The "RESCUE" Trial: 11β-Hydroxysteroid Dehydrogenase Type 1 (HSD-1) Inhibition for ACTH-Dependent Cushing's Syndrome

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#EP111

Rescue
(NCT 05307328)

ABSTRACT:

BACKGROUND: HSD-1, an intracellular enzyme, converts cortisone to cortisol in tissues where cortisol excess is associated with morbidity including liver, adipose, bone, brain, muscle, skin, and eye. SPI-62 is a potent and specific HSD-1 inhibitor in development for treatment of Cushing's syndrome and autonomous cortisol secretion, and as adjunctive therapy to prednisolone in polymyalgia rheumatica. In Phase 1 clinical trials SPI-62 was generally well tolerated and associated with maximal liver and brain HSD-1 inhibition.

SPI-62 decreased urinary cortisol metabolites indicating a similar decrease of hepatocellular cortisol in this important target tissue. After a corresponding transient decrease, circulating cortisol homeostasis was restored by ACTH increase which also resulted in a moderate adrenal androgen increase. SPI-62's effects on androgens did not result in adverse effects. Urinary free cortisol was unaffected. The RESCUE trial will assess SPI-62 safety and efficacy in patients with a dysregulated HPA axis, i.e., ACTH-dependent Cushing's syndrome.

METHODS: In this randomized, placebo-controlled, crossover, multinational, Phase 2 clinical trial, adult patients (N=26) with ACTH-dependent Cushing's syndrome with active and consistently elevated urinary free cortisol (UFC) will be randomized to receive SPI-62 and placebo for 12 weeks each. A diagnosis of an inadequately treated pituitary adenoma (Cushing's disease) or ectopic ACTH or CRH producing tumor based on established criteria is required. Evidence of Cushing's associated morbidities including at least 2 of A) insulin resistance/type-2 diabetes mellitus, B) dyslipidemia, C) hypertension, or D) osteopenia is required. Subjects must not have had recent Cushing's surgical, radiation other approved or experimental medical therapies for cortisol excess. Medical conditions or treatments likely to interfere with study assessments or subject safety are also excluded.

The primary outcome is pharmacological suppression of the urinary ratio of hepatic 5- and 3-steroid reductase metabolites of cortisol and cortisone (tetrahydrocortisol + allotetrahydrocortisol) / tetrahydrocortisone). Safety is assessed by adverse events, vital signs, ECG, and clinical laboratory analyses including effects on HPA/HPG axis biomarkers. Efficacy is assessed by reduction of Cushing's features and morbidities of hyperglycemia, dyslipidemia, adiposity, hepatic steatosis, hypertension, glaucoma, osteopenia, muscle strength, sleep, and mood. Assessments include tumor-imaging by MRI, ocular tonometry, timed up-and-go and hand-grip strength tests, dual-energy x-ray absorptiometry, oral glucose tolerance, continuous glucose monitoring, and ambulatory blood pressure monitoring.

RESULTS: This trial is ongoing; results are pending.

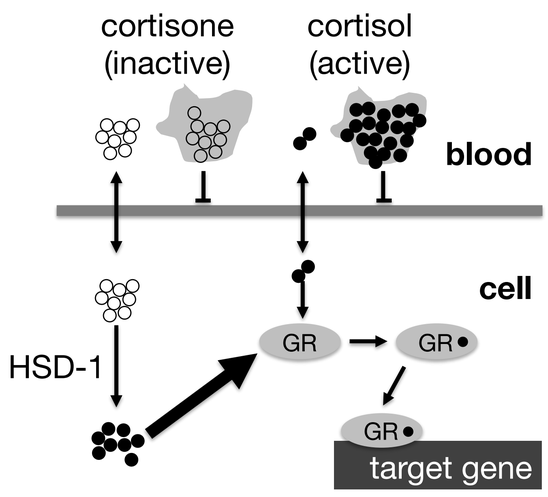
DISCUSSION: This Phase 2 explores SPI-62 safety, HSD-1 inhibition, effects on HPA/HPG axes, and clinical effects in patients with ACTH-dependent Cushing's syndrome.

