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SOUNDING BOARD

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New technology assessment and current and upcoming therapies for underactive bladder

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Background and Aims: Stakeholders from around the world came together to address the unmet needs of underactive bladder (UAB) at the 3rd International Congress for Underactive Bladder.

Methods: The main recommendation from the regulatory working group is a need for a meeting of UAB stakeholders and regulatory agencies including the FDA to discuss guidance for regulatory trial design for devices, drugs, and/or biologics for UAB.

Results: The following issues to be discussed and agreed upon for UAB trials: 1) Appropriate inclusion and exclusion criteria. 2) Should residual urine volume be the primary outcome parameter and how often should it be measured? 3) Are there secondary measures that should have a place in UAB trials, such as change in the number of catheterizations, quality of life measures, etc.? 4) Use and format of bladder voiding and catheterization diary for trials. 5) Define role and technique of urodynamics in UAB trials. Are urodynamics required to monitor, and possibly exclude, individuals with high pressure voiding induced by bladder prokinetic therapies? 6) Development and use of UAB questionnaires.

Discussion and Conclusion: The UAB regulatory working group recognizes the path forward should include engaging the FDA and other regulatory organizations that may harmonize and formalize guidance for regulatory trial designs for therapeutics for UAB.

KEYWORDS
aging; incontinence, retention, stake holders, underactive bladder, urodynamic

1 | INTRODUCTION

"Helpless"—that is how many patients feel when they cannot void or effectively empty their bladder, a condition referred as underactive bladder (UAB). While treatments for overactive bladder (OAB) have continued to improve, there are still no effective treatments for patients with the converse condition—UAB. The current mainstay of UAB treatment for urinary retention is clean intermittent catheterization (CIC) or indwelling catheters to empty the bladder.[1] However, complications and adverse effects can arise, especially during long-term use. Current research and treatment under consideration for UAB is described in detail in the summary paper from the second International Congress on Underactive Bladder.[2] The burden of UAB will rapidly

Alan Wein led the peer-review process as the Associate Editor responsible for the paper.

rise with the aging population across the world. UAB describes the troubling symptoms including straining, incomplete bladder emptying, hesitancy, and frequent urination or leakage due to overflow incontinence. UAB can be caused by myogenic and neurogenic conditions as well as aging and medication side-effects. UAB is therefore acceptable by most authorities as a complex and multifactorial condition of significant unmet medical needs.

A recent study highlighted the levels of prevalence and lack of awareness of underactive bladder in the general population. The survey revealed that 23% of men and women reported having a problem emptying the bladder completely yet only 11% had ever heard of UAB.[3] UAB is a big medical problem for society and getting bigger with the aging population and rapidly increasing rate of diabetes that may cause UAB.

Stakeholders from around the world have come together to address the unmet needs of UAB research and care. The first International Congress for underactive bladder (CURE-UAB), sponsored by the National Institute of Aging, National Institute of Diabetes and Digestive and Kidney Diseases, Aikens Center for Neurourology Research at Beaumont Health System and the Underactive Bladder Foundation was held in February 2014 in Washington DC. The second International meeting was in December 2015 in Denver, CO and the third CURE-UAB was held in March 2017 in Washington DC.

The regulatory working panel at the third International Congress on Underactive Bladder (CURE-UAB 3.0) discussed what treatments for UAB have been approved by regulatory agencies as well as identifying the current gaps in development of new therapies. Furthermore, there is little guidance for a currently approved drug or device to seek Food and Drug Administration (FDA) approval for the treatment of UAB. The working panel deliberated on recommendations for the best path forward with regulatory agencies, especially the US FDA, and the development of valid and reasonable measurements for UAB treatment efficacy. Members of this working panel included stakeholders interested in advancing health care and research in UAB including those from academia, industry, regulation, and advocacy. The panel called out the great unmet need in clarity of regulatory approval pathways for products to treat UAB, including drugs, devices, and biologics.

Recently, the American Urological Association (AUA) Quality Improvement & Patient Safety Committee (QIPS) developed a white paper on the diagnosis of non-neurogenic chronic urinary retention based on the U.S. Department of Health and Human Services Agency for Healthcare Research and Quality (AHRQ) and other relevant literature.[4,5] Chronic urinary retention was defined as an elevated post-void residual (PVR) greater than 300 mL that persists for at least 6 months and is documented on two or more separate occasions. Chronic urinary retention may be caused by either UAB, bladder outlet obstruction, or both. The work group proposes that chronic urinary retention be stratified by identifiable high-risk factors and by degree of symptoms. Appropriate follow-up and treatment is based on these stratifications. It is proposed that four outcome measurements be incorporated into future chronic urinary retention treatment studies: assessment of symptoms, reduction of risk, ability to void without catheterization, and stability or progression of symptoms/risk over time.

