CME

Cushing Disease/Syndrome Research Highlights

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Disclosures

Contracted Research

- Novartis Pharmaceuticals
- Neurocrine Biosciences
- Spruce Biosciences
- Corcept Therapeutics
- Sparrow Pharmaceuticals
- Diurnal, LTD

Consultant

- Corcept Therapeutics
- Novartis Pharmaceuticals
- Neurocrine Biosciences
- Quest Diagnostics
- Janssen Pharmaceuticals
- Xeris Pharmaceuticals
- Crinetics Pharmaceuticals
- Adrenas Therapeutics
- PhaseBio Pharmaceuticals
- OMass Therapeutics
- Recordati Rare Diseases
- Novo Nordisk
- H Lundbeck A/S

What is Cushing disease?

- **Rare endocrine disorder characterized by chronic hypercortisolism.**
- **Cushing syndrome from pituitary adenoma producing excessive ACTH, prompting excessive production of cortisol.**
- **Since it is a rare condition, data presented at large medical conferences, like ENDO 2022, can get overlooked.**

Symptoms include:

- **Weight gain in face, above collar bone, and on back of neck**
- **Central obesity w/ thin arms and legs**
- **Skin thinning**
- **Hirsutism, amenorrhea, balding in females**
- **Muscle weakness**
- **Hypertension**
- **Poor wound healing**
- **Diabetes mellitus**

Treatment Options

Neuromodulators of ACTH Release:

- Pasireotide
- Cabergoline

Adrenal Steroidogenesis Inhibitors:

- Ketoconazole
- Mitotane
- Etomidate
- Levoketoconazole
- Osilodrostat

Glucocorticoid Receptor Blockers:

- Mifepristone

+ combinations

Diagnosis, Morbidities, and Biomarkers

Weight Trajectory as a Predictor of Cushing Disease **

- Can weight-gain trajectories differentiate pts with Cushing disease (CD) from those without, even in a population that is predominantly overweight or obese?
- The data demonstrate that pts with CD are significantly more likely to gain at least 2kg (4.4 lbs) over a 6-month period compared to a similarly overweight/obese population without clinical CD, independent of the use of insulin in the setting of diabetes mellitus.
- A weight increase of ≥2kg can potentially allow weight to continue to be used as a helpful sign of CD despite increasing incidence of obesity.
- Collectively, these data suggest value in using weight trajectories, rather than absolute BMI, as a clinical variable when assessing the pretest probability of CD.

	CD	NF-ACTH+
Age (mean)	45.9 yrs	54.2 yrs
Sex	86% female	50% female
BMI	34.5 kg/m^2; >90% pts had BMI >25 kg/m^2	33.8 kg/m^2; >90% pts had BMI >25 kg/m^2
Median weight change in 6 months prior to surgery	2.5 kg	-0.5 kg
% gained weight in 6 months before surgery	77%	43%
>2 Kg	56.4%	21.4%
>3 Kg	46%	14.3%

Thavaraputta S et al. Weight Trajectory as a Predictor of Cushing's Disease. *J Endo Soc* 2022; 6 (suppl 1): A517-A518.

Bone Health in Adrenal Disorder Patients

- **The aim of this investigation was to determine the impact of cortisol and aldosterone excess on bone density.**
- **Preliminary analysis of data conducted from multicenter, prospective observational study of adult pts with adrenocortical hormone excess & referent subjects w/out adrenal disorders (January 2019 - March 2022).**
- **Pts were diagnosed with non-functioning adenoma (NFA), Mild adrenal Cushing syndrome (MACS, defined as cortisol following an overnight 1-mg dexamethasone suppression test [DST]>1.8 mcg/dL), overt adrenal or pituitary Cushing syndrome (CS), primary aldosteronism (PA), and concomitant PA-MACS. Referent subjects were pts undergoing cross-sectional imaging for reasons other than adrenal disease.**
- **All pts interviewed about bone health, and had bone density measurements. Bone disease was defined as osteopenia (T-score -1.1 to -2.4), or osteoporosis (T-score < -2.5).**
  - **A total of 417 participants, including 156 referent subjects and 261 pts.**
  - **Pts were diagnosed with NFA (51, 19%), PA (46, 17%), MACS (122, 47%), PA-MACS (12, 5%), and Cushing's syndrome (30, 12%).**
- **Overall, the prevalence of osteopenia and osteoporosis appears to increase proportionally to the increase in post-DST cortisol concentrations. Pts with Cushing's syndrome, and those with MACS and post-DST cortisol > 5mcg/dL have the highest prevalence of bone disease.**

When compared to referent subjects, sex- and age-adjusted analysis demonstrated an increased prevalence of bone disease only in pts with CS, but not in other adrenal disorders.