11β-HYDROXYSTEROID DEHYDROGENASE (HSD) ENZYMES

The HSD enzymes control intracellular levels of cortisone & cortisol.

- HSD-1 converts inactive cortisone to active cortisol. HSD-1 is expressed in tissues (e.g., liver, adipose, bone, brain, skin, muscle, eye) in which elevated cortisol levels cause morbidity in patients with Cushing's syndrome or autonomous cortisol secretion.
- HSD-2 converts cortisol to cortisone in mineralocorticoid-sensitive tissues (e.g., kidney), where it serves a protective function.

Much of the intracellular cortisol that can act on intracellular receptors is made by HSD-1. Cortisol is highly bound by plasma proteins, so only a small fraction is free to enter cells. Cortisone is less protein bound. It enters cells in larger quantities and is then converted by HSD-1 to cortisol, which can bind receptors, translocate to the nucleus, and regulate target genes.[1]



EVIDENCE FOR POTENTIAL BENEFIT IN CUSHING'S SYNDROME:

HSD-1 inhibition in liver and adipose tissue may mitigate hyperglycemia, dyslipidemia, adiposity, and hepatic steatosis. Six weeks of SPI-62 nominally improved glucose, HbA1c, cholesterol, and triglycerides, compared to placebo in subjects with type 2 diabetes (data on file). An HSD-1 inhibitor improved hepatic fat content, compared to placebo at 12 weeks, in subjects with non-alcoholic fatty liver disease.[2] A pilot open-label clinical trial of another HSD-1 inhibitor in subjects with hypercortisolism showed positive trends on glycemic control and body habitus at 12 and 24 weeks.[3]

HSD-1 inhibition in vasculature and kidney may reduce hypertension. HSD-1 inhibitors have been assessed as anti-hypertensive medications with inconclusive results using in-clinic BP assessments. In this study, 24-hour ambulatory blood pressure monitoring (ABPM) and at-home diurnal blood pressure measurements will be conducted. HSD-1 knockout mice resisted the pressor effect, measured during the murine sleep cycle, of exogenous corticosteroid administration.[4]

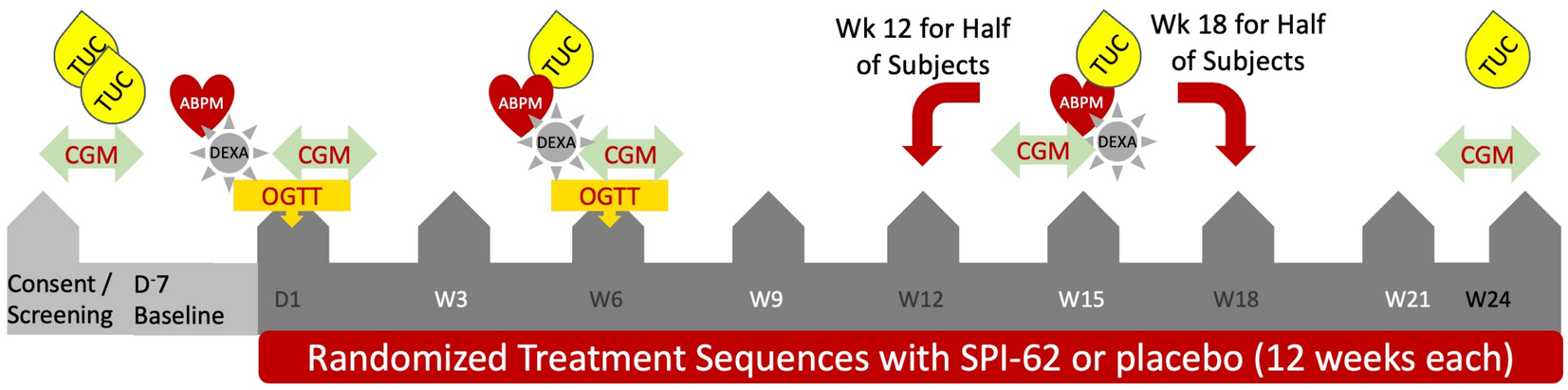
HSD-1 inhibition in brain may improve mood, cognition, and sleep. Higher HSD-1 activity has been associated with progressive brain atrophy and decline in processing speed in older men.[5] HSD-1 inhibition improved cognitive function in elderly men.[6] Evidence from experiments with transgenic mice suggests HSD-1 inhibitor reduction of hippocampus and brain cortisol enhances synaptic plasticity and improves cognition and memory[7-10]. SPI-62 prevented adverse cognitive and anxiolytic effects of exogenously administered corticosteroid.

