Autologous Muscle Derived Cells-Urethral Sphincter Repair (AMDC-USR) for stress urinary incontinence

SUMMARY
Autologous Muscle Derived Cells-Urethral Sphincter Repair (AMDC-USR) is a first in-class autologous stem cell-based therapy in which autologous muscle derived cells (AMDC) are isolated from skeletal muscle biopsies, expanded ex vivo and injected into the urethral sphincter where it is hoped they may act to incorporate into host tissue (urinary sphincter) and improve muscle function. AMDC-USR is intended for the treatment of stress urinary incontinence (SUI) in women and is administered by transurethral injection as a single dose comprised of 150 (±20%) x 10^6 cells.

SUI is the most common form of urinary incontinence in women and is characterised by involuntary urine leakage on effort, exertion, sneezing or coughing. SUI is usually the result of the weakening or damaging of the muscles that are used to prevent urination, including the pelvic floor muscles and the urethral sphincter. Prevalence estimates for urinary incontinence vary widely due to differences in definition, and because many of those affected do not admit to having continence difficulties. Where the most inclusive definitions have been used (patient reporting SUI ‘ever’, ‘any’, or ‘at least once in the last 12 months’), estimates suggest prevalence rates of between 5-69% in women and 1-39% in men. Most studies report a prevalence of 25-45%, and whilst one study stated that 34.2% of women reported urinary incontinence at times, only 3.5% experienced the symptoms on a daily basis and 11.8% on a weekly basis.

In 2012-13 there were 14,982 admissions (including 14,454 women) for SUI in England, resulting in 8,825 bed days and 15,032 finished consultant episodes.

AMDC-USR is currently undergoing two phase III clinical trials evaluating its efficacy in reducing stress leaks, and safety against placebo transurethral injections. These studies are expected to complete in 2017.
TARGET GROUP

- Stress urinary incontinence (SUI): women.

TECHNOLOGY

DESCRIPTION

Autologous Muscle Derived Cells-Urethral Sphincter Repair (AMDC-USR) is an autologous stem cell-based therapy in which autologous muscle derived cells (AMDC) are isolated from skeletal muscle biopsies, expanded ex vivo and injected into the urethral sphincter where they may act to incorporate into host tissue (urinary sphincter) and improve muscle function. AMDC-USR is a first in-class advanced therapy medicinal product (ATMP) intended for the treatment of SUI in women. AMDC-USR is administered by transurethral injection as a single dose comprised of 150 (±20%) x 10^6 cells. A single cryopreserved vial of cells is provided to the physician and diluted in saline immediately prior to administration.

Autologous muscle derived cells are also in phase II clinical trials for faecal incontinence.

INNOVATION and/or ADVANTAGES

If licensed, AMDC-USR will offer a novel, minimally invasive, non-surgical treatment option for adult women with SUI. It has the potential to become a one-off therapy, without the need for on-going or repeated treatment.

DEVELOPER

Cook MyoSite, Inc (a division of Cook Medical).

AVAILABILITY, LAUNCH OR MARKETING

Currently in phase III clinical trials.

This technology is registered as an advanced-therapy medicinal product (ATMP).

PATIENT GROUP

BACKGROUND

SUI is the most common form of urinary incontinence in women and is characterised by involuntary urine leakage on effort, exertion, sneezing or coughing\textsuperscript{1}. SUI is usually the result of the weakening or damaging of the muscles that are used to prevent urination including the pelvic floor muscles and the urethral sphincter\textsuperscript{2}.

SUI is more common among older women but also occurs in younger, active, healthy women\textsuperscript{3}. Obesity, smoking, family history of incontinence, chronic cough (which places frequent strain on the pelvic floor muscles) and menopause are risk factors for development of SUI. Pregnancy and childbirth also increase the chances of SUI as they may stretch, weaken, or damage the pelvic floor muscles, resulting in bladder leakage\textsuperscript{3}. Nerve injuries to the lower back and pelvic surgery are also potential risk factors\textsuperscript{3}.
NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:


CLINICAL NEED and BURDEN OF DISEASE

Prevalence estimates for urinary incontinence (UI) vary widely due to differences in definition, and because many of those affected do not admit to having continence difficulties. Where the most inclusive definitions have been used (patient reporting SUI ‘ever’, ‘any’, or ‘at least once in the last 12 months’), estimates suggest prevalence rates of between 5-69% in women and 1-39% in men. Most studies report a prevalence of 25-45%, and whilst one study stated that 34.2% of women reported UI at times, only 3.5% experienced the symptoms on a daily basis and 11.8% on a weekly basis.

However, not all of those experiencing even moderate or severe symptoms inform their GP. Only 1 in 9 of those reporting clinically significant symptoms in the above study felt the need for help with their symptoms. In another study, the prevalence of UI known to the health and social service agencies was 0.2% in women aged 15–64 years and 2.5% in those aged 65 and over – considerably lower than the estimates of underlying prevalence.

Stress UI appears to be the most common UI type and overall 50% of incontinent women in the Epidemiology of Incontinence in the County of Nord-Trondelag (EPINCONT) survey (Hannestad et al. 2000) reported this as their only symptom; 11% described only urgency UI and 36% reported mixed UI.