The UAB regulatory workgroup recognizes the path forward should include engaging the FDA and other regulatory organizations that may harmonize and formalize guidance for regulatory trial designs for therapeutics for UAB. This includes:

- Defining appropriate inclusion and exclusion criteria for patient selection in a clinical trial. One example is what to do with concurrent or suspected bladder outlet obstruction (BOO).
- Primary outcome measurement(s), secondary outcome(s), and survey instruments.
- Define role and technique to measure PVR and bladder diary entries.
- Define role and importance of urodynamics in screening and follow-up.
- Development and use of UAB questionnaire.

2 | UAB APPROVED PRODUCTS

2.1 | Bethanechol chloride for UAB

Bethanechol chloride (common brand names include Urecholine, Duvoid, Myotonachol, and Urocarb) is a synthetic parasympathomimetic and has been available for over 50 years to treat urinary retention, yet accurate information of its regulatory pathway is limited in the public domain. There appears to be only a single double-blind study of 20 adults with "decompensated bladder" conducted at a single center.[6] The key variable reported was "detrusor reaction" as measured by modified cystometry, testing the effectiveness of oral and subcutaneous doses of bethanechol chloride on the stretch response of bladder muscle in patients with urinary retention. Bethanechol chloride should not be employed when increased muscular activity of the gastrointestinal tract or urinary bladder might prove harmful, such as when the strength or integrity of the gastrointestinal or bladder wall is in question or in the presence of mechanical obstruction (Table 1).

Bethanechol chloride dosage must be individualized, depending on the type and severity of the condition to be treated. The usual adult oral dose ranges from 10 to 50 mg, given 3–4 times a day. The minimum effective dose is determined by giving 5–10 mg initially and repeating the same amount at hourly intervals until satisfactory response occurs, or until a maximum of

50 mg has been given. The effects of the drug sometimes appear within 30 min and are usually maximal within 60–90 min. The drug effects persist for about 1 h. Bethanechol can also be administered subcutaneous injection at lower doses and a quicker duration for response, however, the patient must be monitored for possible severe reactions. If necessary, the effects of the drug can be abolished promptly by atropine.

At CURE-UAB 3, our panel noted that available data via meta-analysis show little beneficial effect of other parasympathomimetic agents in treating or preventing UAB.[7]

2.2 | Sacral neuromodulation (SNM)

The SNM device, Interstim® (Medtronic, Minneapolis, MN), was approved by the FDA for the indications of refractory urge incontinence in 1997 and subsequently approved in 1999 (Premarket Approval P97004/S4) for the expanded indication of refractory, non-obstructive urinary retention. For the retention study population, the primary efficacy variable was the catheter volume per catheterization, which refers to urine volume obtained at the time of catheterization. Secondary outcomes included the number of CIC events/day and improvements in quality of life (Table 1).

The pivotal prospective, randomized multicenter trial included randomization to either a treatment group (immediate implant) or control group (delay to implant).[8] All qualified delay group patients were offered the opportunity for the implant after 6-months of follow-up. To qualify for randomization, patients were required to demonstrate a ≥50% reduction in catheter volume during percutaneous test stimulation compared to baseline (no stimulation). Secondary efficacy outcomes included analysis of a voiding diary, urodynamics, and quality of life assessment by the SF-36 Health Survey and Beck Depression Inventory.[9] A total of 177 retentive patients were enrolled and 68 met criterion for randomization. Results at 6 month follow-up demonstrated a statistically significantly reduction in catheterization volume ($P < 0.001$) in implant compared to control patients (Table 2). At 6 months 69% (20/29) implants stopped catheterization while only 9% (2/22) of controls stopped catheterization.

