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

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ClinicalTrials.gov number: NCT02697734

MRC-E1033-20220714

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Disclosures

- Speaker fees from Novartis, Recordati, Ipsen, Pfizer, Crinetics Pharmaceuticals and Novo Nordisk
- Attended advisory boards for Novartis, Novo Nordisk, Recordati and Crinetics Pharmaceuticals

Background

- Cushing's disease is a rare disorder of chronic hypercortisolism that is associated with significant clinical burden, decreased QoL and increased risk of mortality[1]
- Many patients require long-term medical therapy to control their hypercortisolism and alleviate comorbidities associated with Cushing's disease[2]
- Osilodrostat, a potent oral 11β-hydroxylase inhibitor, normalized mUFC in most patients with Cushing's disease and was well tolerated during the 48-week LINC 4 core study (NCT02697734)[3]
  - A significantly greater proportion of patients achieved mUFC normalization at week 12 with osilodrostat versus placebo (77% vs 8%)

Here, we present final long-term efficacy and safety results from the LINC 4 study following completion of an optional extension period

1. Pivonello R *et al. Lancet Diabetes Endocrinol* 2016;4:611–29; 2. Pivonello R *et al. Endocr Rev* 2015;36:385–486; 3. Gadelha M *et al. J Clin Endocrinol Metab* 2022; doi: 10.1210/clinem/dgac178

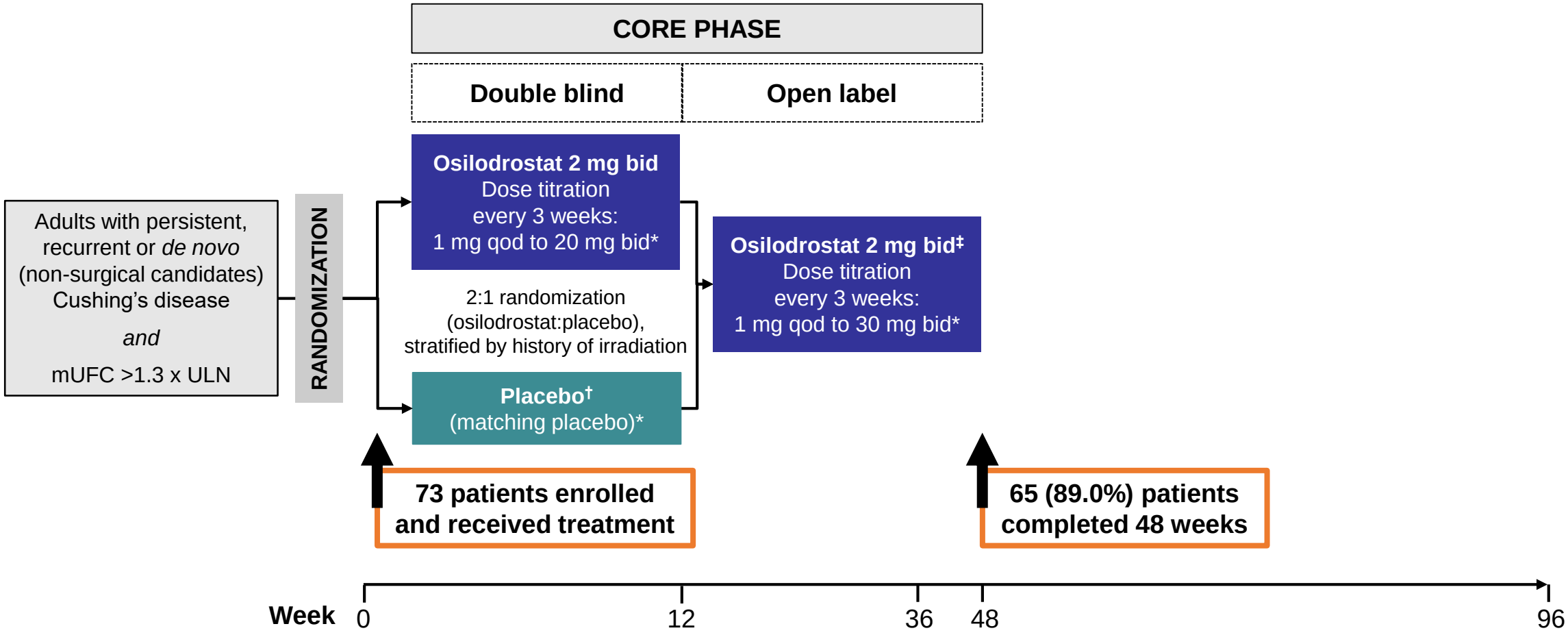
mUFC, mean urinary free cortisol; QoL, quality of life

Completed Phase II and Phase III clinical trials of osilodrostat for the treatment of Cushing's disease

