PII-LBA7
IN TWO PHASE III STUDIES, ENDROXAL™ (ENCLOMIPHENE CITRATE) SIGNIFICANTLY IMPROVES TOTAL TESTOSTERONE LEVELS COMPARED TO ANDROGEL 1.62%, WITHOUT SUPPRESSION OF SPERMATOGENESIS AND TESTICULAR FUNCTION IN OVERWEIGHT MALES WITH SECONDARY HYPOGONADISM.
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INTRODUCTION AND OBJECTIVES: Epidemiological studies of hypogonadism have unequivocally shown that the majority of men with clinically low testosterone levels have secondary hypogonadism. This disorder is primarily associated with being overweight (BMI > 25) or obese (BMI > 30) and is neither idiopathic nor due to normal aging. The secondary hypogonadal male has functional but under-stimulated testes. These men are typically fertile but exhibit low total testosterone that results from sub-optimal stimulation of the Leydig cells due to suppressed LH secretions by the pituitary. The reduced LH release in turn is due to negative feedback of estrogen on the hypothalamus-pituitary axis. These men are typically fertile but exhibit low total testosterone that results from sub-optimal stimulation of the Leydig cells due to suppressed LH secretions by the pituitary. The reduced LH release in turn is due to negative feedback of estrogen on the hypothalamus-pituitary axis.

METHODS: Two double-blind, double-dummy, placebo-controlled, 16 week studies in 256 men. Men less than 60 years of age, with BMI > 25 were enrolled if they exhibited sperm counts in the normal range at baseline (> 15 million/mL) and morning testosterone of < 300 ng/dL.

RESULTS: Endroxal™ was found to restore T levels in the majority of secondary hypogonadal men (Table 1). The magnitude of the effect was much greater and more consistent than with Androgel. In contrast to the characteristic and well-documented suppression of spermatogenesis with Androgel, Endroxal™ exhibited no negative effect on spermatogenesis compared to placebo.

CONCLUSIONS: Endroxal™ is a high affinity estrogen antagonist (IC50:16nM) with substantially higher antagonist activity than its agonist (IC50:16nM) with substantially higher antagonist activity than its agonist. More than 40% of commercial clomiphene, is poorly metabolized and accumulates (10 fold greater than clomiphene). These pharmacological and pharmacokinetic differences between the two isomers could lead to and improved therapeutic window for Endroxal™ over clomiphene.

Overall, the data show that T restoration with Endroxal™ could provide an advantageous clinical profile over gel-induced T replacement.

Source of Funding: none

PII-LBA8
USE OF LINEAR DISCRIMINANT ANALYSIS IN A URINE-BASED TEST FOR BLADDER CANCER DIAGNOSIS
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INTRODUCTION AND OBJECTIVES: We aim to develop a rapid, accurate and non-invasive molecular assay for bladder cancer diagnosis for use on the GeneXpert® (Cepheid, Sunnyvale CA) platform with sample-in-answer-out capability. Linear discriminant analysis (LDA) was used both to help choose the best markers for the assay, and to optimize the assay's ability to discriminate negative and positive samples.

METHODS: Appropriate local IRB approvals were obtained. The GeneXpert® Instrument Systems automate and integrate sample purification and multiplex RT-qPCR detection. The systems utilize single-use cartridges that hold the reagents and conduct the RT-qPCR process. The assay requires less than two minutes of hands-on time and results are available in approximately 90 minutes. A training set of 497 urine samples collected from 18 sites was tested for the expression levels of ABL1, CRH, IGFR, ANXA10, KRT20, AR, PIK3CA, UPK1B, UPK2 and MGEA5 mRNA. The ten markers were analyzed using stepwise logistic regression to choose the best 5 marker signature and develop an LDA equation to determine test outcome. An assay was developed for the mRNA detection of a 5 marker signature that includes a sample adequacy control and an internal RT-qPCR control. The assay with integrated LDA equation was tested with a set of 243 urine samples from 7 sites to validate the signature.

RESULTS: Backwards stepwise regression was used with the training set of samples and data with 10 markers to reduce the model and obtain the best 5-marker multivariable equation to determine test results. The resulting LDA equation using Ct values for ABL1, CRH, IGFR, ANXA10 and UPK1B was shown to yield sensitivities of 98% (79/81) for high grade cancer (papillary and CIS combined), 78% (31/40) for low grade and specificity of 83% (78/94) with patients undergoing hematuria workup.

An assay for detection of ABL1, CRH, IGFR, ANXA10 and UPK1B mRNA was formulated and optimized for use on the GeneXpert®. A validation set of 243 urine samples was tested with the new assay to evaluate equivalence relative to the prior training set results. The new assay's sensitivity was 92% (12/13) for high-grade cancer (papillary and CIS combined) and 86% (12/14) for low-grade. The specificity was 89% (24/27) for patients undergoing workup for hematuria and 96% (144/150) with healthy volunteers. A prospective study with the newly developed test is underway.

CONCLUSIONS: We have developed a simple to use and accurate test for the detection of bladder cancer. The assay utilizes a proven diagnostic platform of GeneXpert® with automated sample preparation providing test results within 90 minutes.

Source of Funding: Repros Therapeutics

PII-LBA9
EFFICACY AND SAFETY OF MIRABEGRON ADD-ON TREATMENT TO SOLifenacin IN INCONtinENT OAB SUBJECTS WITH AN INADEQUATE RESPONSE TO INITIAL 4-WEEK SOLifenacin MONOTHERAPY
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INTRODUCTION AND OBJECTIVE: The objective of this Phase IIb study was to evaluate the efficacy and safety of solifenacin 5 mg (SOLI) in combination (COMBN) with mirabegron 50 mg (MIRA) vs SOLI 5 mg monotherapy, in incontinent OAB patients with an inadequate response to initial 4 weeks of SOLI 5 mg monotherapy.

METHODS: Adult patients with symptoms of OAB for ≥3 months entered a 2-week washout period, followed by single-blind SOLI 5 mg daily for 4 weeks. Eligible subjects still reporting ≥1 incontinence episodes during a 3-day micturition diary were then randomized at baseline (1:1:1) to daily double-blind treatment with COMBN (SOLI 5 mg + MIRA 50 mg; first 4 weeks MIRA 25 mg), SOLI 5 mg, or SOLI 10 mg for 12 weeks. The primary efficacy endpoint was change from baseline to end of treatment (EoT) in mean number of incontinence episodes/24 h. Key secondary efficacy variables were change from baseline to EoT in mean number of micturi-}