In 2012-13 there were 14,982 admissions (including 14,454 women) for SUI (N39.3) in England, resulting in 8,825 bed days and 15,032 finished consultant episodes.

The population likely to be eligible to receive AMDC-USR could not be estimated from routine, available published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

CURRENT TREATMENT OPTIONS

There are a number of options for the management of SUI and many factors are considered when determining optimal therapy, including: bladder capacity, renal function, sexual function, severity of the leakage, associated conditions, degree of patient discomfort and patient acceptability.

- **Initial management options**:  
  - Behavioural modifications: weight loss, smoking cessation, modification of fluid intake, scheduled voiding and physical exercise.  
  - Pelvic floor muscle and bladder training.  
  - Electrical stimulation and/or biofeedback for women who are unable to actively contract pelvic floor muscles.

- **Drug therapy**:  
  - Duloxetine hydrochloride is approved in the EU for the treatment of moderate to severe SUI and may be used as an alternative to surgical therapy. This treatment is rarely used in the UK because of significant adverse events.

- **Surgical treatment**:  
  - Intramural bulking agents: glutaraldehyde cross-linked collagen, silicone, carbon-coated zirconium beads, or hyaluronic acid/dextran co-polymers. Injected at sites around the urethra to reinforce the closing capacity. Repeat injections are often required to achieve efficacy.  
  - Mid-urethral tape procedures with macroporous polypropylene meshes are largely used as first line surgical therapy in the UK. In addition open colposuspension or autologous rectus fascial sling are also used, usually following failed mid-urethral tape procedures.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT01893138; AMDC-USR vs placebo; phase III.</th>
<th>NCT01382602; AMDC-USR vs placebo; phase III.</th>
<th>NCT01008943; AMDC-USR; phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source of information</td>
<td>Trial registry, manufacturer.</td>
<td>Trial registry, manufacturer.</td>
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</tr>
<tr>
<td>Location</td>
<td>USA only.</td>
<td>EU (incl UK), Canada and Hong Kong.</td>
<td>Canada only.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=267 (planned); aged ≥18 years; females; SUI ≥6 months duration; previously attempted conservative treatment; ≤2 episodes of</td>
<td>n=246 (planned); aged ≥18 years; females; SUI; previously attempted conservative treatment ≥1 month; ≤2 episodes of</td>
<td>n=16; aged ≥18 years; females; SUI; normal detrusor activity; bladder capacity &gt;200mL; no improvement in symptoms ≥6 months; failed prior</td>
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awakening to void during normal sleeping hours; no symptoms of pure urge or mixed urinary incontinence where urge incontinence is the predominant factor.

normal sleeping hours; no symptoms of pure urge or mixed urinary incontinence where urge incontinence is the predominant factor.

treatments (e.g. behaviour modification, bladder exercises, biofeedback, electrical stimulation, bulking injections, urethra; suspensions and/or drug therapy); no known vesicoureteral reflux, vaginal prolapse beyond the introitus, or other significant pelvic floor abnormalities with high pressure instability; no neuromuscular disorders, uncontrolled diabetes or morbid obesity.

Schedule

Randomised to AMDC-USR 150 (±20%) x 106 cells or placebo, both via transurethral injection at baseline, 1 month, 3 months, 6 months, 12 months, and 24 months.

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Patients received AMDC-USR 150 (±20%) x 106 cells via transurethral injection at baseline, 1 month, 3 months, 6 months, 12 months.

Follow-up

Primary outcome: 1 year. Secondary outcomes: 2 years.

For primary outcome: 1 year. For secondary outcome: 2 years.

Primary outcome: 1 year. Secondary outcomes: 1 year.

Primary outcome/s

≥50% reduction in stress leaks; safety.

>50% reduction in stress leaks; safety.

Safety.

Secondary outcome/s

≥50% reduction in pad weight; quality of life (QOL).

QOL.

≥50% reduction in stress leaks or ≥50% reduction in pad weight; QOL.

Key results

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Not reported.

Adverse effects (AEs)

No serious AEs related to product or process.

No serious AEs related to product or process.

No serious AEs related to product or process.

Expected reporting date

Estimated study completion date Oct 2017.

Estimated study completion date Aug 2017.

Previously reported as Oct 2012.

Trial

NCT00847535; AMDC-USR, transurethral vs periurethral administration; phase II.

AMDC, transurethral and periurethral administration; phase II.

AMDC; phase II.

Sponsor

Cook Myosite.

Cook Myosite

Cook Myosite

Status

Complete, published in abstract.

Complete, published.

Complete, published.

Source of information

Abstract19, trial registry20, manufacturer.

Publication21, manufacturer.

Publication22, manufacturer.

Location

USA and Canada.

Canada only.

Canada only.

Design

Randomised, open label.

Randomised.

Non-randomised, uncontrolled.