	LINC 2 Phase II[1]	LINC 3 Phase III[2]	LINC 4 Phase III[3]
	22 weeks + optional extension **Open label** (expansion of LINC 1)	**48 weeks** + optional extension **8-week**, double-blind, **randomized withdrawal** (RW) period	**48 weeks** + optional extension **Initial 12-week**, double-blind, **randomized,** **placebo-controlled** period
	n=19 mUFC >1.5 x ULN	**n=137** mUFC >1.5 x ULN	**n=73** mUFC >1.3 x ULN
	78.9% of patients had mUFC ≤ULN or ≥50% reduction from baseline at week 22	**Significantly more patients** **(86.1% vs 29.4%; *P*<0.0001)** maintained mUFC ≤ULN with osilodrostat than placebo after RW	**Significantly more patients** **(77.1% vs 8.0%; *P*<0.0001)** achieved mUFC ≤ULN with osilodrostat than placebo at week 12
	Osilodrostat was generally **well tolerated**; AEs were as expected based on the mechanism of action of osilodrostat		

1. Fleseriu M *et al. Pituitary* 2016;19:138–48; 2. Pivonello R *et al. Lancet Diabetes Endocrinol* 2020;8:748–61;
3. Gadelha M *et al. J Clin Endocrinol Metab* 2022; doi: 10.1210/clinem/dgac178

Study design: Phase III study with an upfront, 12-week, randomized, double-blind, placebo-controlled phase



*Dose adjustments to normalize mUFC or to address safety reasons were permitted; decisions were made by non-blinded independent endocrinologists up to week 12. Dose-titration sequence: 2 mg bid → 5 mg bid → 10 mg bid → 20 mg bid (maximum dose in double-blind phase) → 30 mg bid (maximum dose in open-label phase). Doses below 2 mg bid (1 mg bid, 1 mg qd, 1 mg qod) were allowed if necessary; †The placebo arm had simulated dose titrations to maintain blinding; ‡All patients on doses of ≥2 mg bid started open-label osilodrostat 2 mg bid at week 12, while patients on <2 mg bid continued on their most recent dose. Patients who discontinued treatment at any time or completed the core phase and did not enter the extension phase completed a post-treatment follow-up 30 days after their last dose

bid, twice daily; qd, every day; qod, every other day; ULN, upper limit of normal

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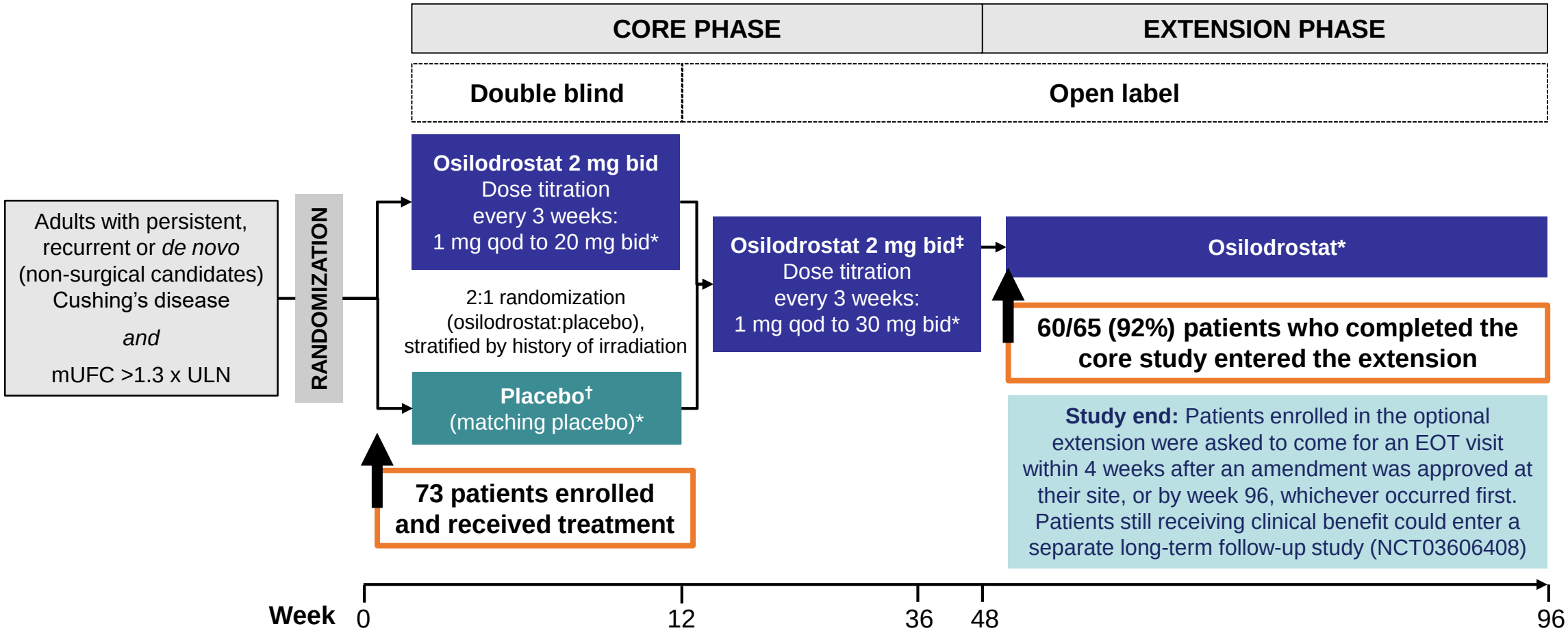

