

# LESSONS LEARNED FROM A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF AUTOLOGOUS MUSCLE DERIVED CELLS FOR URINARY SPHINCTER REPAIR

## Hypothesis / aims of study

Autologous Muscle Derived Cells for Urinary Sphincter Repair (AMDC-USR) are being investigated as a novel, durable therapy for treatment of stress urinary incontinence (SUI) in women. The technology is an intrasphincteric injection of muscle cells designed to augment sphincter function. Herein, we describe the challenges of progressing from early phase clinical studies to a randomized controlled trial (RCT) and discuss how initial RCT results have influenced the strategic design of current and future studies including 1) selection of clinically meaningful efficacy endpoints based on incontinence episode frequency (IEF) reduction, 2) improved understanding of the estimated placebo rate, and 3) refinement of patient selection criteria to match AMDC-USR's proposed mechanism of action.

## Study design, materials and methods

Women with predominant SUI who had diary-reported stress IEF of  $\geq 3$  leaks over 3 days,  $\geq 3$  g 24-hour pad test, and  $\geq 3$  g in-office pad test were enrolled. Patients with recurrent or persistent SUI after incontinence surgery could be included in the study. After muscle biopsy to acquire tissue for AMDC-USR production, patients were randomized 2:1 to receive injection of  $150 \times 10^6$  AMDC-USR or vehicle placebo. Patients were additionally randomized 1:1 to receive 1 or 2 treatments, with second treatment administered approximately 6 months after first treatment. SUI was assessed with 3-day diaries of stress IEF, 24-hour pad tests, in-office pad tests, and Incontinence Quality of Life (IQOL) questionnaires. The primary composite efficacy endpoint was the percentage of patients with  $\geq 50\%$  IEF reduction or  $\geq 50\%$  reduction in either pad test 12 months post-treatment. Patients were unblinded after completing 12-month visits, and placebo patients could opt to receive an open-label injection of AMDC-USR. Patients were followed for 2 years after initial treatment.

## Results

Overall, 150 patients were biopsied, 143 patients were treated (93 AMDC-USR, 50 placebo), 141 patients completed 12-month visits (91 AMDC-USR, 50 placebo), 49 placebo patients received open-label AMDC-USR, and 129 patients completed 2-year visits (83 original AMDC-USR, 46 open-label AMDC-USR). AMDC-USR and placebo groups had similar baseline characteristics and similar rates of adverse events. With the composite endpoint, responder rates for both AMDC-USR and placebo exceeded 80%; therefore, enrollment was halted at 61% (150/246) of the planned study size. To identify alternate, clinically meaningful endpoints, we examined the correlation of IEF reduction with improvement in IQOL scores (Figure 1). Patients with  $\geq 50\%$  IEF reduction had greater IQOL score improvement than patients with  $< 50\%$  IEF reduction, and patients with  $\geq 75\%$  IEF reduction and  $\leq 1$  stress leak/3 days displayed even greater IQOL improvement.

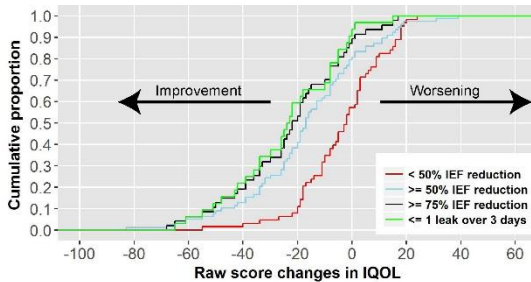


Figure 1. Cumulative distribution function plot examining correlation of IQOL score change at 12 months with IEF reduction endpoints. Analysis independent of treatment received.

With clinically meaningful IEF reduction endpoints, a potential treatment effect was detected at 3, 6, and 12 months for the entire patient cohort (Figure 2A) and was enhanced for a subgroup of 17 patients (11 AMDC-USR, 6 placebo) with recurrent or persistent SUI after incontinence surgery (Figure 2B).