After excluding pts with CS, those with post-DST cortisol >5 mcg/dL demonstrated a higher prevalence of bone disease when compared to pts with post-DST cortisol between 1.8-5 mcg/dL and those with post-DST cortisol <1.8 mcg/dL.

Pts with MACS and post-DST cortisol between 1.8-5 mcg/dL did not demonstrate increased sex and age-adjusted prevalence of bone disease compared to those with post-DST <1.8 mcg/dL or referent subjects.

However, using post-DST cortisol as a continuous variable, and adjusting for sex and age, the risk of bone disease in pts increased by 13% for every 1 mcg/dL increase in post-DST cortisol.

Dogra P et al. Bone Health in Patients with Adrenal Disorders. *J Endo Soc* 2022; 6 (suppl 1): A151.

IPSS For Predicting Tumor Lateralization **

There were no cases where BIPSS lateralization was correct when MRI lateralization was incorrect.

- In 22/27 (81%) pts, the result of the IPSS lateralization was concordant with MRI findings.
- When MRI and BIPSS lateralization agreed, 21/22 (95%) were confirmed by surgical pathology.
- Of 5 cases with discordant MRI and BIPSS laterality, the operative report was consistent with MRI lateralization in 3/5; 2 bilateral.
- Overall, MRI correctly lateralized 26/27 cases (96%), whereas BIPSS correctly lateralized 23/27 (85%).
- Of 13 pts with tumors measuring <6mm on, MRI lateralization was correct in all 13 (100%) cases; BIPSS lateralization in 11/13 (85%).
- Adverse events associated with BIPSS were noted in 4 pts (15%) ranging from hematoma to headache.
- Among the 5 pts who did not have successful BIPSS cannulization, 1 experienced transient severe headache.

- There is controversy surrounding the value of bilateral IPSS (BIPSS) for tumor lateralization in Cushing disease.
- The aim of this investigation is to compare lateralization results between BIPSS and pituitary imaging against gold-standard surgical localization.
- A retrospective chart review was conducted in pts with pathology-confirmed Cushing disease, visible tumor on MRI (with and without contrast), and who underwent BIPSS between 2003-2020.
- Of 32 pts with Cushing disease, visible tumor on MRI, and BIPSS testing, 27 (84%) pts had technically successful BIPSS catheterization and are the subjects of this study.
- When a tumor is visible on MRI, regardless of its size (≥ 3mm), BIPSS did not add to the accuracy of determining tumor lateralization. Further studies are required to determine the value of BIPSS in lateralizing the source of CD in pts without visible tumor.

Lundholm MD et al. In Patients with Cushing's Disease and a Visible Tumor on MRI, IPSS Does Not Add to the Accuracy of Predicting Tumor Lateralization. *J Endo Soc* 2022; 6 (suppl 1): A542-A543.

What Androgens are Responsible for Hyperandrogenemia in Cushing disease?

- **Symptoms of hyperandrogenism are common in patients with CD, but they cannot be sufficiently explained by measured concentrations of circulating conventional androgens.**
- **This study included 23 females with CD (treatment naïve), 26 female controls, and females with CD treated with metyrapone or osilodrostat (5 each). Patients' saliva was tested for cortisol and cortisone; the conventional androgens androstenedione (A4) and testosterone (T); and the 11-oxygenated C19-steroids (11oxC19) 11-hydroxyandrostenedione (11OHA4) and 11-ketotestosterone (11KT) by liquid chromatography tandem mass spectrometry. Morning baseline levels of serum gonadotropins and estradiol, sex hormone-binding globulin, cortisol and dehydroepiandrosterone sulfate (DHEAS) were obtained as in serum and adrenocorticotropic hormone in plasma.**
- **Treatment naïve females with CD showed significantly elevated area under the curve (AUC) of saliva 11OHA4 and 11KT throughout the day compared to controls, whereas A4, T and DHEAS were comparable to controls.**
- **Patients with more symptoms of hyperandrogenism displayed higher concentrations of 11oxC19 androgens and had significantly lower SHBG concentrations.**
- **Treatment with osilodrostat and metyrapone efficaciously blocked 11oxC19 synthesis. In metyrapone but not in osilodrostat treatment a trend towards increased concentrations of T and significantly increased A4-concentrations were observed.**