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EOT, end of treatment

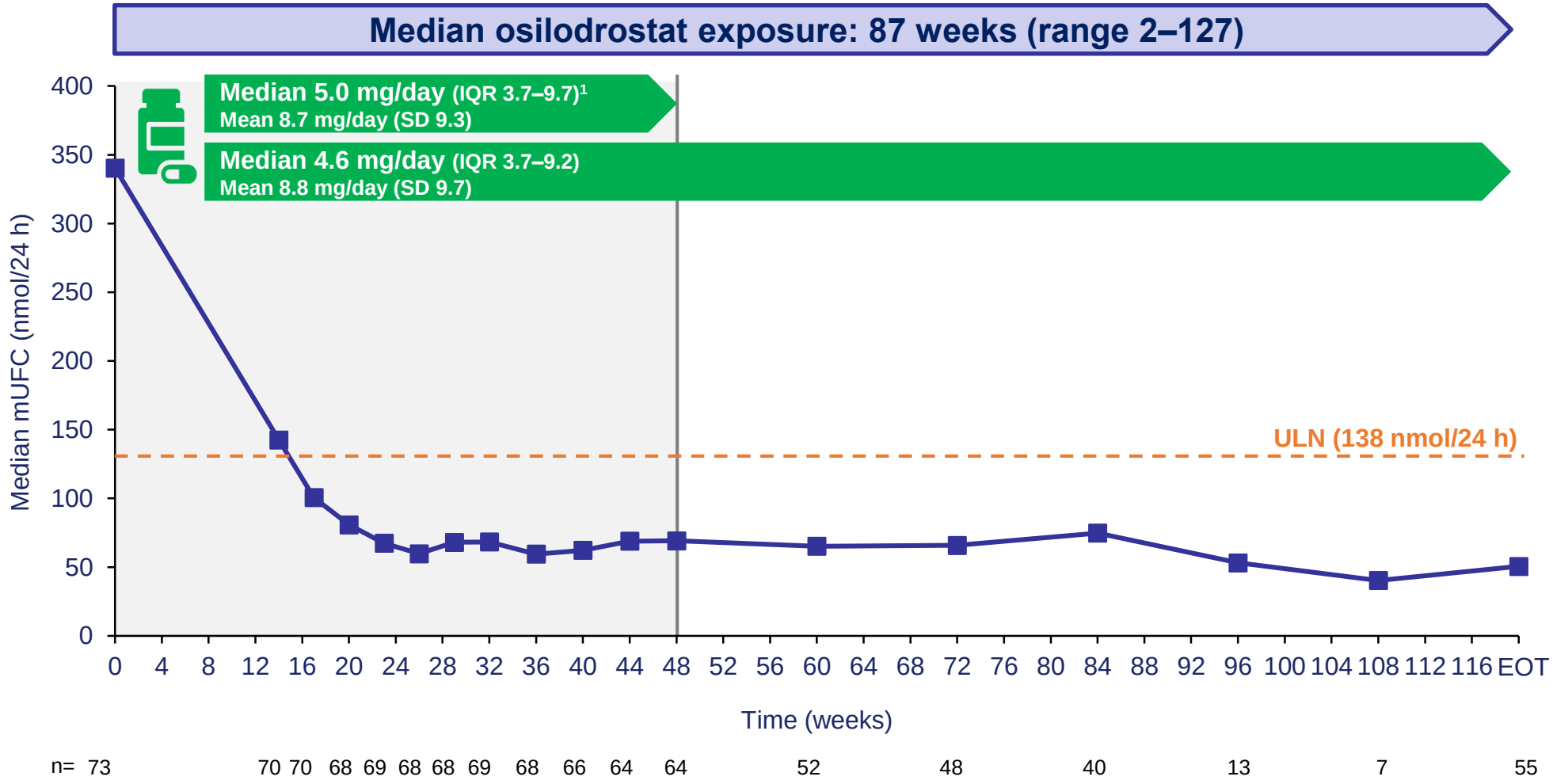
Patient demographics and baseline characteristics

	All patients, N=73
Median age, years (range)	39.0 (19.0–67.0)
Female, n (%)	61 (83.6)
Median time since diagnosis, months (range)	67.4 (26.4–93.8)
Cushing's disease status, n (%) Persistent/recurrent *De novo*	 70 (95.9) 3 (4.1)
Previous pituitary surgery, n (%)	64 (87.7)
Previous medical therapy for Cushing's disease, n (%)	45 (61.6)
Previous pituitary irradiation, n (%)	9 (12.3)
mUFC, nmol/24 h Mean (SD) Median (range)	 434 (388) [3.1 x ULN] 340 (21–2607) [2.5 x ULN]

mUFC calculated as the mean of two samples collected immediately before study visit. ULN for mUFC = 138 nmol/24 h

