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POD-03.01

Efficacy and safety of a novel, oral SH2-containing inositol-5′-phosphatase 1 activator, AQX-1125, in subjects with moderate to severe interstitial cystitis/bladder pain syndrome

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Introduction and Objectives: AQX-1125, a novel SH2-containing inositol-5′-phosphatase 1 (SHIP1) activator previously demonstrated to modulate inflammation. We conducted a double-blind, placebo-controlled phase 2 trial of the safety and efficacy of AQX-1125 (plus existing therapy) for the treatment of interstitial cystitis/bladder pain syndrome (IC/BPS).

Methods: 69 women with moderate to severe IC/BPS were randomized to daily 200 mg AQX-1125 or placebo for six weeks. Daily average and maximal pain scores were recorded and urinary frequency prior to visits. The O'Leary-Sant Interstitial Cystitis Symptom and Problem Indexes (ICSI/PI), Bladder Pain IC Symptom Score (BPIC-SS) and Short-Form 12v2 questionnaires were administered. Safety data was collected through treatment and four weeks followup.

Results: At six weeks, average daily e-diary pain (primary efficacy outcome), clinic average pain, maximum pain (e-diary and clinic), and percent change in average pain decreased more with AQX-1125. Significant benefits were noted for the ICSI/PI and BPIC-SS. No safety issues were noted in either group.

Conclusions: AQX-1125 provided greater reduction in bladder pain and symptoms at six weeks, compared to placebo in women with moderate to severe IC/BPS and was well-tolerated. This data supports the development of AQX-1125 as a novel, once-daily oral therapy for IC/BPS.

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POD-03.02

Mirabegron add-on treatment to solifenacin in incontinent overactive bladder patients: A responder analysis of a randomized, double blind, phase 3b study

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Introduction and Objectives: Incontinence is detrimental to health-related quality of life (HRQoL). This study (NCT01908829) assessed responder rates for efficacy and patient-reported outcomes (PROs) after treatment with a combination (COMBN) of a β3-adrenoceptor agonist, mirabegron (MIRA) and an antimuscarinic, solifenacin (SOLI), in incontinent overactive bladder (OAB) patients with inadequate response to SOLI 5 mg.

Methods: Incontinent adults with OAB for ≥3 months received a two-week wash-out and four weeks single-blind daily SOLI 5 mg. Patients still reporting ≥1 incontinence episodes during a three-day diary were randomized (1:1:1) to daily double-blind treatment with COMBN (SOLI 5 mg + MIRA 25 mg, increasing to MIRA 50 mg at four wks), SOLI 5 mg or 10 mg for 12 weeks. At end of treatment, responder rates for incontinence (zero episodes post-Baseline ['dry rate'], ≥50% decrease in episodes/24 hours); micturition reduction to <8 micturitions/24hours; and PROs (exceeding minimally important differences (MID) threshold in patient perception of bladder condition (PPBC) and OAB-questionnaire (OAB-q) Symptom Bother/total HRQoL scores) were evaluated individually or as double/triple responder analyses (50% reduction in incontinence plus OAB-q and/or PPBC).

Results: Baseline characteristics were similar between groups (COMBN, n=707; SOLI 5 mg, n=705; SOLI 10 mg, n=698). Odds for achieving full continence were 47% and 28% higher for COMBN vs. SOLI 5 mg or 10 mg, respectively; improvements in OAB-q outcomes were statistically significant. Responder rates for ≥50% decreased incontinence, micturition reduction, and PPBC were also improved for COMBN vs.SOLI 5 mg.

Table 1. POD-03.01. Efficacy results (change from baseline to 6 weeks)

	Placebo (N=32)	AQX-1125 (N=37)		
	Mean (SE)		LS mean difference	*p* value
Average pain (e-diary)	-1.4 (0.3)	-2.4 (0.4)	1.0 (0.5)	0.061
Average pain (clinic)	-1.1 (0.4)	-2.6 (0.5)	1.6 (0.6)	**0.008**
Percent change from baseline	-21.1 (4.8)	-38.1 (5.8)	16.5 (7.8)	**0.039**
Maximum pain (e-diary)	-1.4 (0.4)	-2.6 (0.4)	1.3 (0.6)	**0.030**
Maximum pain (clinic)	-1.1 (0.5)	-2.8 (0.6)	1.6 (0.7)	**0.028**
O'Leary-Sant ICSI	-1.4 (0.6)	-3.8 (0.6)	2.7 (0.9)	**0.005**
O'Leary-Sant ICPI	-1.6 (0.5)	-3.6 (0.7)	2.5 (1.0)	**0.014**
BPIC-SS	-4.0 (1.2)	-8.8 (1.4)	5.4 (2.1)	**0.011**