Adaway Jet al. 11-Oxygenated C19 Steroids Are the Predominant Androgens Responsible for Hyperandrogenemia in Cushing's Disease . *J Endo Soc* 2022; 6 (suppl 1): A524-A525.

Clinical Trials

Osilodrostat

- Oral inhibitor of 11β-hydroxylase – enzyme responsible for catalyzing final step of cortisol synthesis
- Decreases cortisol production
- Increases adrenal hormones proximal to blockade
- LINC-3 and LINC-4 clinical trial data presented at ENDO 2022 & JES

Osilodrostat – LINC 3: Long-Term Results

- **Long term evaluation found adrenal hormone levels frequently change upon initiation of osilodrostat but stabilize during long-term treatment. AEs associated with these changes can occur and are manageable without osilodrostat discontinuation.**
- These AEs should be closely monitored and treatment initiated as needed to achieve optimal patient outcomes.

Adrenal hormone precursor accumulation-related AEs		
Occurred in	58.4% (80/137) pts	
Managed w/ additional therapy	36.5% (50/137)	
Led to discontinuation	1.5% (2/137)	
Most common adrenal hormone precursor accumulation-related AEs		
	% (n)	Managed w/ concomitant med.
Hypertension	17.5% (24/137)	17/24
Peripheral edema	16.1% (22/137)	6/22
Hypokalemia	13.1% (18/137)	14/18

	Week 48	Week 72
Mean DHEAS levels		
Females	1.6 µmol/L	1.0 µmol/L
Males	3.4 µmol/L	3.0 µmol/L
Hirsutism scores		
Improved	34.2% (26/76)	34.4% (22/64)
Stabilized	48.7% (37/76)	51.6% (33/64)
Testosterone levels		
Males	**Stabilized, after initial increase in core phase**	
Females	**Decreased towards baseline levels, after initial increase in core phase**	
Aldosterone levels		
	Decreased and stabilized	

Fleseriu M et al. Effect of Osilodrostat on Androgens and Adrenal Hormones in Patients With Cushing's Disease: Long-Term Findings From the Phase III, Prospective LINC 3 Study. *J Endo Soc* 2022; 6 (suppl 1): A546-A547.

Osilodrostat – LINC 3: Comorbidities

mUFC+LNSC controlled				
Weight	Systolic BP	Distolic BP	FPG	HbA1c
-5.9 kg	-14.4 mmHg	-8.6 mmHg	-16.9 mg/dL	-0.4%

LNSC controlled				
Weight	Systolic BP	Distolic BP	FPG	HbA1c
-2.2 kg	-7.4 mmHg	-8.2 mmHg	-15.0 mg/dL	-0.9%

mUFC controlled				
Weight	Systolic BP	Distolic BP	FPG	HbA1c
-.3.3 kg	-8.0 mmHg	-4.8 mmHg	-4.8 mg/dL	-0.3%

mUFC+LNSC uncontrolled				
Weight	Systolic BP	Distolic BP	FPG	HbA1c
-3.8 kg	-3.0 mmHg	-4.0 mmHg	-11.0 mg/dL	0.0%

