November 6, 2023

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Draft Guidance: Endogenous Cushing's Syndrome: Developing Drugs for Treatment
Guidance for Industry - ID FDA-2023-D-3518-0002

Dear members of the FDA Committee,

We would like to take this opportunity to comment on the draft guidelines on Cushing's syndrome titled above. We represent the leadership of the international Pituitary Society and the Endocrine Society and are highly experienced with pharmaceutical trials involving Cushing's syndrome.

We agree with the FDA that clear biochemical guidelines should be used for the initial diagnosis of Cushing's syndrome (CS). We strongly agree with the FDA that inclusion in clinical trials for drugs treating Cushing's syndrome should be limited to patients with clear confirmation of history of CS, as well as active disease at the time of inclusion criteria. In these guidelines, a priority is placed on use of urine free cortisol (UFC) for the diagnosis, as this test has been used for many years in evaluating patients with hypercortisolemia. However, we would like to highlight the role of salivary cortisol in the diagnosis of CS in general, as well as cyclic CS and for recurrence of Cushing's disease. Measurement of late night salivary cortisol (LNSC), performed in a well accredited laboratory, has the highest specificity and sensitivity for diagnosis of CS (except adrenal adenoma causing CS), as well as cyclic CS and for recurrence of CS. International Pituitary Society consensus guidelines (with involvement of over 50 international Cushing's experts from 5 continents) clearly state the utility of LNSC for the diagnosis of CS, and that multiple, periodic, sequential LNSC tests are particularly useful for the longitudinal surveillance needed in the diagnosis of cyclic CS patients who exhibit weeks to months of normal cortisol secretion interspersed with episodes of cortisol excess.

The international panel concluded that among the tests available, LNSC is the most sensitive for detecting recurrence and should be done annually after HPA axis recovery

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postoperatively *(moderate quality, strong recommendation).* This recommendation was based on several studies which showed that LNSC usually shows abnormal results before DST and UFC, sometimes even with a year or so. LNSC elevation might precede urinary free cortisol (UFC) elevation in nearly half of patients, resulting in enhanced diagnostic accuracy for a specific LNSC assay cut-off (7.4 nmol/l) compared with a 1.6-fold increase of 24-h UFC (area under the curve 0.87 and 0.82, respectively). Monitoring for recurrence should also take into consideration which specific tests showed abnormal results for an individual patient at initial diagnosis *(moderate quality, strong recommendation).*

Additionally, patients with elevated LNSC and normal UFC could have milder disease and thus represent a population which has not been studied well yet for medical therapy or other treatments. These patients would also have a higher likelihood of being included in a study with placebo arm.

Given the known variability and limitations of UFC measurements, we feel that LNSC should be used as the diagnostic biochemical marker for CS, as well as cyclic CS and CS recurrence. UFC and dexamethasone suppression tests (with measurement of plasma dexamethasone levels) may be used in addition. We agree that UFC may be utilized as a biochemical target for all drug trials in CS, except for those involving glucocorticoid receptor antagonists.

We also have concern regarding the use of placebo-controlled studies in CS. The guidelines state: "Although some stakeholders have raised concerns about the ethics of a placebo control, this design is regarded as acceptable…and other protocol safeguards can ensure the safety of subjects". Our concerns include the fact that CS is a multisystem and highly morbid condition, and patients are often quite ill. Use of placebo studies may 1) limit recruitment of patients who desire direct involvement on therapeutic trials, and 2) may cause safety concerns by allowing patients to maintain untreated hypercortisolism. We therefore feel that studies involving comparison studies to FDA approved medications would be more appropriate.

Please consider the following updated reference list for these guidelines:

1. Fleseriu M, Auchus R, Bancos I, Ben-Shlomo A, Bertherat J, Biermasz NR, Boguszewski CL, Bronstein MD, Buchfelder M, Carmichael JD, Casanueva FF, Castinetti F, Chanson P, Findling J, Gadelha M, Geer EB, Giustina A, Grossman A, Gurnell M, Ho K, Ioachimescu AG, Kaiser UB, Karavitaki N, Katznelson L, Kelly DF, Lacroix A, McCormack A, Melmed S, Molitch M, Mortini P, Newell-Price J, Nieman L, Pereira AM, Petersenn S, Pivonello R, Raff H, Reincke M, Salvatori R, Scaroni C, Shimon I, Stratakis CA, Swearingen B, Tabarin A, Takahashi Y, Theodoropoulou M, Tsagarakis S, Valassi E, Varlamov EV, Vila G, Wass J, Webb SM, Zatelli MC, Biller BMK . Consensus on diagnosis and management of Cushing's disease: a guideline update. Lancet Diabetes Endocrinol. 2021 Oct 20:S2213-8587(21)00235-7. doi: 10.1016/S2213-8587(21)00235-7. PMID: 34687601.

2. Nowak E, Vogel F, Albani A, Braun L, Rubinstein G, Zopp S, Ritzel K, Beuschlein F, Theodoropoulou M, Reincke M. Diagnostic challenges in cyclic Cushing's syndrome: a

systematic review. Lancet Diabetes Endocrinol. 2023 Aug;11(8):593-606. doi: 10.1016/S2213-8587(23)00150-X. Epub 2023 Jul 7. PMID: 37429301.

3. Raff H. Late Night Salivary Cortisol in the diagnosis of neoplastic hypercortisolism (including cyclic Cushing's syndrome). Pituitary. 2022 Oct;25(5):698-700. doi: 10.1007/s11102-022-01214-2. Epub 2022 Mar 25. PMID: 35334030.

4. Amlashi FG, Swearingen B, Faje AT, Nachtigall LB, Miller KK, Klibanski A, Biller BM, Tritos NA. Accuracy of Late-Night Salivary Cortisol in Evaluating Postoperative Remission and Recurrence in Cushing's Disease. J Clin Endocrinol Metab. 2015 Oct;100(10):3770-7. doi: 10.1210/jc.2015-2107. Epub 2015 Jul 21. PMID: 26196950.

5. Carroll TB, Javorsky BR, Findling JW. POSTSURGICAL RECURRENT CUSHING DISEASE: CLINICAL BENEFIT OF EARLY INTERVENTION IN PATIENTS WITH NORMAL URINARY FREE CORTISOL. Endocr Pract. 2016 Oct;22(10):1216-1223. doi: 10.4158/EP161380.OR. Epub 2016 Jul 13. PMID: 27409817

6. Reincke M, Fleseriu M. Cushing Syndrome: A Review JAMA. 2023 Jul 11;330(2):170-181. doi: 10.1001/jama.2023.11305. PMID: 37432427.

7. Fleseriu M, Varlamov EV, Hinojosa-Amaya JM, Langlois F, Melmed S An individualized approach to the management of Cushing disease. Nat Rev Endocrinol. 2023 Oct;19(10):581-599. doi: 10.1038/s41574-023-00868-7. Epub 2023 Aug 3. PMID: 37537306.

Thank you for your consideration,

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