

# 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.

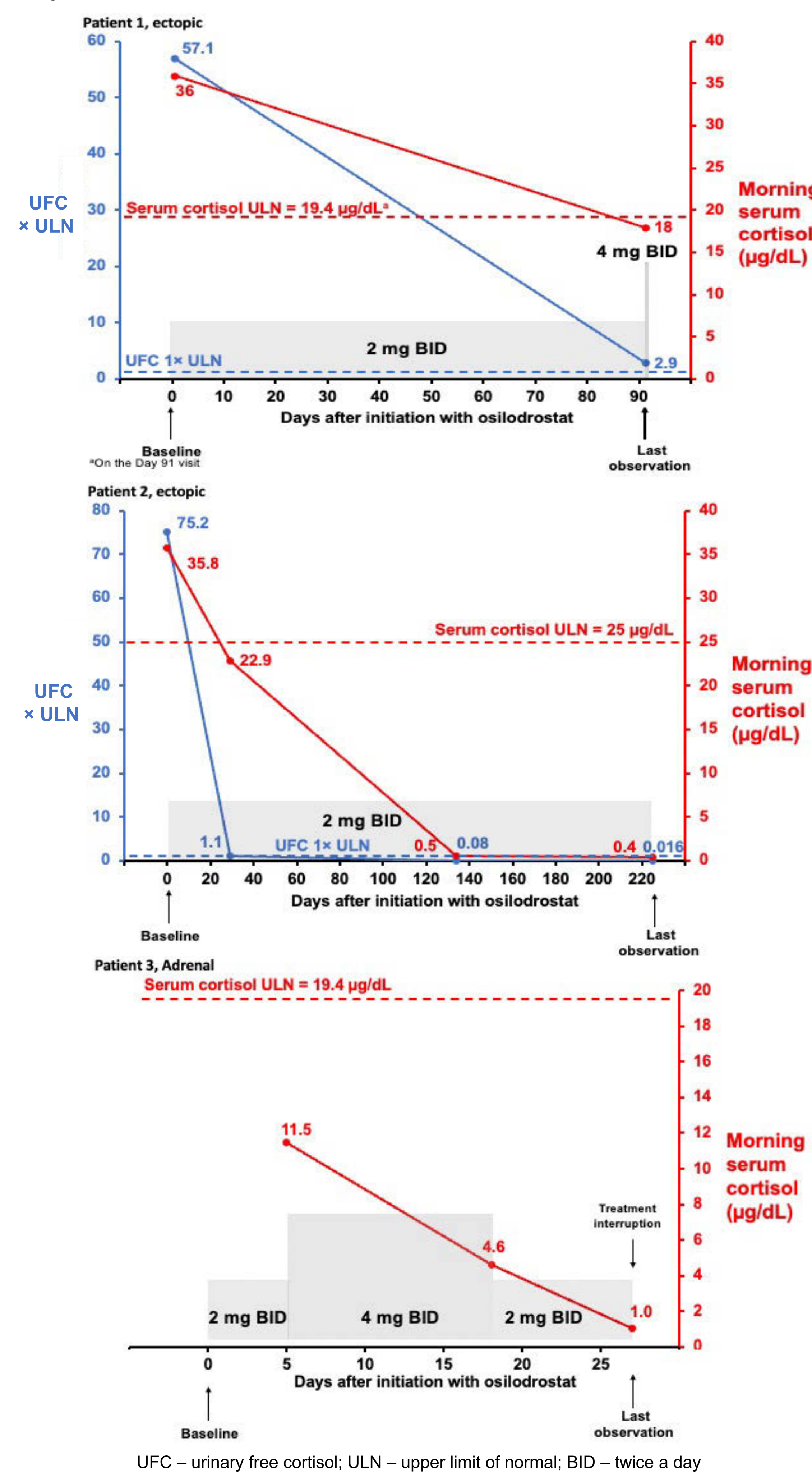
## Methods

- 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
<b>Total, n (%)</b>	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**



- 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 patients 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.