SD, standard deviation

mUFC over time and osilodrostat average daily dose

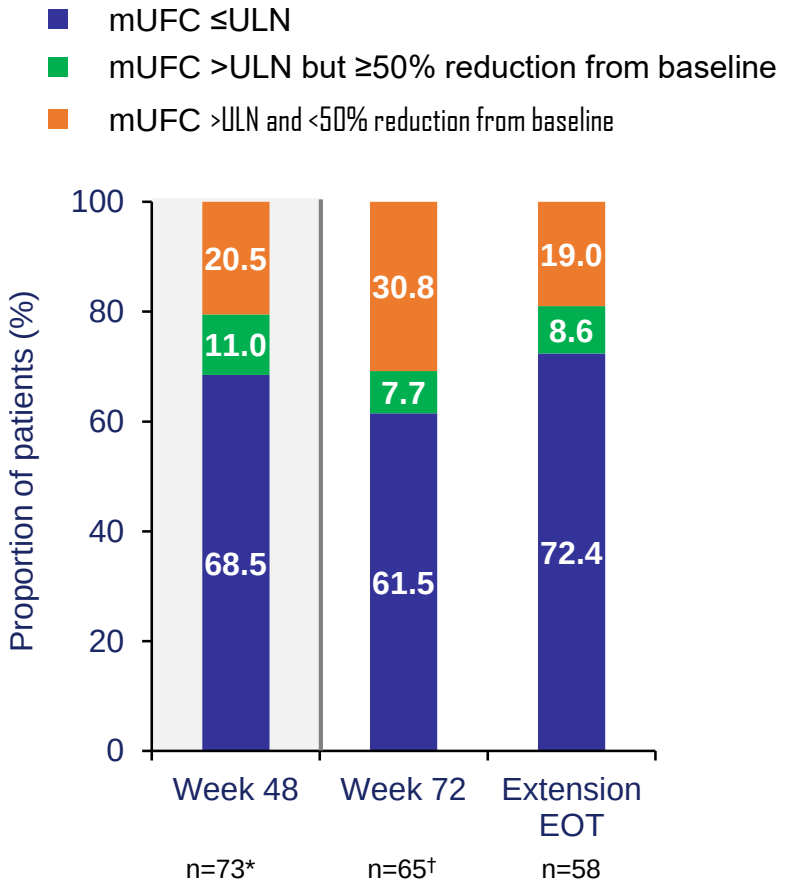


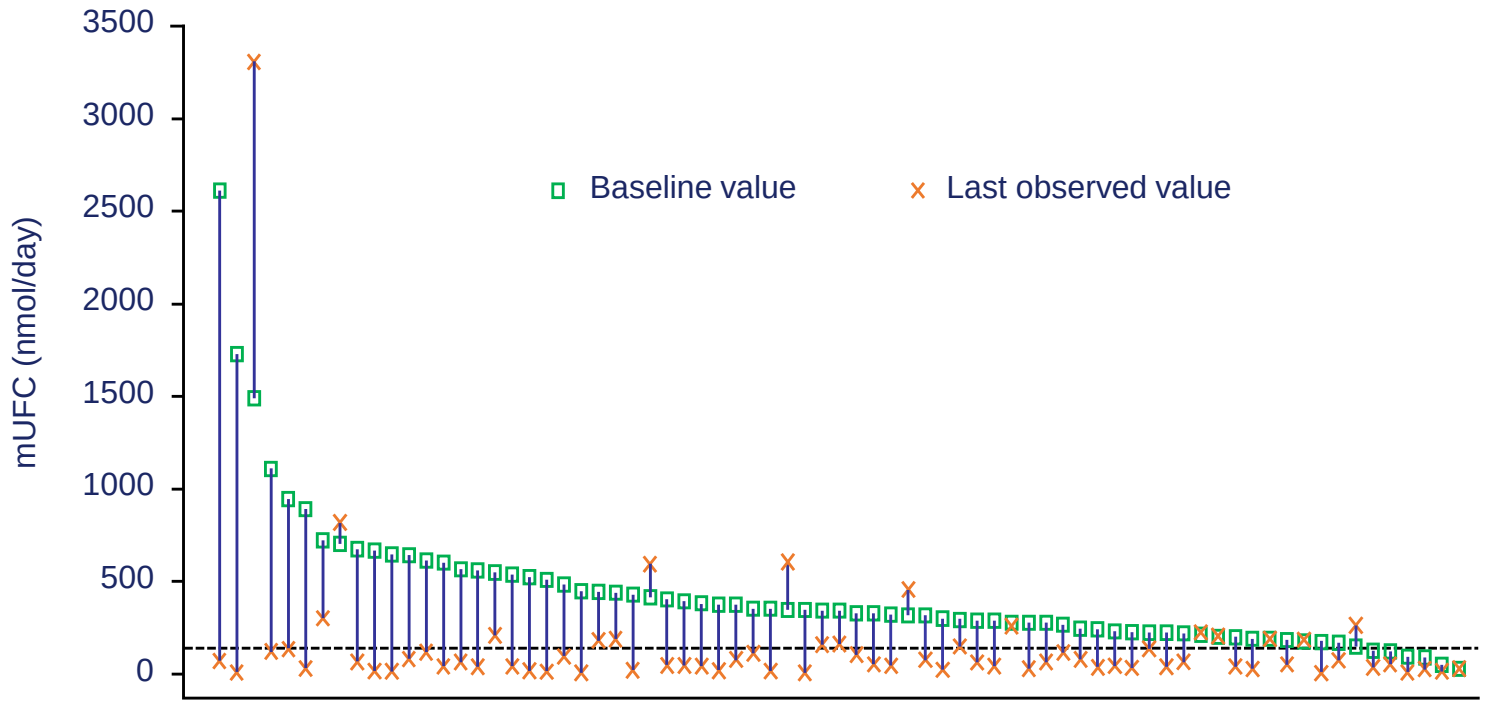
n is the number of patients who contributed to the mean; shaded area represents the 48-week core phase; excludes data in placebo arm collected during placebo-control period. Mean osilodrostat exposure: 81 weeks (SD 29)