HSD-1 inhibition in bone is hypothesized to prevent osteopenia. HSD-1 inhibition prevented corticosteroid-induced osteocalcin decline.[11]

HSD-1 inhibition in muscle and skin may slow their atrophy. HSD-1 knockout mice, compared to controls, resisted corticosteroid-induced skeletal muscle and dermal atrophy.[13] HSD-1 inhibitors prevented corticosteroid-induced wound healing impairment in mice.[14,15]

HSD-1 inhibition in eye is hypothesized to alleviate glaucoma risk. A low potency HSD-1 inhibitor partially prevented intraocular pressure increase associated with intravitreal triamcinolone in rabbit.[16]

*** ASSESSMENT SCHEDULE:**



Home BP monitoring (baseline to Week 24 visit)

- Twice-weekly for 25 weeks, bedtime sitting, afternoon sitting
- Home orthostatic tests (lying then standing at 1 and 3 min) as needed

ABPM – 24-hr ambulatory blood pressure monitoring
DEXA – dual-energy, x-ray absorptiometry scan
TUC – 24-hr timed urine collection
CGM – 14-day continuous glucose monitoring
OGTT – 2-hr oral glucose tolerance test
Dark grey = treatment, white visits – telephone calls

***Recent amendment has significantly reduced assessment frequency and inclusion criteria; Updated study details will be available at https://www.clinicaltrials.gov/ct2/show/NCT05307328**

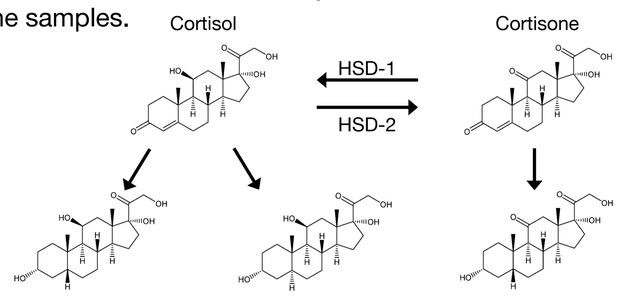
STUDY OBJECTIVES & ENDPOINTS:

- The primary endpoint of this study is the urinary HSD-1 ratio at Week 6, to characterize the pharmacologic effect of SPI-62 in subjects with ACTH-dependent Cushing's disease.
- Secondary objectives of this study are to evaluate the safety of SPI-62 in subjects with ACTH-dependent Cushing's syndrome, including changes on HPA and HPG axis biomarkers and associated AEs.
- Exploratory objectives of this study are to estimate SPI-62's effect on clinical parameters across Cushing's features including:
  hyperglycemia, dyslipidemia, adiposity, hepatic steatosis, hypertension, glaucoma, mood, osteopenia, and muscle strength.

USA, ROMANIA & BULGARIA STUDY CENTER LOCATIONS:

THE HSD-1 RATIO – OUR PRIMARY ENDPOINT

- HSD-1 activity is substantially higher in liver than other tissues.
- In liver, cortisol & cortisone are metabolized to tetrahydro metabolites which are rapidly and extensively excreted in urine.
- The metabolite ratio is a sensitive measure of liver HSD-1 activity.
- The urinary ratio cortisone / cortisol is a sensitive measure of kidney HSD-2 activity.
- Both HSD-1 and HSD-2 activity ratios can be measured in spot urine samples.