Table 1. POD-03.02. Proportion of responders at end of treatment (EoT) and odds ratios for COMBN vs SOLI 5 mg and 10 mg

	COMBN	SOLI 5 mg	SOLI 10 mg
Zero incontinence episodes/24 h at EoT ('dry rate')			
Responders, n (%)	325 (46.0) [n=706]	267 (37.9) [n=704]	280 (40.2) [n=697]
Odds ratio COMBN vs SOLI 5 mg (95% CI)	1.47 (1.17, 1.84) p=0.001		
Odds ratio COMBN vs SOLI 10 mg (95% CI)	1.28 (1.02, 1.61) p=0.033		
50% decrease in mean number of incontinence episodes/24 h			
Responders, n (%)	503 (71.2) [n=706]	444 (63.1) [n=704]	464 (66.6) [n=697]
Odds ratio COMBN vs SOLI 5 mg (95% CI)	1.51 (1.20, 1.90) p<0.001		
Odds ratio COMBN vs SOLI 10 mg (95% CI)	1.25 (0.99, 1.57) p=0.063 NS		
Mean of ≥8 micturitions at baseline and average of <8 micturitions/24 h at EoT			
Responders, n (%)	213 (30.2) [n=706]	176 (25.0) [n=704]	193 (27.7) [n=697]
Odds ratio COMBN vs SOLI 5 mg (95% CI)	1.29 (1.02, 1.64) p=0.036		
Odds ratio COMBN vs SOLI 10 mg (95% CI)	1.12 (0.89, 1.42) p=0.334 NS		
MID (≥10-point improvement from baseline) in OAB-q symptom bother			
Responders, n (%)	567 (81.7) [n=694]	490 (71.7) [n=683]	504 (74.6) [n=676]
Odds ratio COMBN vs SOLI 5 mg (95% CI)	1.75 (1.34, 2.30) p<0.001		
Odds ratio COMBN vs SOLI 10 mg (95% CI)	1.54 (1.17, 2.02) p=0.002		
MID (≥10-point improvement from baseline) in OAB-q total HRQoL			
Responders, n (%)	476 (68.6) [n=694]	414 (60.6) [n=683]	406 (60.1) [n=676]
Odds ratio COMBN vs SOLI 5 mg (95% CI)	1.50 (1.17, 1.91) p=0.001		
Odds ratio COMBN vs SOLI 10 mg (95% CI)	1.47 (1.15, 1.89) p=0.002		
MID (≥1-point improvement from baseline) in PPBC			
Responders, n (%)	533 (76.5) [n=697]	478 (69.5) [n=688]	491 (71.9) [n=683]
Odds ratio COMBN vs SOLI 5 mg (95% CI)	1.43 (1.11, 1.84) p=0.006		
Odds ratio COMBN vs SOLI 10 mg (95% CI)	1.26 (0.97, 1.63) p=0.081 NS		

Odds ratios, two-sided 95% CIs for odds ratios, and p-values are from a logistic regression model including treatment group, sex, age group (<65, ≥65 y), 4-wk incontinence episode reduction group (after 4 wks of SOLI 5mg in the single-blind treatment period, patients were classified into groups based on the level of reduction in incontinence episodes - <50% or ≥50%), geographic region as factors and baseline value as covariate. p<0.05 indicates superiority in favour of COMBN treatment vs SOLI monotherapy. NS: non-significant.

Significant improvements in favour of COMBN vs. SOLI 5 mg were found for all double/triple responder analyses (p<0.001) and three variables for COMBN vs. SOLI 10 mg (p<0.05).