1. Gadelha M *et al. J Clin Endocrinol Metab* 2022; doi: 10.1210/clinem/dgac178

IQR, interquartile range

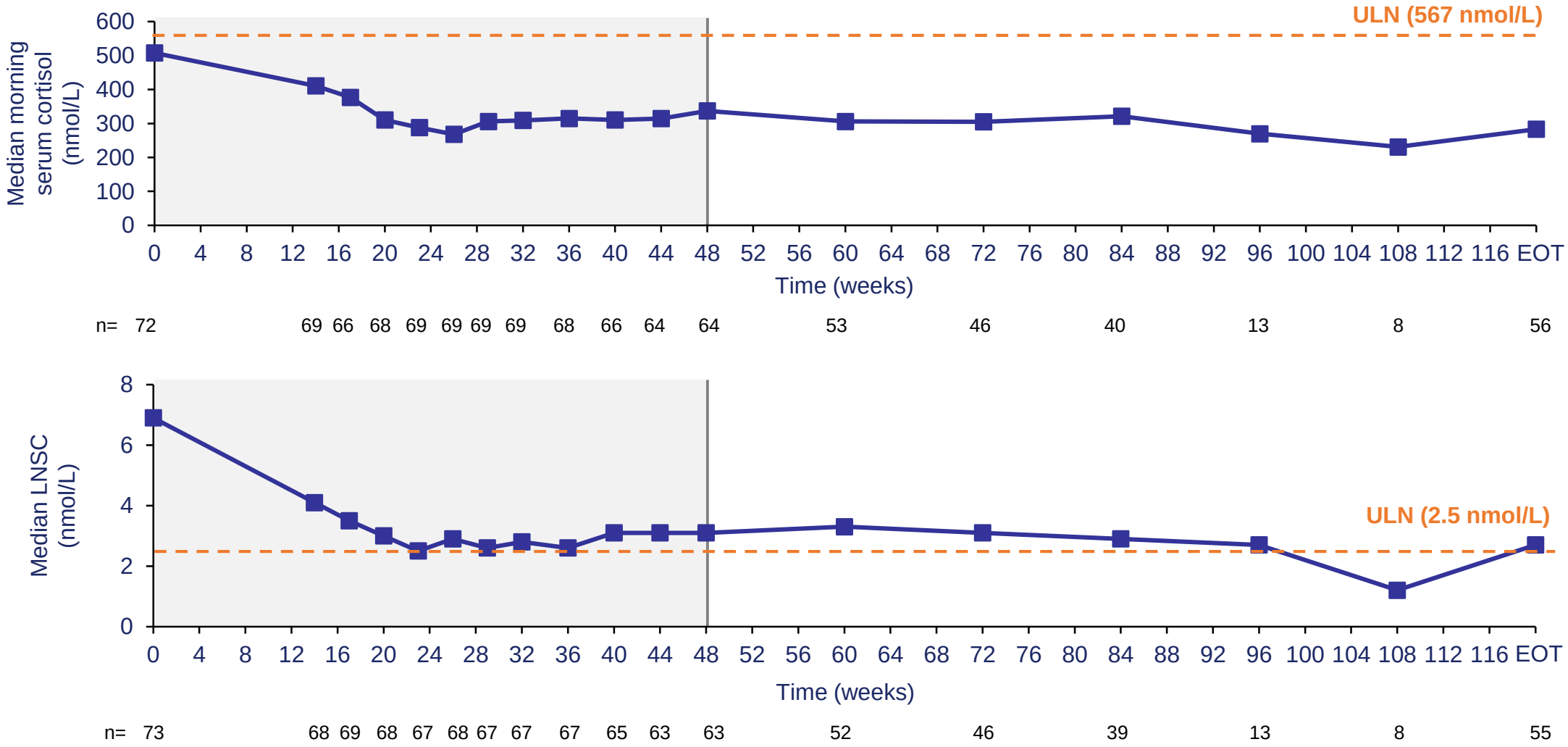
Proportion of mUFC responders over time and individual patient mUFC change from study baseline to last visit