2.3 | InFlow

In 2015, the FDA approved the inFlow Intraurethral Valve-Pump device (Vesiflo, Redmond, WA) for use in women 18 years of age or older who have incomplete bladder emptying due to impaired detrusor contractility of neurologic

TABLE 1 Approved products to treat UAB discussed at CURE-UAB 3

Device—mechanism of action	Indication	Approval	Primary + key secondary efficacy variables	Key inclusion + exclusion criteria
Bethanechol—synthetic parasympathomimetic[6,7]	For the treatment of acute post-operative and post-partum non-obstructive (functional) urinary retention and for neurogenic atony of the urinary bladder with retention	1960–1970s	Unknown	Unknown
Sacral neuromodulation (SNM)—implantable device for electrical stimulation of sacral nerve[8,9]	InterStim® approved in 1997 (P97004) for treatment of urinary urge incontinence and expanded in 1999 to include urinary urgency-frequency, and urinary retention	1999	Refractory non-obstructive retention •Ability to reduce or eliminate catheter use •At 6 months with the stimulation off, the mean volume per CIC increased back up to 264 mL	Inclusion of idiopathic, non-obstructive UAB
InFlow[10]	Women ≥18 years old with incomplete bladder emptying due to impaired detrusor contractility of neurologic origin and who are capable of operating device, or who have trained caregivers. The device must be replaced every 29 days (or less)	2015	Residual urine volume measurement compared between CIC and inFlow device Secondary endpoint: QOL measurement	Impaired detrusor contractility using CIC

TABLE 2 Catheterization volume per catheterization 6 months SNM implantation

	Catheterization volume (mL) pre-treatment	Catheterization volume (mL) 6 months post-treatment
Treatment ($n = 29$)	339 ± 176	49 ± 106
Control ($n = 22$)	350 ± 152	319 ± 195

origin, and who are capable of operating it in accordance with instructions or who have trained caregivers. The inFlow device must be replaced every 29 days (Table 1). InFlow is a non-surgical urinary prosthesis intended to provide bladder drainage for women with UAB.[10]

Regulatory approval was primarily based on a clinical trial that enrolled 273 women with impaired detrusor contractility using CIC. Over half of the women stopped using the device as a result of discomfort and/or leakage of urine. All subjects with PVR data available for both baseline and treatment were able to participate in the study, which resulted in a total of 115 eligible subjects. A total of 98% (113/115) of subjects had a median inFlow treatment PVR that was no greater than the median CIC baseline PVR or both medians were <50 mL, with median PVR at each visit during inFlow treatment ranging from 10 to 20 mL. A key secondary endpoint was quality of life (QOL) measurement. Among those subjects with both baseline and treatment QOL data, patient scores for the Wagner I-QOL increased by a mean of 25 points on a 100 point scale ($P < 0.0001$) while using the inFlow. The median percent improvement was 54%. The results were both statistically and clinically significant.

3 | UAB INVESTIGATIONAL PRODUCTS

3.1 | Autologous muscle-derived cells (AMDC) for underactive bladder

Regenerative medicine, through the application of either stem or progenitor cells, is now in clinical trial for the treatment of UAB. AMDC are harvested by muscle biopsy, are purified and expanded at an external specialized lab (Cook MyoSite, Inc.), and are then injected into the detrusor of enrolled patients. Degeneration or loss of detrusor smooth muscle is regarded as one of contributors to UAB associated with aging. Skeletal muscle-derived cells injected into the bladder wall show evidence of smooth muscle phenotype and induced innervation, with urodynamic evidence of enhanced detrusor contraction.[11] An initial compassionate use case demonstrated feasibility and safety at Beaumont Health System in Michigan and that has led to an ongoing clinical trial, which is currently in progress (Clinical Trials.gov Identifier NCT02463448) (Table 3).

3.2 | A new drug for UAB in development

Dignify is developing neurokinin2 receptor (NK2R) agonists as "on-demand, rapid-onset, short-duration, drug-induced, voiding therapy" for individuals who require catheterization and do not have BOO.[12] The lead candidate (DTI-100) is a seven amino acid peptide analog of neurokinin A that produces highly efficient voiding (VE > 85%) within 5 min of intravenous (i.v.) or subcutaneous (s.c.) dosing in >85% of awake rats, dogs, minipigs, and monkeys at doses that are surprisingly well tolerated (Table 3).