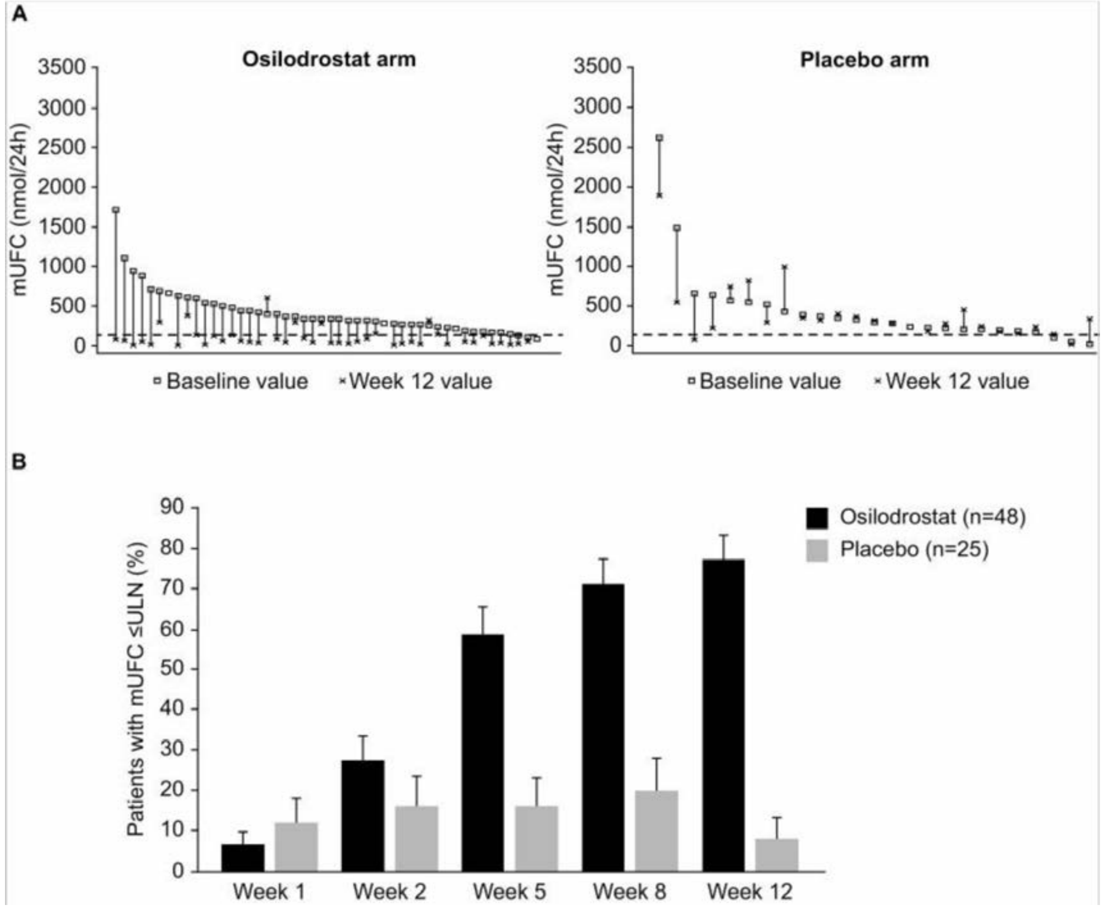
- **The goal of this investigation was to explore cardiovascular/metabolic-related parameters, physical features and health related QoL according to mUFC and/or LNSC control.**
- Analyses presented for pts w/ both mUFC and LNSC assessments, defined as:
  - both mUFC+LNSC controlled
  - only mUFC controlled
  - only LNSC controlled
  - both mUFC+LNSC uncontrolled
- **CushingQoL/BDI-II scores improved from baseline to Week 48 irrespective of mUFC and/or LNSC control**.
- **At Week 48, over half the evaluable pts had both mUFC+LNSC controlled following osilodrostat treatment**. Improvements in clinical signs of hypercortisolism and health related QoL occurred irrespective of mUFC and/or LNSC control; however, **for some clinical outcomes, improvements were greater in pts with both mUFC+LNSC controlled.**