Patients with missing mUFC at any visit were counted as non-responders. Shaded area represents the 48-week core phase; excludes data in placebo arm collected during placebo-control period. *The proportion of patients with mUFC ≤ULN at week 48 was calculated using the full analysis set (patients who had discontinued treatment were classified as non-responders); †Beyond week 48, patients who completed the extension were included in the denominator until their individual EOT visit (patients who discontinued treatment prior to week 72 were classified as non-responders at this time point)

Median serum cortisol and LNSC over time



n is the number of patients who contributed to the mean; shaded area represents the 48-week core phase

LNSC, late-night salivary cortisol

Adverse events (>20% of all patients)

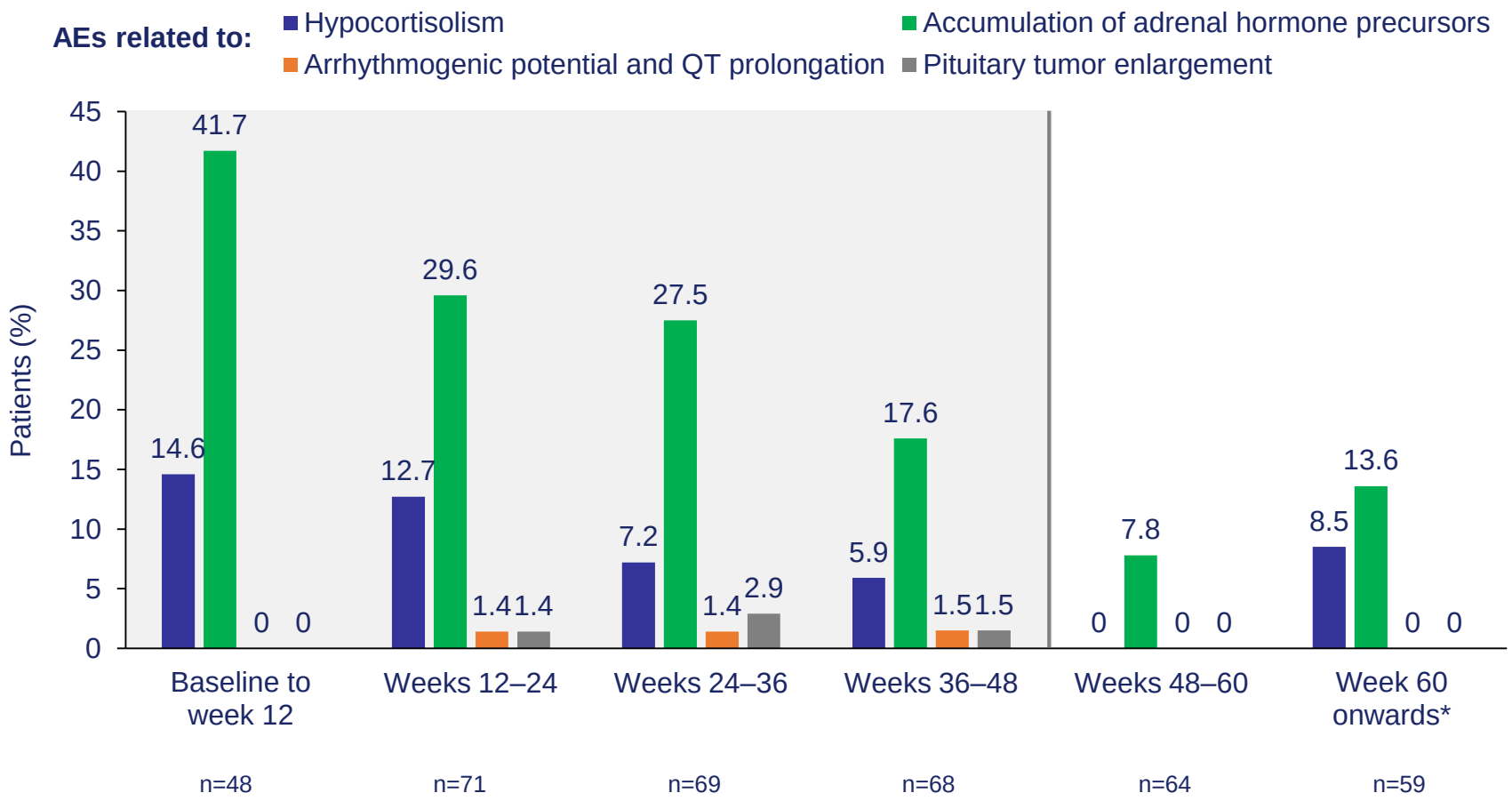
Median osilodrostat exposure: 87 weeks (range 2–127)

	All patients, N=73	
	All grades, n (%)	Grade ≥3, n (%)
Decreased appetite	34 (46.6)	1 (1.4)
Arthralgia	33 (45.2)	2 (2.7)
Fatigue	29 (39.7)	3 (4.1)
Nausea	27 (37.0)	1 (1.4)
Headache	25 (34.2)	1 (1.4)
Dizziness	22 (30.1)	0
Adrenal insufficiency	19 (26.0)	3 (4.1)
Increased blood testosterone	18 (24.7)	0
Myalgia	18 (24.7)	5 (6.8)
Asthenia	17 (23.3)	2 (2.7)
Diarrhea	17 (23.3)	0
Hypertension	16 (21.9)	9 (12.3)
Upper respiratory tract infection	16 (21.9)	0

