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### ► To cite this version:

Maria Fleseriu, Frederic Castinetti, Monica Gadelha, Andrea Giustina, Andre Lacroix, et al.. Osilodrostat for the treatment of Cushing's disease: efficacy, stability, and persistence Reply. LANCET DIABETES & ENDOCRINOLOGY, 2022, 10 (6), pp.385-387. hal-03780355

**HAL Id: hal-03780355**

**<https://amu.hal.science/hal-03780355>**

Submitted on 18 Apr 2023

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## **Osilodrostat for the treatment of Cushing's disease: efficacy, stability, and persistence – Authors' reply**

We thank Olivier Chabre and colleagues for their thoughtful comments on our Review.<sup>1</sup>

We agree with the authors, as emphasised in our Review, that pituitary surgery is the first line of treatment for Cushing's disease. As

most studies on medical therapy include patients not cured by surgery or who had disease recurrence after surgery, a direct head-to-head comparison of medical therapies versus surgery is not feasible. Further-more, as the authors highlight, and as we discussed in the Review,<sup>1</sup> direct comparison of drug efficacy between medical therapies is not possible due to differences in study design and an absence of head-to-head trials. In our Review,<sup>1</sup> we noted: "As designs, medication up-titration schemes, comparator arms, inclusion and exclusion criteria, and primary endpoints differ even among prospective studies, it is difficult to directly compare treatment outcomes, either for efficacy or for adverse effects. Furthermore, some drugs have not been prospectively studied for Cushing's syndrome". Rather, we extensively and individually discussed benefits, as well as safety, of each available medication.

Notably, published biochemical control percentages differ for each medication at different timepoints across studies in patients with Cushing's syndrome. Therefore, to maximise clinical use for readers, table 2 in our Review<sup>1</sup> showed the study design (eg, open label or randomised withdrawal) and the primary specified endpoint—either urinary free cortisol (UFC) normalisation or clinical improvements on active treatment—for all published phase 3 prospective trials of approved medications: osilodrostat, metyrapone, levoketoconazole, pasireotide, and mifepristone. Although it has since been approved by the US Food and Drug Administration, at the time of publication of our Review,<sup>1</sup> levoketoconazole was an investigational medication with a published phase 3 study.<sup>2</sup> For this reason, we felt it important to list it in table 2 and note its investigational status, but we did not discuss

levoketoconazole in the text, as we did with all the other approved medications.

We agree with Chabre and colleagues regarding the caveats of a randomised withdrawal study design and, in discussing the osilodrostat phase 3 trial,<sup>3</sup> we specified information regarding selection for randomisation and the source of the 86% of 24-h UFC normalisation rate cited in table 2, which was the primary endpoint of the trial. "After 12 weeks of open-label dose-titrated treatment and 12 additional weeks of open-label dose-optimised treatment, 72 (53%) patients had maintained normal UFC and were eligible for randomisation. By week 34, at the end of the randomised treatment period, 31 (86%) of 36 randomly assigned to osilodrostat maintained normal UFC versus 10 (29%) of 35 randomly assigned to placebo (OR 13·7, 95% CI 3·7–53·4; p<0·0001)."

Furthermore, patient selection (eg, baseline UFC), dosing titration, definition of disease control, and study duration are also paramount when discussing results, as we reviewed.<sup>1</sup> Because follow-up intervals differed between drugs, with some lasting only 12 weeks and others up to 48 weeks with intermediate results reported at varying intervals, we elected to show in table 2 of our Review<sup>1</sup> the prespecified primary endpoint of each study to ensure consistency across the prospective trials. We explained study design caveats in the text. For osilodrostat, the primary endpoint in the largest study published at that time, LINC 3,<sup>3</sup> was therefore included in table 2. We agree that whole-population analyses represent an important clinical measure for long-term treatment. However, even when analysing the whole patient population for each osilodrostat study, long-term efficacy rates vary widely, ranging from 78·9% at week 22 in LINC 2<sup>4</sup> to

71.5% at week 12, 68% at week 24, and 66% at week 48 in LINC 3,<sup>3</sup> and 81% (95% CI 69.9–89.1) at week 36 in LINC 4.<sup>5</sup> With regard to the primary endpoint in LINC 4, which had a placebo up-front design, UFC normalisation at week 12 was reached in 77% of patients receiving osilodrostat compared with 8% of those receiving placebo.<sup>5</sup> These data further affirm what we noted in our Review<sup>1</sup> about the need for close follow-up in all patients on medical therapy for Cushing's disease, to ensure they are controlled long-term, as doses might need to be adjusted (up or down).

