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A Phase 2 Study - Tengion Autologous Neo-Bladder Augment™ (NBA) for Augmentation Cystoplasty in Subjects with Neurogenic Bladder Secondary to Spinal Cord Injury

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ABSTRACT:

Introduction:
Augmentation cystoplasty utilizing gastrointestinal tissue is the mainstay of surgical treatment for medically refractory neurogenic bladder (NGB). We conducted a prospective, multicenter, Phase-2 study utilizing an autologous cell-seeded biodegradable scaffold in adults with NGB secondary to spinal cord injury (SCI).

Methods:
Male or female subjects 18 years or older, with NGB due to SCI of at least 12 months, underwent implantation with the NBA if, despite maximal tolerable anticholinergic medication, they required augmentation cystoplasty for bladder detrusor pressure ≥40 cmH20 and/or new onset of upper tract changes. Following an open bladder biopsy, urothelial and smooth muscle cells were grown ex vivo and then seeded onto a biodegradable scaffold to form the NBA. The implanted NBA served as a template for bladder tissue regeneration. The primary endpoint was change from baseline in maximum detrusor pressure (Pdetmax) at 12 months post-NBA. Exploratory endpoints included a responder analysis based on volume and Pdetmax at terminal contraction and continence.

Results:
Four centers enrolled 7 subjects. A total of six patients (4 males, 2 females) were implanted. Mean age was 28.7 (range 17-42) years. There were four serious adverse events (SAE) considered related to the NBA by the investigators. There were two asymptomatic post operative bladder leaks which resolved spontaneously within days, one construct leak secondary to MRSA infection which resolved with antibiotics and one bladder perforation during the month 9 visit urodynamic study (UDS) procedure which resolved with conservative treatment. This patient underwent an elective enterocystoplasty. The mean change from baseline to 12 months in Pdetmax was -17 (range -61 - 27) cm H2O. There were 2 responders, 2 partial responders and 2 non-responders based on an exploratory analysis. These results are similar at the 2 year follow-up.

Discussion:
The study supports the feasibility of regenerative medicine in bladder augmentation. Long term follow-up is ongoing. Additional studies are needed to confirm the benefits of this technology.

I. OBJECTIVE:

A prospective, multicenter, Phase 2 study in the United States was undertaken to evaluate whether augmentation cystoplasty using an autologous neo-bladder construct would decrease maximum detrusor pressure in subjects with neurogenic bladder secondary to spinal cord injury that was refractory to medical treatment.

II. METHODS:

This was an open label, single arm study in which up to 10 subjects were to be implanted with the NBA.

Inclusion Criteria:

- Male and female subjects at least 18 years of age
- Neurogenic bladder secondary to spinal cord injury at least 12 months prior to study entry.
- Utilization of maximally-tolerated dose and regimen of medical therapy (e.g. anticholinergics) for at least 1 month or failure to tolerate /contraindication to such agents
- Subjects on anticholinergic agents at study entry were permitted to remain on same dosing during study participation.
- Medical need for bladder augmentation, as defined by the presence of:
  - Maximum detrusor pressure ≥40 cmH20 during urodynamic evaluation, **OR**
  - New-onset of upper urinary tract changes (hydronephrosis, vesicoureteral reflux) in the last 12 months

Exclusion Criteria:

- Any prior bladder augmentation or urinary diversion procedure
- Bladder capacity ≤100 mL
- Vesicoureteral reflux > grade 3
- Requirement for concomitant urological surgical procedure (e.g. ureteral re-implantation)

Eligibility was confirmed by a Steering Committee.

Endpoints:

Primary Outcome Measure:

- Change from baseline in maximum detrusor pressure as assessed by standardized urodynamic measurements (UDS) at 12 months
- Overall safety assessment and events of special interest during the primary analysis phase (1st 12 months)

Secondary Outcome Measures (through month 60) included:

- Bladder capacity
- Bladder volume at first involuntary contraction
- Continence, as assessed by voiding diary
- Functional capacity (maximum catheterized volume during the recording period)

Exploratory Analysis:

- Responder analysis based on volume and Pdetmax at terminal contraction per UDS, combined with clinically relevant assessment (i.e. continence per voiding diary, radiographic findings, subjective quality of life (QoL) per patient narratives)

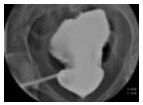
Procedures:

- Open bladder biopsy to procure autologous urothelial and smooth muscle cells
- Urothelial and smooth muscle cells grown ex vivo for 5 – 7 weeks, then seeded onto a biodegradable scaffold to form the NBA
- NBA surgically attached to the dome of the native bladder
- Neo-vascularization of NBA optimized with wrapping with omentum at time of implant
- Subjects cycled bladder post operatively by intermittent clamping and releasing of suprapubic catheter
- Urodynamic, clinical and radiographic assessments performed at 6, 9 and 12 months post implantation
- Long term follow up for up to 60 months post implantation
- UDS read by independent central reader


Neo-Bladder Construct


Surgical Implantation


Omentum-wrapped Construct


Cystogram, POD 10

III. RESULTS:

- Four centers enrolled and implanted subjects:
  - The Methodist Hospital - Houston, TX
  - Rancho Los Amigos National Rehab Center - Downey, CA
  - Shepherd Center, Inc. – Atlanta, GA
  - Thomas Jefferson University Hospital – Philadelphia, PA
- 7 subjects were enrolled
- Six patients (4 males, 2 females) were implanted. One subject withdrew prior to biopsy.
- Mean age of enrolled patients was 28.7 (range 17-42) years.
- Due to recruitment challenges across all sites, enrollment in the study was discontinued after implantation of 6 patients.