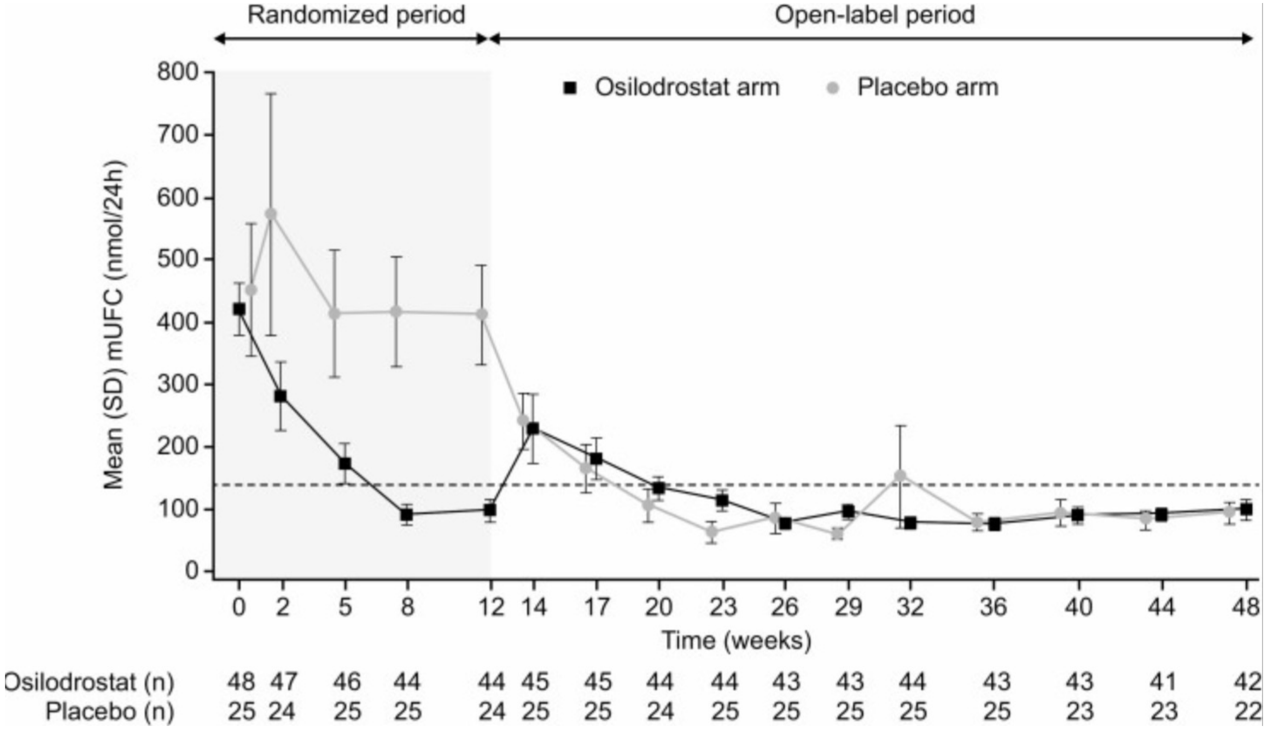
Biller BMK et al. Improvements in Clinical Signs of Hypercortisolism and Quality of Life According to Urinary and Late-Night Salivary Cortisol Levels in Patients with Cushing's Disease Treated with Osilodrostat. *J Endo Soc* 2022; 6 (suppl 1): A545.

Osilodrostat – LINC 4

- Study design:
  - 12-week, randomized, double-blind, placebo-controlled period
  - 36 weeks of open-label osilodrostat
  - Optional extension phase in adults with Cushing's disease and mUFC >1.3xULN
    - * Of 65 pts completing Week 48, 60 entered the extension
    - * Dose adjustments were permitted based on efficacy/tolerability (range during open-label treatment 1–30 mg bid)
    - * Ended when all pts transitioned to a separate long-term safety study or discontinued treatment
- Cardiovascular/metabolic-related parameters, physical features of hypercortisolism, and CushingQoL score evaluated at core baseline, every 2, 4, 12, or 24 weeks (depending on study phase/parameter) and at EoT extension visit.
- Numerous abstracts at ENDO but also recently published in peer reviewed journal

LINC 4 Efficacy Results: *J Clin Endocrinol Metab*





Gadelhiet al. Randomized trial of osilodrostat for the treatment of Cushing disease. *J Endocrnol Metab* 2022; 107: e2882-e2895. Creative Commons licence.