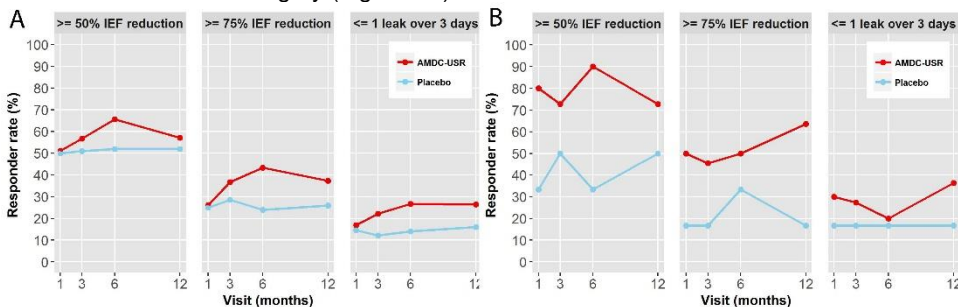


Figure 2. Responder rates for IEF reduction endpoints for (A) entire patient cohort and (B) patients with recurrent or persistent SUI after incontinence surgery

## Interpretation of results

As outlined in the table below, results from our first cell therapy RCT for women with SUI have provided critical data to support the selection of clinically meaningful efficacy endpoints, to estimate placebo response rates, and to refine patient selection criteria

for current and future studies.

Original study design element	Lessons learned	Impact on current and future study design
Primary composite endpoint defined success as $\geq 50\%$ diary-reported IEF reduction <u>or</u> $\geq 50\%$ improvement in 24-hour pad test <u>or</u> $\geq 50\%$ improvement in in-office pad test at 12 months	<p><math>\geq 80\%</math> responder rate for both AMDC-USR and placebo; composite endpoint was too liberal to detect treatment differences</p> <p>FDA does not recommend the use of pad tests as primary efficacy endpoints for SUI studies. 24-hour pad tests may be confounded in patients with mixed urinary incontinence and in-office pad tests are not reproducible if bladder fill volumes are inconsistent</p> <p>Post hoc analyses correlating IEF reduction with QOL score improvement suggest that <math>\geq 50\%</math> IEF reduction, an accepted endpoint in SUI studies [1, 2], and more stringent endpoints of <math>\geq 75\%</math> IEF reduction and <math>\leq 1</math> stress leak/3 days are clinically meaningful endpoints</p>	<p><math>\geq 50\%</math> IEF reduction used as primary efficacy endpoint and <math>\geq 75\%</math> IEF reduction and <math>\leq 1</math> stress leak/3 days used as secondary efficacy endpoints</p>
Power calculation assumed 30% responder rate for placebo	<p><math>&gt;80\%</math> responder rate for placebo with composite efficacy endpoint; rates were lower with IEF reduction endpoints</p>	<p>Placebo responder rate adjusted for IEF reduction endpoints</p>
Urethral hypermobility not assessed and not included as part of selection criteria	<p>AMDC-USR is designed to augment sphincter function. Patients with SUI primarily due to urethral hypermobility may not demonstrate significant improvement with AMDC-USR treatment</p> <p>Mid-urethral sling and bladder neck suspension address urethral hypermobility; therefore, patients who underwent prior incontinence surgery likely have SUI due to sphincter deficiency. For this population, outcomes for <math>\geq 50\%</math> IEF reduction favor AMDC-USR over placebo</p>	<p>Q-tip test result of <math>&gt;30^\circ</math> deflection used to exclude patients with notable urethral hypermobility</p> <p>Patients with recurrent or persistent SUI after incontinence surgery will continue to be included in studies. To ensure equal allocation of prior incontinence surgery patients to treatment groups, randomization is stratified based on whether patients have undergone prior incontinence surgery</p>

#### Concluding message

Lessons learned from our first RCT strengthen the design and scientific rigor of current and future AMDC-USR studies.

Placebo effects are likely influenced by many variables (e.g., invasiveness of treatment, duration of follow-up, expectations of study population) and understanding their impact on outcome measures is critical to successful development of new treatments. Yet, knowledge of such effects is currently limited for SUI therapies. Likewise, SUI outcome measures must be viewed in terms of their sensitivity to placebo effects, clinical meaningfulness, and regulatory agency acceptance. From data collected in our first RCT, we correlated QOL improvement with diary-reported IEF reduction to identify clinically meaningful endpoints and estimated the placebo response rate for a cell therapy SUI trial with 12-month follow-up. Importantly, IEF reduction is viewed favorably by regulatory agencies as a primary outcome in SUI studies.

Our data also suggest that patients with minimal urethral hypermobility (e.g., patients with recurrent or persistent SUI after incontinence surgery) may represent ideal candidates for sphincter augmentation, which aligns with the proposed mechanism of action for AMDC-USR. Future studies will focus on this patient population by excluding patients with notable urethral hypermobility at screening.

#### References

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- Yalcin I, Peng G, Viktrup L, Bump RC. Reductions in stress urinary incontinence episodes: what is clinically important for women? *Neurourol Urodyn*. 2010;29(3):344-347.

#### Disclosures

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