Defecation accompanies DTI-100-induced micturition in virtually all cases in these behavioral experiments, and DTI-100 administration to anesthetized animals produces

TABLE 3 UAB products in trials discussed at CURE-UAB

	Indication	Primary + key second outcome	Key inclusion + exclusion criteria
Autologous muscle-derived cells[11]	Biological use of patients' own stem cells derived from a muscle biopsy and injected into the bladder wall for chronic UAB symptom relief—see clinical trial NCT02463448	1. Safety 2. Questionnaire voiding and CIC diary 3. PVR	Inclusion: adult men and women History of UAB > 6 months, PVR > 150 mL, UAB-Q ≥ 3 Exclusion: known BOO, including pelvic prolapse beyond the introitus
Dignify therapeutics[12]	On-demand induction of voiding in individuals who previously required catheterization to void urine and are without BOO	1. Safety 2. Voiding efficiency (VE), questionnaire, and diary	Inclusion: individuals who require catheterization to void urine Exclusion: BOO
Lilium	Bladder volume for residual urine measurement and sensory impaired UAB	Bladder volume measurement comparable to catheterization volume	N/A

rapid (<2 min), short duration (10 min), powerful contractions of both the bladder (>40 mm Hg) and rectum (>30 mm Hg) across a similar time course. This effect on the rectum to induce defecation may be considered a therapeutic benefit for those who require a "bowel program" to defecate (e.g., spinal-injured individuals), or it may be considered an inconvenient side effect requiring anal wiping each time micturition is desired. All effects on the bladder and rectum are completely blocked by an NK2R antagonist, GR159897. Emesis, signs of GI discomfort, and hypotension are seen at higher doses and are expected to be the dose-limiting side effect in clinical trials. Dosing four times/day for 5 days with DTI-100 in dogs showed consistent responses throughout the study with voiding occurring within 5 min after administration of 85% doses. Defecation was also produced 85% of the time during four times/day dosing.

Peptide NK2R agonists may provide an on-demand voiding therapy in that is both rapid onset, yet short in duration thereby allowing an individual to control when micturition (and/or defecation) occur and reduce or eliminate the need for catheterization (and a bowel program). Although animals studies (to date) have not detected clinically significant increases in bladder pressure (i.e., >40 mm Hg) during voiding cystometry or under bladder isovolumetric cystometry conditions in acute spinal rats, voiding pressures were briefly elevated (up to 60 mm Hg) in anesthetized rats with an intact spinal cord.[12] Studies in individuals with bladder outlet obstruction or detrusor sphincter dyssynergia are planned for these special populations.

3.3 | A bladder scanner for the patient and caregiver

Measurement of PVR is accepted by most authority as a primary measurement for the diagnosis and follow-up of UAB. There is an increased risk of urinary tract infection in UAB patients with large PVR, therefore catheterization should be avoided and the use of ultrasound is the standard of care. Progress is being made to advance the technology of bladder ultrasound scanners to make it a convenient and inexpensive test that can be done at the point of care. One example is a miniature bladder residual scanner recently introduced in Japan (Table 3).

Lilium Otsuka Co., Ltd. (Kanagawa, Japan) received regulatory approval in Japan in 2015 for a continuous, non-invasive bladder urine volume sensor called the Lilium α-200. Lilium α-200 is a hand-held urine volume sensor which measures the residual bladder volume. Because the bladder ultrasound scanner makes it possible to continuously monitor volumes, it can also provide alerts on appropriate timing for CIC. The small size and easy use of the scanner allows for better urination schedules and catheterization volume in patients with UAB or those with diminished sensation of bladder filling. The device is planned for seeking regulatory approval and introduction in the United States.

4 | SUMMARY AND NEXT STEPS

The main recommendation from the regulatory working group is a need for a meeting of UAB stakeholders and regulatory agencies including the FDA to discuss guidance for regulatory trial design for devices, drugs, and/or biologics for UAB. The following issues to be discussed and agreed upon for UAB trials include:

- Appropriate inclusion and exclusion criteria.
- Should PVR be the primary outcome parameter and how often should it be measured?
- Are there secondary measures that should have a place in UAB trials, such as change in the number of CIC, quality of life measures, etc.?
- Use and format of bladder voiding and catheterization diary for trials.
- Define role and technique of urodynamics in UAB trials. Are urodynamics required to monitor, and possibly exclude, individuals with high pressure voiding induced by bladder prokinetic therapies?
- Development and use of UAB questionnaires.

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CONFLICT OF INTEREST

Michael B. Chancellor is one of the inventors of the autologous muscle-derived cell (AMDC) process and has received royalty payments for the stem cell process and payments for consulting from Cook MyoSite. Ronald Jankowski and Ryan Pruchnic are Cook Myosite employees. Karl Thor is an employee of Dignify Therapeutics, which is developing DTI-100.

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