Conclusions: Mirabegron add-on treatment to solifenacin significantly improved responder rates, notably 'dry rate,' and PROs, and may be beneficial for incontinent OAB patients with an inadequate response to solifenacin.

POD-03.03

A randomized controlled trial examining dose response of cranberry in the treatment of lower urinary tract infections in women and human urine cranberry metabolites

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Introduction and Objectives: Studies examining the use of cranberry to prevent urinary tract infection (UTI) in human subjects have demonstrated variable effectiveness with varying exposure. This sudy aimed to establish if UTI has a dose response to oral cranberry juice and to demonstrate cranberry metabolites in human urine via quantification of peonidin-3-O-galactoside (P3Ga) post-consumption.

Methods: This was a randomized, controlled trial of placebo vs. low- and medium-dose exposure to twice daily oral cranberry juice intake for one year. Human urine was collected prior to and during exposure. Physicians, nursing staff, urine chemistry team and statistician were blinded to treatment assignment. Primary outcome was the number of symptomatic UTIs (culture positive, single organism, acute symptoms).

Results: 263 women (19-85 years) participated. When treated as a categorical variable, using all 263 cases (intent to treat) there was no statistical difference in the number of UTIs between groups. If only subjects completing six months or more are considered, there is a weakly statistically significant difference between placebo (43% one or greater UTIs compared with 25% and 28% in low and moderate groups). If treated as a continuous variable using all 263 cases (intent to treat), statistics support weak evidence of a difference in mean UTIs. If restricted to those completing six months or more, there is strong evidence of a difference in the three groups (p=0.029). Kruskal-Wallis test confirms these findings. Increasing amounts of P3Ga are detectable in human urine, confirming cranberry anthocyanins post-ingestion.

Conclusions: Intent-to-treat analysis supports weak evidence or no difference between placebo and cranberry depending on treatment as a continuous or categorical variable. Subjects continuing for six months to one year demonstrated a statistical difference between placebo and cranberry, with no difference low and medium doses. Increasing amounts of P3Ga are detectable in human urine with twice daily cranberry intake.

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POD-03.04

The efficacy and safety of onabotulinumtoxinA or solifenacin compared to placebo in solifenacin-naïve patients with overactive bladder: Results from a multicentre, randomized, double-blind trial

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Introduction and Objectives: We compared the efficacy and safety of onabotulinumtoxinA (onabotA) 100 U or solifenacin (soli) with placebo (pbo) in soli-naïve patients with overactive bladder (OAB) who were inadequately managed by anticholinergic medications. A post-hoc analysis compared onabotA and soli.

Methods: This double-dummy, double-blind study randomized patients 2:2:1 to onabotA 100 U/oral pbo (n=145), soli 5-10 mg/pbo injection (n=151), or double pbo (n=60). Assessments (Week 12) included least-squares (LS) mean change from baseline (BL) in urinary incontinence (UI; co-primary), micturition and nocturia episodes/day, mean percent reduction in UI, proportion of patients with 100% (co-primary) and ≥50% UI reduction, treatment-emergent adverse events (TEAEs), and initiation of clean intermittent catheterization (CIC).

Results: 356 patients were randomized; discontinuations due to AEs and lack of efficacy were 3.1% and 0.3%, respectively. For the onabotA, soli, and pbo groups, mean UI reductions/day were -3.2*, -2.6*, and -1.3, respectively; proportion of patients achieving 100% UI reduction were 33.8%*, 24.5%*, and 11.7%, respectively; and proportions of patients achieving ≥50% UI reduction were 77.2%*, 64.9%*, and 33.3%, respectively. Mean reductions in micturition episodes were -2.3*, -2.1*, and -1.06 for the onabotA, soli, and pbo groups, respectively, and reductions in nocturia episodes were -0.6, -0.5, and -0.3, respectively. In the post-hoc analysis, mean UIE reductions/day were significantly greater with onabotA versus soli (p=0.022). Higher proportions of onabotA-treated patients achieved 100% (p=0.107) and ≥50% (p=0.025) UIE reduction versus soli. Most common TEAEs were UTI, bacteriuria, and dry mouth. CIC rates were 6.2% (onabotA), 0.7% (soli), and 0.0% (pbo).