Table 1: Primary Outcome Measure: Change from Baseline in Maximal Detrusor Pressure at Month 12

Pdet Max - Baseline	Pdet Max - 12 mos post-op	Pdet Max - Change from Baseline
N=6 Mean: 77 cm H20 Min – Max: [45 – 131]	N=5* Mean: 63.8 cm H20 Min – Max: [29 – 102] 95% CI [28.2 – 99.4]	N=5* Mean: -17 95% CI [-61.4, 27.4]

Data not available for 1 subject due to perforation at Month 9

Table 2: Urodynamic Results (based on Central Reader) and Functional Capacity Over Time by Subject

Patient	Volume at terminal contraction (mL)			Max Pdet at terminal contraction (cmH20)			Cystometric Capacity			Functional Capacity*		
	Baseline	M12	M24	Baseline	M12	M24	Baseline	M12	M24	Baseline	M12	M24
001-002	128	320	407	131	80	81	128	320	390	160	650	700
002-001	NA	92	105	NA	29	55	113	92	105	Unk	200	200
002-002	NA	278	94	NA	63	45	398	278	94	Unk	1200	900
002-004	NA	NA	NA	NA	NA	NA	377	354	354	300	350	300
004-001	150	229	172	93	102	71	150	229	172	300	300	350
006-001	NA	ND	ND	NA	ND	ND	291	ND	ND	300	Unk	Unk

** Functional capacity was defined as the highest catheterized volume based on voiding diary data*
NA = no terminal contraction
ND = subject experienced bladder perforation during month 9 UDS, has not had any subsequent study UDS performed
Unk = Diary data not available

Radiographic Changes:
Subject 002-004 had minimal hydronephrosis at baseline, which was resolved at month 12 and month 24. This same subject had grade I reflux at baseline, which increased to grade III at month 12 and month 24. No other subjects had hydronephrosis or reflux noted at any study visit.

Exploratory Responder Analysis:
An exploratory analysis incorporating routinely utilized clinical parameters to assess outcome was employed in order to apply a more robust, clinically relevant context by the investigators. In this analysis, subjects were retrospectively classified as responders, partial responders or non-responders based upon a comparison of each subject's baseline status (e.g. UDS, continence, QoL per patient narratives) with month 12 and month 24 results.

- 2 subjects showed UDS and clinical improvement and were considered responders at month 12 and 24
- 2 subjects were considered partial responders, based upon increased capacity and/or decreased leakage
- 2 subjects were considered non-responders at month 12 and 24

Table 3: Clinical Outcome as Determined by Exploratory Responder Analysis

Patient	Response M12	Response M24	Clinical Outcome Description
001002	Responder	Responder	Improved continence and capacity with reduced pressures at M12 and M24
002004	Responder	Responder	Reduced filling pressures, reduction in UTIs at M12 and M24; Improved hydronephrosis but increase in reflux at M12 and 24 (Grade 1 to III)
002001	Partial Responder	Partial Responder	Similar capacity at baseline, M12 and M24; but some improvement in continence
004001	Partial Responder	Partial Responder	Similar capacity at baseline, M12 and M24; however decreased urgency and improved continence
002002	Non Responder	Non Responder	No meaningful change in UDS or continence
006001	Non Responder	Non Responder	Bladder perforation during the month 9 visit UDS procedure which resolved with conservative treatment. The patient subsequently underwent an elective enterocystoplasty.

Safety:

Event	N	Event	N
Urinary tract infection	6	Pyrexia	3
Nausea	5	Post procedure urine leak	3
Vomiting	3	Procedural pain	3
Oedema peripheral	3	Anxiety	2

N= number of subjects experiencing each event; subjects are only counted once per event

Four serious adverse events (SAE) considered related to the NBA were reported by the investigators within the first 24 months post implantation:

- 2 asymptomatic post operative bladder leaks which resolved spontaneously within days
- 1 construct leak secondary to MRSA infection which resolved with antibiotics
- 1 bladder perforation during the month 9 visit UDS procedure which resolved with conservative treatment. This patient underwent an elective enterocystoplasty.

One patient developed a small bowel obstruction postoperatively related to abdominal surgery and not involving the NBA. This was managed conservatively.

IV. CONCLUSIONS:

- NBA implantation procedure generally well tolerated in study patients
- NBA implantation did decrease maximal detrusor pressure from baseline to month 12, but this did not appear to be clinically meaningful in this study population
- Clinical benefit was seen in some patients on exploratory responder analysis
  - Predictors for response not clear
  - For those with clinical benefit, response has been durable at 24 months
  - Evaluation of urodynamics with clinical criteria (voiding diaries, incidence of incontinence and catheterization frequency), and imaging (reflux, hydronephrosis) may be more clinically relevant
- Adverse events are as expected in this challenging patient population[1,2,3].

References

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