Participants

n=64; aged ≥18 years; females; SUI; normal detrusor activity; bladder capacity >200mL; no improvement in symptoms ≥6 months; failed prior treatments

n=38; aged ≥18 years; females; SUI; no improvement in symptoms ≥12 months; no known vesicoureteral reflux, significant pelvic floor abnormalities, or history of

n=8; aged ≥18 years; females; SUI; normal detrusor activity on filling cystogram; bladder capacity >200mL; no improvement in symptoms ≥12 months; failed prior
| Schedule | Patients randomised to transurethral or periurethral injection of 10 million, 50 million, 100 million, or 200 million AMDC. Multiple injections were used to administer the total dose of cells circumferentially around the urinary sphincter. | Phase 1  
20 patients randomised to receive 1, 2, 4, 8, or 16 $10^6$ AMDC via cytoscope assisted periurethral injection.  
Phase 2  
Patients randomised to receive 32, 64, or 128 $10^6$ AMDC via cytoscope assisted periurethral injection.  
Phase 3  
9 patients (3 per group received 16, 32, or 64 $10^6$ AMDC under transvaginal ultrasound guidance. Patients could elect to receive a second treatment of the same dose after 3-month follow-up. | Patients received AMDC 18-22 x $10^5$ via up to 4 circumferential transurethral injections at the 3, 6, 9, and 12 o’clock positions, using one of three different routinely performed injection techniques. |
| Follow-up | Follow-up to 12 months following treatment. | Follow-up to 18 months after initial treatment. | Follow-up to 12 months after injection. |
| Primary outcome/s | Safety. | Safety. | Safety. |
| Secondary outcome/s | 3-day diary of incontinence episodes; 24-hour pad weight; Urogenital Distress Inventory (UDI-6); Incontinence Impact Questionnaire (IIQ-7). | 1-hour standardised International Continence Society pad test; frequency of diary reported stress leaks during 3 days; IIQ-7 and UDI-6. | 3-day diary of incontinence episodes; 24-hour pad weight; Urogenital Distress Inventory (UDI-6); Incontinence Impact Questionnaire (IIQ-7). |
| Key results | Some patients in each dose group (numbers not given) reported ≥50% improvement in the occurrence of stress leaks and urine leakage during 24-hour pad test at 6 and 12 months (including ≤1 stress leaks and/or <1.3kg pad | For patients who received two AMDC treatments, high dose vs low dose groups, respectively: ≥50% reduction in pad weight, 88.9% vs 61.5%; ≥50% reduction in diary reported stress leaks, 77.8% vs 53.3%; ≤1 reported leak during final 3 months. | 3 patients withdrew from the study 1 month post-injection. Improvement in SUI was observed in 5/8 patients with 1 patient achieving total continence (maintained at 12-month study endpoint). |
Improvement was greater in two higher dose groups compared to lower dose groups. Improvements in UDI-6 and IIQ-7 scores reported for all groups.

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<th>Adverse effects (AEs)</th>
<th>days of follow-up, 88.9% vs 33.3%.</th>
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<tbody>
<tr>
<td>No serious AEs related to AMDC treatment reported. Treatment-related AEs occurring within 30 days of AMDC injection were limited to pelvic/abdominal pain or cramping (4.7%) dysuria (4.7%), gross haematuria (3.1%), vaginal and/or urethral itching (3.1%), haematoma at the biopsy site (3.1%), increased frequency (1.6%), and transient sensation of a foreign object in the urethra (1.6%). All events were easily treated or self-resolved.</td>
<td>No serious AEs or major complications related to treatment were reported. Pain and/or bruising at the biopsy site (7.9%) and pain at the injection site (10.5%) were the most commonly reported procedure related events. Symptomatic lower urinary tract infection, mild self-limiting urinary retention, dysuria, increased urinary frequency, pelvic/abdominal pain or cramping, and worsening incontinence each affected 2 patients (5.3%) within 30 days of AMDC treatment. Two patients experienced dizziness, shortness of breath, pruritus and/or periorbital oedema after injection (transient and did not require intervention).</td>
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**ESTIMATED COST and IMPACT**

**COST**

The cost of AMDC-USR is not yet known. A 56-cap pack of duloxetine (Yentreve) 40mg costs £36.96\textsuperscript{23}.

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival  
- Reduced symptoms or disability  
- Other: improved patient convenience due to non-surgical, minimally invasive administration and potential to become a one-off therapy, without the need for on-going or repeated treatment.
- No impact identified
### Impact on Health and Social Care Services

- Increased use of existing services
- Decreased use of existing services: non-surgical outpatient procedure. Has potential to become a one-off therapy, without the need for on-going or repeated treatment.
- Re-organisation of existing services
- Need for new services
- Other: need for ultrasonography and new staff training requirements due to transurethral administration.
- None identified

### Impact on Costs and Other Resource Use

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs: additional staff training required and additional costs for administration in clinic.
- Other reduction in costs: reduced use of secondary care specialist services, reduced need for interventional procedures and reduced social care costs.
- None identified

### Other Issues

- Clinical uncertainty or other research question identified: expert clinical opinion states that the concept of bulking of the sphincter does not necessarily treat other important aspects in the mechanism and pathophysiology of SUI, in particular weak pelvic floor musculature.
- None identified

### REFERENCES


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*a* Expert clinical opinion.