Conclusions: OnabotA resulted in greater reductions in daily UIE and higher proportions of patients with 100% and ≥50% UIE reductions than soli or pbo, with 1/3 of patients becoming 'dry.' No new safety signals were observed.

$p<0.05$ vs. pbo.

POD-03.05

Cardiovascular assessments in a randomized, double-blind, phase 3b trial of mirabegron add-on treatment in incontinent overactive bladder patients

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Introduction and Objectives: Mirabegron (MIRA) is a potent, selective β3-adrenoceptor agonist. Cross-reactivity with β1-adrenoceptors in the cardiovascular (CV) system is low. This study (NCT01908829) assessed efficacy endpoints, vital signs, and electrocardiogram (ECG) changes after treatment with a combination (COMBN) of MIRA and an antimuscarinic solifenacin (SOLI), in incontinent overactive bladder (OAB) patients with inadequate response to SOLI 5 mg.

Methods: Incontinent adults with OAB for ≥3 months received a two-week wash-out and four weeks single-blind daily SOLI 5 mg. Patients still reporting ≥1 incontinence episode(s) during a three-day diary were randomized (1:1:1) to daily double-blind treatment with COMBN (SOLI 5mg + MIRA 25 mg, increasing to MIRA 50 mg after four weeks), SOLI 5 mg, or SOLI 10 mg for 12 weeks. Vital signs assessed in the clinic included changes from baseline (BL) to end of treatment (EoT) in pulse rate (PR) and systolic/diastolic blood pressure (SBP/DBP). BL to EoT changes in Fridericia's corrected QT interval (QTcF) were determined from 12-lead ECG.

Results: All treatment groups had similar baseline characteristics (COMBN, n=725; SOLI 5 mg, n=728; SOLI 10 mg, n=719). The 1 mmHg SBP difference for COMBN vs. SOLI 10 mg resulted from decreased SBP with SOLI rather than increased SBP with COMBN. Percentage of patients with increased PR, SBP, or DBP at EoT meeting change from BL criteria was similar across groups, except a slight increase in those with ≥15 mmHg in DBP in both SOLI 5 mg and 10 mg vs. COMBN. Tachycardia incidence (PR ≥100 bpm during any assessment) was low (≤1.7%). Small dose-related BL to EoT increases in QTcF were observed for SOLI 10 mg, as in previous trials. QTcF changes were similar for COMBN and SOLI 5 mg. No clinically meaningful between-group differences were seen for BL to EoT changes for any vital sign. No additional effects were observed in ECG or QTcF findings for COMBN therapy.

Conclusions: In OAB patients with refractory incontinence, mirabegron add-on treatment to solifenacin results in an acceptable CV profile.

POD-03.06

Impact of prostatectomy modality on successful management of urethral complications after radical prostatectomy

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Introduction and Objectives: Although radical prostatectomy has been significantly refined by the use of robot-assisted surgery, urethral complications, such as vesicourethral stenosis (VUS) and incontinence, still occur. It is unclear if the type of prostatectomy influences successful management of post-prostatectomy complications. Our objective is to determine if prostatectomy modality impacts successful treatment of urethral complications after radical prostatectomy.

Methods: Review of 292 patients over a 10-year period with VUS managed endoscopically, or patients with post-prostatectomy incontinence (PPI) treated with insertion of an artificial urinary sphincter (AUS) or urethral sling were included in the study. Patients were divided into two groups: those undergoing open radical prostatectomy (ORP) and or robot-assisted prostatectomy (RALP). Patients were excluded if type of prostatectomy was not explicitly clear. Treatment success of VUS was defined as no evidence of recurrent stenosis <16 Fr on cystoscopy and resolution of incontinence (<1 pad/day) for patients with post-prostatectomy incontinence.

Results: 292 patients required 442 treatments for either VUS (292) or incontinence (68 AUS, 82 slings). 125 patients underwent ORP, while 167 underwent RALP. Groups did not differ with regard to age, stage, body mass index (BMI), radiation, and comorbidities. Treatment success of individual procedures was 57%, with a mean followup of 10 months. When stratified by prostatectomy modality, overall treatment success was significantly higher in patients with a history of RALP (62%) compared to ORP (52%; p=0.03). On subgroup analysis, there was no significant difference in AUS (p=0.34) and VUS (p=0.78) treatment success when stratifying for prostatectomy modality. However, patients treated with a urethral sling had significantly higher success in the RALP group (89.8%) compared to the ORP group (69.6%; p=0.02). On multivariate analysis prostatectomy modality remained significantly associated with treatment success (OR 4.2; 1.1-16.1; p=0.04), whereas age (p=0.57) and cancer stage (p=0.57) were not.