Overall, 9/73 (12.3%) patients discontinued the study because of an AE*

*Adverse events (AEs) leading to discontinuation included adrenal insufficiency (n=3), pituitary tumor (n=2), hyperbilirubinemia (n=1), hypokalemia (n=1), arthralgia (n=1), headache (n=1), and depression (n=1); patients can have experienced more than one AE that led to discontinuation

Occurrence of AEs of special interest by time interval

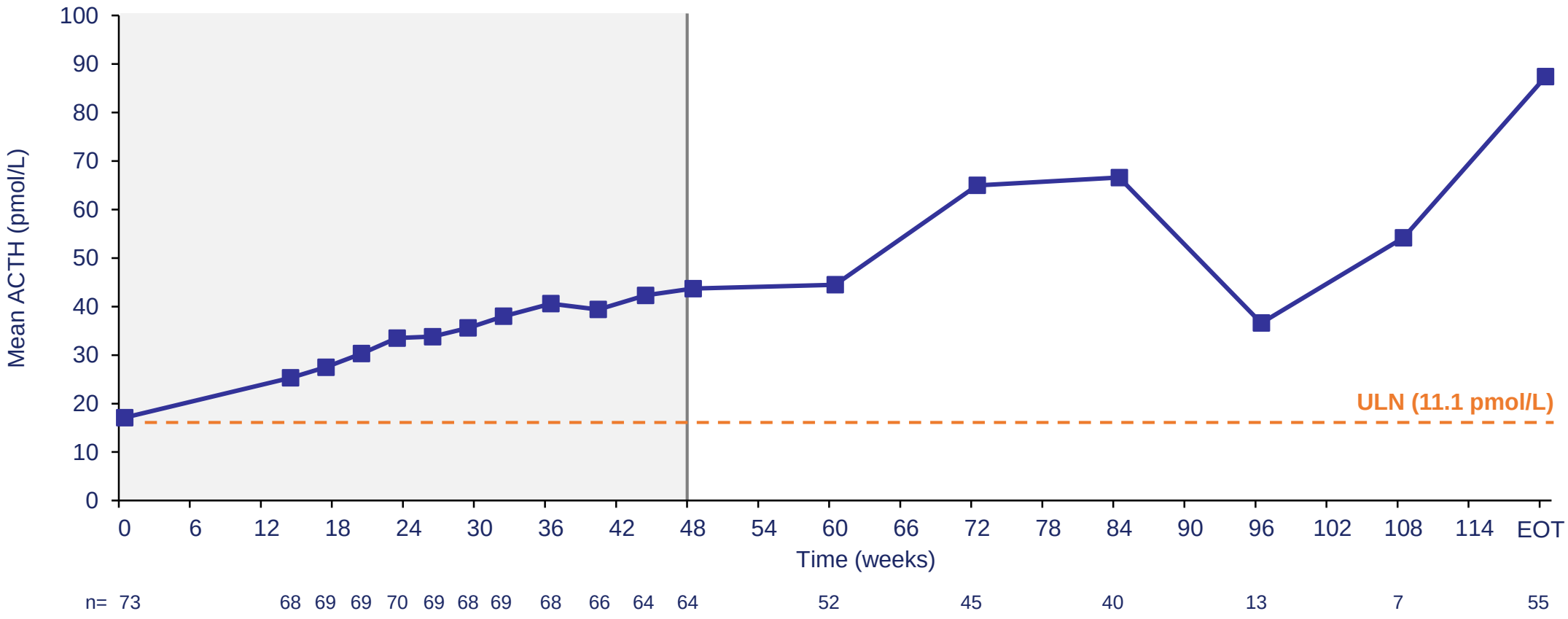


Few patients discontinued because of AEs related to hypocortisolism (n=3) or accumulation of adrenal hormone precursors (n=1)

After week 48, only one patient had new/worsening hirsutism (reported as an AE)

n for each time period only included patients who had at least one scheduled visit, or at least one observed AE, during that period. A patient with multiple occurrences of an AE within the same period is counted only once in that period; however, if an AE ends and occurs again in different period, it is counted in both periods. Excludes data in placebo arm collected during placebo-control period. Shaded area indicates the core phase. *Maximum duration of follow-up was 127 weeks