LINC 4 Results: CV Risk Factors and QoL

- Median osilodrostat exposure from core baseline to study end: 87.1 weeks; median average dose: 4.6 mg/day.
- **Physical features of hypercortisolism improved or remained stable from core baseline to end-of-treatment in most pts.**
- **Most cardiovascular/metabolic-related parameters continued to improve during long-term osilodrostat treatment.**

Cardiovascular/Metabolic-related Parameters			
	Baseline	Mean Change at Week 48	Mean Change at EoT
Systolic BP (mmHg)	131.5	-9.7	-12.4
Diastolic BP (mmHg)	87.5	-4.2	-5.6
FPG (mg/dL)	95.3	-3.1	-3.5
Cholesterol (mmol/L)	5.5	-0.5	-0.6
Weight (kg)	78.8	-4.3	-6.8
Waist Circum. (cm)	102.8	-4.5	-7.6
QoL Parameter			
	Baseline	Mean Change at Week 48	Mean Change at EoT
CushingQoL score	51.8	12.0	17.1

Feelders R et al. Osilodrostat Provides Sustained Clinical Benefits and Improves Health-Related Quality of Life in Patients with Cushing's Disease: Results from the Phase III LINC 4 Study. *J Endo Soc* 2022; 6 (suppl 1): A546.

LINC 4 Results: Clinical Features

% of Pts for Which Features of Hypercortisolism Improved or Stabilized		
	Improved	**Stable**
Ecchymosis	21% (10/48)	79% (38/48)
Striae	26% (12/46)	72% (33/46)
Hirsutism	29% (11/38)	61% (23/38
Muscle weakness	33% (16/49)	61% (30/49)
Facial rubor	48% (23/48)	46% (22/48)
Central obesity	55% (27/49)	37% (18/49)
Fat pads (dorsal)	58% (28/48)	31% (15/48)
Fat pads (supraclavicular)	65% (32/49)	35% (17/49)

- **Most physical features of hypercortisolism, including hirsutism, either improved or remained stable.**
- **Osilodrostat is an effective treatment that may alleviate disease burden for many pts with Cushing's disease.**

Feelders R et al. Osilodrostat Provides Sustained Clinical Benefits and Improves Health-Related Quality of Life in Patients with Cushing's Disease: Results from the Phase III LINC 4 Study. *J Endo Soc* 2022; 6 (suppl 1): A546.

LINC 4 Long-Term Cortisol Control

- **Osilodrostat provided long-term control of cortisol production during LINC 4.**

	Baseline	Week 48	Week 72	EoT
% of pts with normal mUFC (≤138 nmol/24h)	N/A	68.5% (50/73)	61.5% (40/65)	72.4% (42/58)
Median mUFC	2.5xULN	0.5xULN	0.5xULN	0.4xULN
Median LNSC	2.8xULN	1.2xULN	1.2xULN	1.1xULN
Median ACTH	1.1xULN	3.0xULN	3.6xULN	3.5xULN

Auchus RJ et al. Long-Term Results from the Phase III LINC 4 Study: Osilodrostat Maintained Normal Mean Urinary Free Cortisol in Patients with Cushing's Disease, with a Favorable Safety Profile. *J Endo Soc* 2022; 6 (suppl 1): A525-A526.

LINC 4 Long-Term Results: AEs

Most common AEs (Entire Study)	
Decreased appetite	46.6%
Arthralgia	45.2%
Fatigue	39.7%
Nausea	37.0%
Headache	34.2%
Dizziness	30.1%
Hypocortisolism-/adrenal-hormone-precursor AEs	
Hypocortisolism-related AEs	28.8% (21/73)
Adrenal-hormone-precursor-accumulation-related AEs	61.6% (45/73)
Additional AEs of interest	
Hirsutism	(1/73)
Acne	(0/73)

** most AEs were grade 1/2 and resolved w/ dose reduction/interruption and/or concomitant medication

Median change in pituitary tumor volume from core baseline to last available assessment was **4.0 mm³**

- Pituitary-tumor-enlargement-related AEs led to drug discontinuation in 2 during the core and in and 0 pts extension.
- No trend was observed between tumor volume change and osilodrostat dose.

- **Fewer AEs related to hypocortisolism and accumulation of adrenal-hormone-precursors occurred during the extension than during the core.**
- Overall, **osilodrostat is an effective and well-tolerated long-term treatment option for pts with Cushing's disease**.