Table 1. POD-03.05. Change from Baseline to EoT in vital signs and QTcF for COMBN vs SOLI 5 mg and SOLI 10 mg monotherapy

	COMBN	SOLI 5 mg	SOLI 10 mg
Change from baseline to EoT in PR	**(n=725)**	**(n=728)**	**(n=719)**
Mean adjusted change in PR, bpm (SE) [95% CI]	0.47 (0.28) [-0.09, 1.02]	0.43 (0.28) [-0.12, 0.98]	0.27 (0.28) [-0.28, 0.83]
Mean treatment difference (COMBN vs monotherapy) (SE) [95% CI]		0.04 (0.40) [-0.75, 0.82]	0.19 (0.40) [-0.59, 0.98]
Patients w/change from baseline, n (%)*	n=710	n=715	n=708
≥5 bpm increase	47 (6.6)	53 (7.4)	59 (8.3)
≥10 bpm increase	14 (2.0)	16 (2.2)	12 (1.7)
≥15 bpm increase	5 (0.7)	2 (0.3)	1 (0.1)
Change from baseline to EoT in SBP	**(n=725)**	**(n=728)**	**(n=719)**
Mean adjusted change in SBP, mmHg (SE) [95% CI]	0.07 (0.38) [-0.68, 0.83]	-0.93 (0.38) [-1.68, -0.18]	-1.28 (0.38) [-2.03, -0.52]
Mean treatment difference (COMBN vs monotherapy) (SE) [95% CI]		1.01 (0.54) [-0.06, 2.07]	1.35 (0.54) [0.29, 2.42]
Patients w/change from baseline, n (%)*	n=710	n=715	n=709
≥10 mm Hg increase	24 (3.4)	31 (4.3)	26 (3.7)
≥15 mm Hg increase	13 (1.8)	13 (1.8)	9 (1.3)
≥20 mm Hg increase	2 (0.3)	4 (0.6)	5 (0.7)
Change from baseline to EoT in DBP	**(n=725)**	**(n=728)**	**(n=719)**
Mean adjusted change in DBP, mmHg (SE) [95% CI]	-0.35 (0.26) [-0.86, 0.16]	-0.45 (0.26) [-0.96, 0.05]	-0.48 (0.26) [-0.99, 0.03]
Mean treatment difference (COMBN vs monotherapy) (SE) [95% CI]		0.10 (0.36) [-0.61, 0.82]	0.13 (0.37) [-0.59, 0.85]
Patients w/change from Baseline, n (%)*	n=710	n=715	n=709
≥5 mm Hg increase	53 (7.5)	56 (7.8)	57 (8.0)
≥10 mm Hg increase	15 (2.1)	18 (2.5)	14 (2.0)
≥15 mm Hg increase	1 (0.1)	4 (0.6)	4 (0.6)
Change from baseline to EoT in QTcF	**(n=725)**	**(n=728)**	**(n=719)**
Mean change from baseline, msec, (SD)	0.49 (13.23)	0.77 (12.98)	3.30 (13.72)

Vital signs were analyzed in the Safety Analysis Set (SAF; all randomized patients who received ≥1 dose of any double-blind treatment). Adjusted change from baseline values and 95% CIs were generated from an ANCOVA model with treatment group, sex, age group (<65, ≥65 years), 4-wk incontinence reduction group (at randomization following 4 wks SOLI 5 mg treatment), and geographic region as fixed factors and baseline as a covariate. *Values are from SAF patients with 3 consecutive post-baseline values.

Conclusions: Type of prostatectomy influences successful treatment of urethral complications post-prostatectomy. Specifically, patients undergoing laparoscopic prostatectomy may have better outcomes with male slings when compared to those who underwent open prostatectomy.