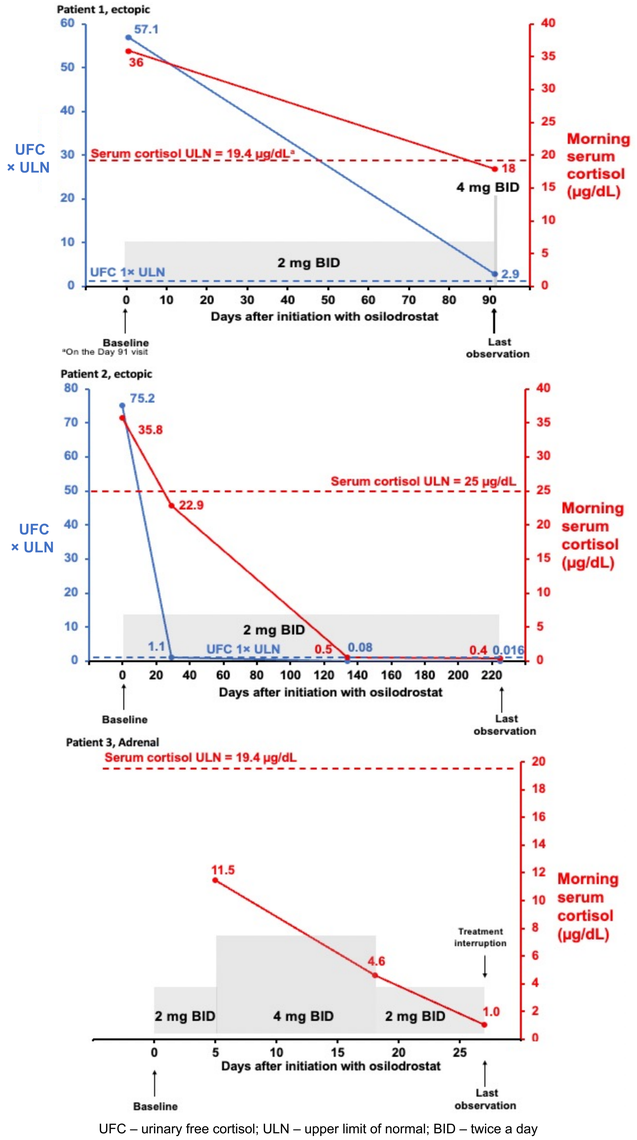
Methods

- The ILLUSTRATE study is a real-world characterization of osilodrostat usage in U.S. patients with endogenous CS treated between May 1, 2020 and October 29, 2021. The study was approved by WIRB on October 29, 2021.
- Forty-two adult patients from 26 U.S. clinics with a confirmed diagnosis of endogenous CS and a prescription for osilodrostat were included in this real-world study.
- We collected medical history including prior use of CS medications, signs and symptoms, laboratory results, and use of concomitant medications.
- We report patient characteristics, osilodrostat dose, efficacy, and safety in the subset of patients with non-pituitary CS (n=8,19%).

Table 1. Patient Characteristics

	Adrenal CS Patients	Ectopic CS Patients	All Patients
Total, n (%)	5 (62.5)	3 (37.5)	8 (100)
Age (years), mean, SD	49.2 (14.0)	66.7 (3.5)	55.8 (14.0)
Age at diagnosis (years), mean, SD	40.0 (14.8)	66.3 (3.1)	53.2 (17.3)
Female n (%)	2 (40)	3 (100)	5 (62.5)
Race n (%)			
White	4 (80.0)	1 (33.3)	5 (62.5)
Black	1 (20.0)	1 (33.3)	2 (25.0)
Asian	0 (0)	1 (33.3)	1 (11.5)
Prior adrenal surgery for CS, n (%)	2 (40.0)	0 (0)	2 (25.0)
Prior CS medical therapy, n (%)	3 (60.0)	2 (66.7)	5 (62.5)

Figure 1: Osilodrostat dosing in representative patients during the study period



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

- Sample of patients showing various trends in response to osilodrostat treatment.
- Patient 1 was started on 2 mg BID with slow up-titration, had marked cortisol reduction, and treatment persistence.
- Patient 2 was started on 2 mg BID with no up-titration, had marked cortisol reduction, and treatment persistence.
- Patient 3 was started on 2 mg BID with up-titration to 4 mg BID on D5. The patient subsequently experienced a decrease in serum cortisol consistent with glucocorticoid withdrawal syndrome and required treatment interruption.

Results

- 8 patients with non-pituitary CS were evaluated (see Figure 1 for representative patients).

Adrenal CS patients (n=5, 62.5%)

- Starting dose ranged from 1–4 mg daily.
- Baseline UFC was 0.42 – 27.76 x upper limit of normal (ULN) in 4 adrenal CS patients (UFC for 1 patient was not available).
- In patients with more than one documented clinical encounter (n=4)
  - 2 patients remained on their starting dose (1 mg BID, 2 mg BID)
  - 1 patient increased from 1 mg QD to 2 mg BID on day (D) 50
  - 1 increased from 2 mg BID to 4 mg BID on D5 and required down-titration on D18 with treatment interruption on D27.

Ectopic CS patients (n=3, 37.5%)

- Baseline urinary free cortisol (UFC) was 2.57 – 75.20 x ULN in patients with ectopic CS.
- Three patients were all started on 2 mg BID
  - 1 patient's dose was unchanged throughout the observation period
  - 2 patients were up-titrated, both on D91

Osilodrostat Tolerance

- Osilodrostat was generally well tolerated.
- One ectopic CS patient had treatment interrupted on D214 for adrenal insufficiency (AI).
- Two of five adrenal CS patients (40%) had symptoms suggestive of glucocorticoid withdrawal (e.g., fatigue, nausea, and headache) and one had an interruption in therapy. Neither patient had documented AI.

Changes in UFC

The two ectopic CS patients with available UFC data experienced substantial UFC reductions (from 57.1 x ULN to 2.9 x ULN at D91 and 75.2 x ULN to 1.1 x ULN at day 29 and 0.08 x ULN at D134).

Conclusions

- In this real-world cohort of patients treated with osilodrostat for non-pituitary CS, large reductions in UFC were seen in two patients with ectopic CS.
- All patents were initiated on ≤ 2 mg BID, with 3 (38%) remaining on their original dose.
- In 3 of 4 patients up-titrated, there was an extended titration interval.
- The observed safety profile in this subset (albeit small) of non-pituitary CS patients was consistent with the known osilodrostat safety profile.

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.

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