We agree with Chabre and colleagues that differences in placebo response rates across various studies of patients with Cushing's syndrome are indeed intriguing and warrant further research. As of now, description of the levoketoconazole randomised withdrawal study is available only as a poster, but study design, including placebo duration, drug titration, and primary endpoints (including definition of loss of disease control) seem to have all differed slightly from that in the osilodrostat trials. Additionally, inclusion criteria and Cushing's syndrome type differed: the osilodrostat trial enrolled only patients with Cushing's disease, whereas patients with non-pituitary Cushing's syndrome were included in the levoketoconazole trial.

As raised by Chabre and colleagues, adrenal insufficiency is indeed an adverse event encountered with all Cushing's disease treatments, including surgery, but with higher rates occurring from potent medications that target adrenal steroidogenesis. A direct effect of osilodrostat on the adrenal glands has, to our knowledge, not been shown. However, recent experience<sup>6</sup> has highlighted the potential for delayed adrenal insufficiency in some patients treated with osilodrostat. Additional studies on this delayed

effect are needed. Furthermore, levoketoconazole has been shown to directly inhibit cortisol production in adrenocortical cells, as well as to potentially affect human corticotroph pituitary adenoma cultures.<sup>7</sup> In agreement with the authors' concerns over adrenal insufficiency when treating patients with this class of agents, we did emphasise this risk and the need to monitor patients during treatment in our Review.<sup>1</sup>

We thank Chabre and colleagues for concurring with our Review regarding the need for further, rigorous study of treatments for Cushing's disease and the importance of personalising therapy to each individual patient's situation.

MF has received grants to the institution from Novartis, Strongbridge, Novo Nordisk, Crinetics, Millendo, Ascendis, and Pfizer; personal honoraria for consulting and advisory boards from Crinetics, HRA Pharma, Novartis, Recordati, Strongbridge, Sparrow, Ascendis, Novo Nordisk, and Pfizer; is Deputy Editor for European Journal of Endocrinology; and has served on the Board for the Pituitary Society. FC has received personal honoraria for consulting, lectures, and support for meeting attendance from Recordati Rare Diseases, Ipsen, and HRA Pharma. MG has received grants to the institution from Novartis and Ipsen; personal honoraria for consulting, lectures, and advisory boards from Crinetics, Recordati Rare Diseases, Novo Nordisk, and Ipsen; has served on the Board of the Brazilian Society of Endocrinology and Metabolism; and is President of the Pituitary Society. AG has received grants to the institution from Pfizer; personal honoraria for consulting and advisory boards from Abiogen, Novo Nordisk, and Recordati; and has served on the Board or as an advisor to the European Hormone and Metabolism Foundation and Glucocorticoid Induced Osteoporosis Skeletal Endocrinology Group. AL has received grants from Recordati and Corcept for clinical trials; personal honoraria and education grants for lectures, support for meeting attendance, and participation in advisory boards from Pfizer, Ipsen, Corcept, Recordati, and the European Journal of Endocrinology; royalties from UpToDate Endocrinology; and has served as a Board member for the International Society of Endocrinology. SM has received grants to the institution from the US Food and Drug Administration; non-financial support from Cyclacel; and has served on the Board of the Pituitary Society. JN-P has received grants and honoraria to the institution for consulting and advisory boards from Diurnal, HRA Pharma, Crinetics, Recordati, and Novartis; and has served as a Board member or advisor for the Pituitary Foundation and Endocrine Society. RP has received grants to the institution from Novartis, Pfizer, Ipsen, Shire, IBSA Farmaceutici,

HRA Pharma,

Cortendo, Corcept Therapeutics, and Merck Serono; personal honoraria for consulting, lectures, support for meeting attendance, and advisory boards from Novartis, Shire, HRA Pharma, Cortendo, Pfizer, Recordati, IBSA Farmaceutici, and Crinetics Pharmaceuticals; and has served on the board of the Pituitary Society. MR has received personal honoraria for consulting, lectures, and advisory boards from Novartis, Recordati, HRA Pharma, and Ipsen; and is President of the European Society of Endocrinology. BMKB has received grants to the institution from Ascendis, Novartis, Strongbridge, and Millendo; personal honoraria for consulting from Aeterna Zentaris, Ascendis, Merck Serono, Novartis, Novo Nordisk, Recordati, Strongbridge, and Sparrow; and has served as an advisor for the Endocrine Society.

*\*Maria Fleseriu, Frederic Castinetti, Mônica Gadelha, Andrea Giustina, André Lacroix, Shlomo Melmed, John Newell-Price, Rosario Pivonello, Martin Reincke, Beverly M K Biller, on behalf of all authors of “Consensus on diagnosis and management of Cushing’s disease: a guideline update”*

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