(Tetrahydrocortisol + Allotetrahydrocortisol) / Tetrahydrocortisone
= HSD-1 ratio

KEY INCLUSION CRITERIA:

1. Male or female adults willing to adhere to reproductive precautions
2. Evidence of active and consistent cortisol excess by UFC
3. Documented diagnosis of ACTH-dependent Cushing's syndrome including Cushing's disease, ectopic ACTH secretion, or ectopic CRH secretion
4. Current evidence of Cushing's morbidities: Defined by having at least 1* of the below criteria:
   a. Diagnosis of insulin-resistance/pre-diabetes or type 2 diabetes
   b. Diagnosis of dyslipidemia
   c. Diagnosis of hypertension
   d. Diagnosis of osteoporosis or osteopenia

KEY EXCLUSION CRITERIA:

1. Recent (within 6 weeks) surgery for Cushing's or surgery planned within 24 weeks of randomization.
2. History of any fractionated radiation therapy for Cushing's within the past 2 years or conventional radiation therapy within 4 years.
3. History of bilateral adrenalectomy or exogenous, pseudo, cyclic, or non-ACTH-dependent Cushing's syndrome (including certain inherited conditions).
4. High risk of acute morbidity from corticotroph adenoma growth (similar to that which occurs with Nelson's syndrome) defined as current evidence of macroadenoma at risk of impingement of vital structures.
5. Any current or prior medical condition, medical or surgical therapies, or clinical trial participation expected to interfere with the conduct of the study or the evaluation of its results, including but not limited to poor venous access or recent receipt or donation of blood products.
6. Women who are currently pregnant, lactating or planning fertility and unwilling to adhere to approved contraceptives or abstinence.

SPI-62 is also in Phase 2 for patients with autonomous cortisol secretion and adrenal Cushing's syndrome (The ACSPIRE Trial) see **ePoster EP112**

More information on SPI-62's effects on the HPA axis, see **Poster Presentation #672** by David Katz 24May at 11:50 am

Authors are employees of, or consultants to, Sparrow.
SPI-62 is investigational. This information is not for use in promotion or product commercialization.

REFERENCES: [1]Bellaire S. et al. Clin. Transl. Sci. 2019;12:291-301; [2]Stefan N, et al. Lancet Diabetes Endocrinol. 2014 May;2(5):406-16. ; [3]Oda S, et al. J Clin Endocrinol Metab. 2021 Jun 18; [4]Morgan SA et al. Proc Natl Acad Sci U S A. 2014 Jun 17;111(24):E2482-91.; [5]MacLullich AM, et al. Neurobiol Aging. 2012 Jan;33(1):207.e1-8.; [6]Sandeep TC, et al. Proc Natl Acad Sci U S A. 2004 Apr 27;101(17):6734-9.; [7]Dumas TC, et al. J Neurosci. 2010 Feb 3;30(5):1712-20.; [8]Mohler EG, et al. J Neurosci. 2011 Apr 6;31(14):5406-13.; [9]Sooy K, et al. J Neurosci. 2010 Oct 13;30(41):13867-72.; [10]Yau JL, et al. J Neurosci. 2007 Sep 26;27(39):10487-96.; [11]Othonos N, et al. J Clin Endocrinol Metab. 2020 Sep 1;105(9):e3316–28.; [12] Morgan SA, et al. Proc Natl Acad Sci USA. 2014 Jun 17;111(24):E2482-91.; [13]Youm JK, et al. Wound Repair Regen. 2013 Sep-Oct;21(5):715-22.; [14]Tiganescu A, et al. Endocrinology. 2018 Jan 1;159(1):547-556.; [15] (Song Z, et al. Mol Vis. 2011;17:2056-64. Epub 2011 Aug 4.