Auchus RJ et al. Long-Term Results from the Phase III LINC 4 Study: Osilodrostat Maintained Normal Mean Urinary Free Cortisol in Patients with Cushing's Disease, with a Favorable Safety Profile. *J Endo Soc* 2022; 6 (suppl 1): A525-A526.

Osilodrostat – ILLUSTRATE

- Retrospective chart review study. Analyzed confirmed endogenous Cushing syndrome pts who initiated osilodrostat treatment May 1, 2020 - October 29, 2021.

- 42 adult pts with endogenous Cushing syndrome and a prescription for osilodrostat were included in this real-world study.

Osilodrostat – ILLUSTRATE: Cushing Disease

- Aim of this investigation was to present osilodrostat dosing and titration information from real-world cohort of endogenous Cushing syndrome pts. Part 1 focused on Cushing disease.
- **33.34% (11/34) of pts were initiated on a dose <4 mg/day (lower than starting dose previously used in clinical trials).**
    - Of 16 pts initiated at 4 mg/day, 4 (25%) required interruption or down-titration and 5 (31%) remained on the initial dose throughout the observation period.
- Overall, consistent with prior research data, **pts with a gradual dose up-titration (i.e., prolonged titration interval) tended to have greater persistence with therapy**. There were **no new safety findings**.

Ioachimescu AG et al. Dosing And Titration Of Osilodrostat In A Real-world Cohort of US Patients with Endogenous Cushing's Disease: Analysis of the ILLUSTRATE Study. *J Endo Soc* 2022; 6 (suppl 1): A473-A474.

Osilodrostat – ILLUSTRATE: Cushing Disease

In CD pts (n=34)		
Dosing		
Mean total daily starting dose	3.4 mg	
Initiated on 1 mg BID	27% (9/34)	
Initiated on 2 mg BID	62% (21/34)	
Initiated on 3 mg BID	3% (1/34)	
Initiated on 1 mg QD	3% (1/34)	
Initiated on 2 mg QD	3% (1/34)	
Initiated on 4 mg QD	3% (1/34)	
Treatment persistence those enrolled ≥6 months prior to study end	95.8%	
Mean duration of therapy	339.2 days	
In pts w/ multiple clinical encounters (n=26)		
Initiated at 4 mg/day (2 mg/BID)	16/26	
Dose interrupted or down-titrated w/in 71 days of initiation	25% (4/16)	** 2/4 experienced hypocortisolism-related symptoms & permanently discontinued
Maintained on 4 mg/day	31% (5/16)	** mean treatment duration, 273 days
Dose up-titration	44% (7/16)	** initial dose increase was incremental (1-2 mg BID) for 6/7 *** mean time to up-titration was 78 days
Initiated at <2 mg BID	10/26	
Did not require dose reduction or interruption	60% (6/10)	** all had up-titration in small increments (1-2 mg/day) and/or first titration at ≥80 days.
Symptoms related to decreased cortisol levels reported	38% (10/26)	**included 3 pts with adrenal insufficiency and 7 pts with glucocorticoid withdrawal symptoms.

Ioachimescu AG et al. Dosing And Titration Of Osilodrostat In A Real-world Cohort of US Patients with Endogenous Cushing's Disease: Analysis of the ILLUSTRATE Study. *J Endo Soc* 2022; 6 (suppl 1): A473-A474.

Osilodrostat – ILLUSTRATE: Cushing Syndrome

- The **aim of this investigation was to report patient characteristics, osilodrostat dose, efficacy, and safety. Part 2 focused on the subset of patients with non-pituitary Cushing syndrome** (n=8/42; 19%).
- **Osilodrostat was generally well tolerated**.
  - 1 ectopic Cushing syndrome patient had treatment interrupted on day 214 for adrenal insufficiency.
  - 2/5 adrenal Cushing syndrome pts had symptoms suggestive of glucocorticoid withdrawal (e. g., fatigue, nausea, and headache) and 1 had an interruption in therapy. Neither had documented adrenal insufficiency.
- In this real-world cohort of pts treated with osilodrostat for non-pituitary Cushing's syndrome, large UFC reductions were seen in 2 pts with ectopic Cushing syndrome.
- **All 8 Cushing syndrome pts were initiated on ≤2 mg BID, with 3 (38%) remaining on their original dose. In the majority of those up-titrated, there was an extended titration interval. The observed safety profile in this subset of non-pituitary Cushing syndrome pts was consistent with the known osilodrostat safety profile.**

Ioachimescu AG et al. Dosing And Titration Of Osilodrostat In A Real-world Cohort of US Patients with Endogenous Cushing's Disease: Analysis of the ILLUSTRATE Study. *J Endo Soc* 2022; 6 (suppl 1): A473-A474.