ACTH levels over time

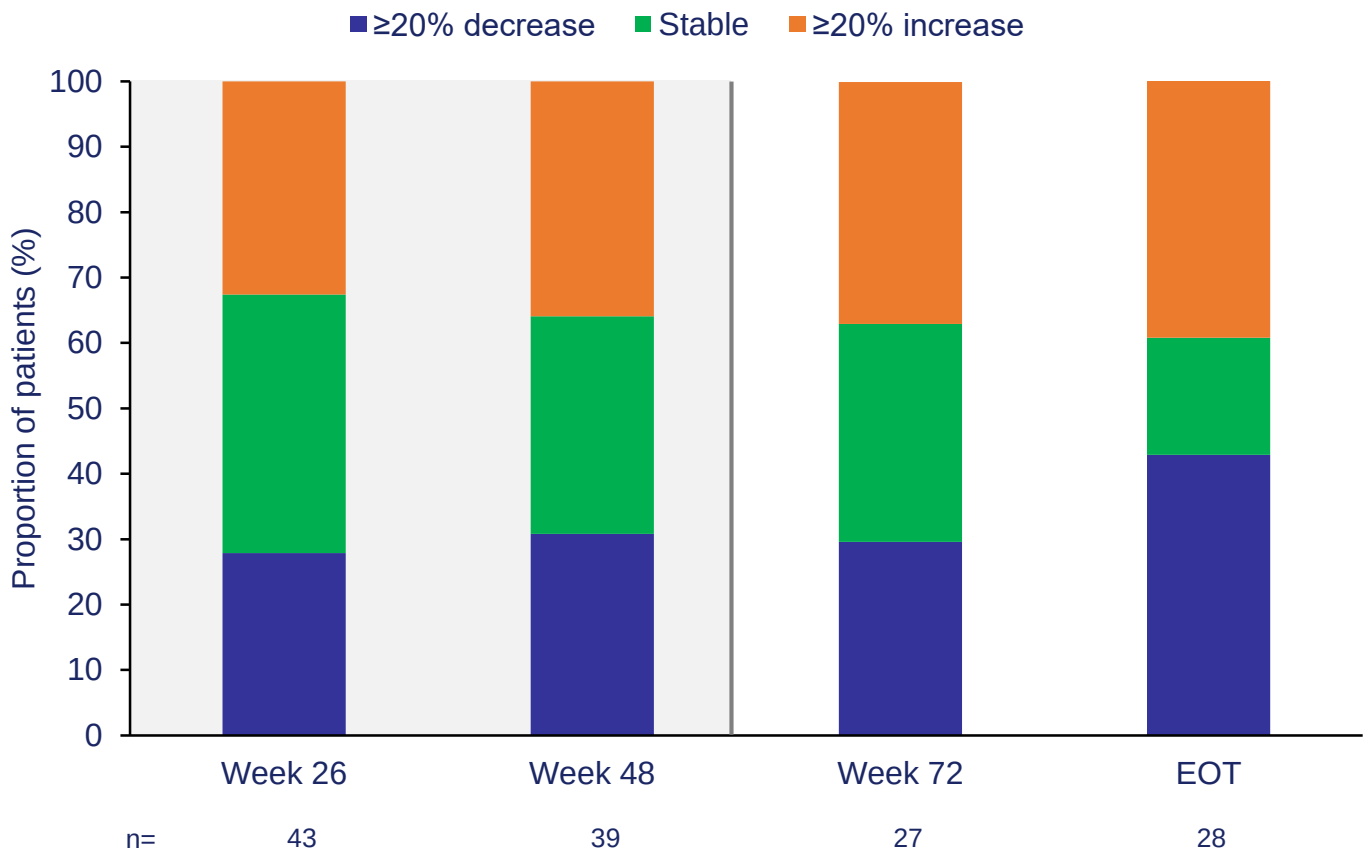


n is the number of patients who contributed to the mean; shaded area indicates the core phase

ACTH, adrenocorticotropic hormone

Change in tumor volume over time

Median change in pituitary tumor volume from baseline to last visit: 4.0 mm^3 (range −377–1776)



No trend was observed between change in tumor volume and osilodrostat dose

Two patients discontinued because of an AE related to pituitary tumor enlargement, both during the 48-week core phase

n is the number of patients with evaluable assessments. Shaded area indicates the core phase. The proportion of patients with a ≥20% decrease, ≥20% increase or <20% change (stable) in tumor volume (by MRI) was calculated based on the proportion of patients with an evaluable assessment at baseline and a later time point

MRI, magnetic resonance imaging

Conclusions

- Long-term treatment with osilodrostat provided sustained control of cortisol production in patients with Cushing's disease during the LINC 4 study
- Osilodrostat was generally well tolerated
  - No new or unexpected safety findings were reported during long-term treatment
  - Few patients discontinued because of AEs
- AEs related to hypocortisolism, accumulation of adrenal hormone precursors, QT prolongation or pituitary tumor enlargement were less frequent during the extension than in the 48-week core period

These results build upon previous clinical trials[1–4] and demonstrate that osilodrostat is an effective and well-tolerated, long-term treatment option for patients with Cushing's disease

1. Bertagna X *et al. J Clin Endocrinol Metab* 2014;99:1375–83; 2. Fleseriu M *et al. Pituitary* 2016;19:138–48;
3. Pivonello R *et al. Lancet Diabetes Endocrinol* 2020;8:748–61; 4. Gadelha M *et al. J Clin Endocrinol Metab* 2022; doi: 10.1210/clinem/dgac178

Acknowledgments

- Thanks to the patients, investigators, nurses and study coordinators who made this study possible
- This study was funded by Novartis Pharma AG
  - As of July 12, 2019, osilodrostat is an asset of Recordati