Title: Mifepristone Improves Global Clinical Status In Patients With Cushing's Syndrome: Results From The SEISMIC Study

Laurence Katznelson, MD, lkatznelson@stanford.edu[1], D Lynn Loriaux, MD, loriauxl@ohsu.edu[3], David Feldman, MS, MD, dfeldman@stanford.edu[1], Glenn Braunstein, MD, braunstein@cshs.org[2], David Schteingart, MD, dschtein@umich.edu[4], Coleman Gross, MD, cgross@corcept.com[5] and Charissa Hogeboom, PhD, Charissa.Hogeboom@iconplc.com[6]. [1]Medicine, Stanford University, Stanford, CA, United States, 94305; [2]Medicine, Cedars Sinai Hospital, Los Angeles, CA, United States, 90048-1865; [3]Medicine, Oregon Health Science University, Portland, OR, United States, 97239; [4]Medicine, University of Michigan, Ann Arbor, MI, United States, 48109; [5]Corcept Therapeutics, Menlo Park, CA, United States, 94025 and [6]ICON Clinical Research, North Wales, PA, United States, 19454.

Rationale: There are limited medical options for the treatment of Cushing's syndrome (CS). We present additional results on clinical response from the SEISMIC study involving use of the glucocorticoid antagonist mifepristone in CS.
Methods: SEISMIC was a 24 wk multicenter, open label trial of mifepristone (300-1200 mg/d) in CS patients with type 2 DM/impaired glucose tolerance (C-DM) or hypertension (C-HT). 46 patients (14M, 32F) are included in analyses of efficacy (modified intent to treat [mITT]). The key secondary endpoint was global clinical response (GCR); a 3 member data review board (DRB) considered 8 clinical data categories and graded study visits in blinded fashion as +1 (improvement), 0 (no change), -1 (worsening) vs. baseline. Positive response was defined as a median score of +1 at any postbaseline visit. A cumulative logistic threshold model was used to estimate intraclass correlation coefficient (ICC) of DRB raters.
Results: The proportion of positive GCRs in mITT increased during the study: wk 6, 43%; wk 10, 50%; wk 16, 78%; wk 24, 83% ($p<0.001$). GCR was 94% at any postbaseline visit in the completer group (N=33). There was 76.6% agreement between members of the DRB, with an ICC of 0.652 (moderate agreement, $p<0.0001$). Overall, the rate of positive GCRs was similar between genders (men 79%; women 91%, p=NS). Men had a high proportion of positive GCRs by wk 6 which then plateaued (wk 6, 64%; wk 10, 57%; wk 16, 71%; wk 24, 64%); in women, there was a gradual increase in proportion of positive GCR (wk 6, 31%; wk 10, 34%; wk 16, 56%; wk 24, 75%) (repeated measures, p=0.003; 1st visit with positive GCR by gender, p=0.02); no such trend was apparent for age. By wk 24, investigator graded Cushingoid appearance was much improved in 52%, somewhat improved in 33%, and unchanged in 15% ($p<0.0001$). Quality of life (SF-36) improved by 24 wk in the following scales (mean±SD): General Health, 4.4±8.3 (p=0.004); Physical Function, 7.1±9.4 ($p<0.0001$); Role Physical, 3.3±10.4 (p=0.05); Social Functioning, 7.7±11.6 (p=0.0003); Vitality, 6.3±11.1 (p=0.002); Mental Health, 4.1±10.5 (p=0.03); Role Emotional, 4.9±12.4 (p=0.03).
Conclusion: Treatment of CS with mifepristone results in early and progressive clinical improvement in most patients, including physical appearance and enhancement of quality of life. The time to achieve GCR in men was shorter than in women, a finding that should be considered when monitoring clinical response.