Osilodrostat – ILLUSTRATE: Cushing's Syndrome

Non-pituitary CS pts	n = 8	Notes
Adrenal CS pts	n = 5	
Starting dose range	1-4 mg/day	
Adrenal CS pts w/ >1 documented clinical encounter	n = 4	
Remained on starting doses	n = 2	starting doses: 1 mg BID, 2 mg BID, respectively
Increased doses	n = 2	1 increased from 1 mg QD to 2 mg BID on day 50 1 increased from 2 mg BID to 4 mg BID on day 5 & required down-titration on day 18 w/ treatment interruption on day 27.
Ectopic CS pts	n = 3	
Starting dose	2 mg BID	
Doses unchanged	n = 1	
Doses up-titrated	n = 2	both on day 91; to 4 mg BID & 5 mg BID, respectively
Pts with available UFC data	n = 3	
Adrenal CS	n = 1	maintained UFC ≤ ULN during osilodrostat treatment
Ectopic CS	n = 2	experienced substantial UFC reductions (57.1×ULN to 2.9×ULN at day 91; 75.2×ULN to 0. 076×ULN at day 134).

Ioachimescu AG et al. Dosing And Titration Of Osilodrostat In A Real-world Cohort of US Patients with Endogenous Cushing's Disease: Analysis of the ILLUSTRATE Study. *J Endo Soc* 2022; 6 (suppl 1): A473-A474.

Abiraterone Acetate - ABACUS Trial

- **Abiraterone acetate (AA) is an irreversible inhibitor of CYP17A1 enzyme. AA is used to treat patients with prostate cancer, in which it leads to suppression of cortisol and androgens.**
- **ABACUS is a Phase 2 study assessing the activity of AA to control cortisol excess in patients with advanced adrenocortical carcinomas and overt Cushing syndrome (N=17).**
- **Patients were treated with AA for a median of 17 days (7-163).**
- **The results of this proof-of-concept study show that AA looks promising and may be viewed as an additional weapon to manage Cushing syndrome in patients with advanced adrenocortical carcinomas.**

	Before AA treatment	After AA treatment
Median 24h UFC	386 ug/24h (121 – 7422)	94 ug/24h (20-1793)
Median Cushing's Syndrome Score	5.0 (2 - 8)	3.5 (1 – 6)

Abate A et al. Activity of Abiraterone Acetate in the management of Cushing syndrome associated to advanced adrenocortical carcinoma: results of the ABACUS trial. . *J Endo Soc* 2022; 6 (suppl 1): A82-A83.

Clinical Pearls

- Cushing syndrome (CS) is a rare endocrine disorder characterized by chronic hypercortisolism. Cushing disease (CD) is CS due to an ACTH-producing pituitary adenoma.
- There may be value in using weight trajectories, rather than absolute BMI, as a clinical variable when assessing the pretest probability of CD.
- DDAVP stimulation test may be a useful tool to assess distinguish CD from non-neoplastic hypercortisolemia.
- IPSS has limited utility for lateralizing the tumor in CD.
- 11-oxygenated C19 steroids may be primarily responsible for hyperadrenogenemia in Cushing disease.
- Overall, the prevalence of osteopenia and osteoporosis appears to increase proportionally to the increase in post-DST cortisol concentrations. Pts with Cushing's syndrome, and those with MACS and post-DST cortisol > 5mcg/dL have the highest prevalence of bone disease.
- Abiraterone may prove valuable in treating Cushing syndrome in advanced adrenocortical carcinoma.
- New data on recently approved therapies demonstrate safety, and efficacy, and durability with improvement of comorbidities, clinical features, and cardiovascular risk factors.