HTA Austria
Austrian Institute for
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GmbH

Drug-coated balloon catheter for the treatment of urethral strictures

Systematic Review

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Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

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Content

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List of abbreviations

AE..... adverse event
CE..... Conformité Européenne
CI..... confidence interval
CSR ..... clinical study report
CTCAE ..... Common Terminology Criteria for Adverse Events
DCB ..... drug-coated balloon
DVIU..... direct vision internal urethrotomy
EAU..... European Association of Urology
EMDN ..... European Medical Device Nomenclature
EUnetHTA ..... European Network of Health Technology Assessment
Fr..... French
HTD..... health technology developer
IIEF..... International Index of Erectile Function
IPSS..... International Prostate Symptom Score
IQWiG..... Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen ("Institute for Quality and Efficiency in Health Care“)
JCA..... joint clinical assessment
LUT..... lower urinary tract
MD ..... mean difference
PROM ..... patient reported outcome measure
PVR..... post-void residual
Qmax..... maximum flow rate
QoL ..... quality of life
RCT..... randomised controlled trial
RoB..... risk of bias
SAE..... serious adverse event
UTI..... urinary tract infection
VAS ..... visual analogue scale

Executive Summary

Introduction

Health Problem

target population: men with recurrent anterior urethral strictures up to 3 cm

Urethral stricture in men is a narrowing of the anterior urethra, a common condition that impacts physical health and quality of life. If untreated, it can lead to complications such as recurrent urinary tract infections, urinary retention, and renal impairment. This assessment focuses on adult men with recurrent anterior urethral strictures up to 3 cm in length and bothersome urinary symptoms. Data on the exact number of affected patients in Austria is unavailable.

treatment options: dilation DVIU urethroplasty DCB dilation with restrictions

The European Association of Urology (EAU) recommends endoscopic treatments (dilation, direct visual internal urethrotomy/DVIU) or urethroplasty for recurrent urethral stricture. Repeated endoscopic treatments after several recurrences are not recommended. If urethroplasty is not an option and the patient has already had at least two failed endoscopic treatments, an alternative treatment drug (paclitaxel)-coated balloon (DCB) dilation is an alternative for short (<3 cm) bulbar strictures.

Description of Technology

Optilume DCB

The Optilume urethral DCB is the only available DCB for treating urethral strictures. It is a urethral dilation balloon pre-coated with paclitaxel, an antiproliferative drug intended to treat anterior urethral strictures in adult males.

allegedly less invasive than standard treatment

DCB was introduced as a novel technology in the EAU guideline in 2023. Compared to standard treatments—urethroplasty, urethrotomy, and dilation—its claimed advantage is lower invasiveness. This technology aims to bridge the gap between repeated endoscopic treatments and open urethroplasty.

Methods

national adaptation and update of a EUnetHTA assessment

This assessment updates and adapts the EUnetHTA joint clinical assessment (JCA) on the Optilume urethral DCB, evaluating its clinical effectiveness and safety.

systematic literature search in 3 databases

A systematic literature search in three databases (Medline, Embase and Cochrane) and a hand search in PubMed was conducted in December 2024 to identify relevant studies published after the search period of the JCA. After deduplication, 34 citations were identified. No additional citations were found by hand search. The Cochrane risk of bias 2.0 tool was used to assess the quality of RCTs. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of evidence. Two independent researchers performed the quality and evidence certainty assessments.

risk of bias assessment

GRADE certainty of the evidence

Domain effectiveness

critical effectiveness endpoints

The following endpoints were considered critical for decision-making: urinary function, treatment success, anatomical success and health-related quality of life.

Domain safety

The following endpoints were considered critical for decision-making: serious adverse events.

critical safety endpoints

Results

Available evidence

One RCT was included (ROBUST III) (n=127) for effectiveness assessment. Additionally, three single-arm studies were included (ROBUST I and II, Alhamdani et al.) (n=86) for safety assessment.

effectiveness: 1 RCT (n=127)
safety: 3 single-arm studies (n=86)

ROBUST III was a manufacturer-sponsored multicenter study conducted in the U.S. and Canada. This study compared Optilume DCB to a control group that received either dilation or urethrotomy. The Optilume group underwent pre-dilation, followed by Optilume DCB, while the control group received various endoscopic treatments without pre-dilation. The study was planned with a crossover design after 6 months, but patients were allowed to switch earlier if medically necessary. Two single-arm studies offer long-term safety results. ROBUST I, where all patients underwent pre-dilation, provided data for up to five years. ROBUST II, offering three-year results, involved pre-dilation in one-third of the patients. The third single-arm study had a very short follow-up period of 30 days.

ROBUST III:
Optilume + pre-dilation vs dilation/DVIU (without pre-dilation), cross-over design

ROBUST I & II: long-term safety data

Clinical effectiveness

At 6 months, the stricture-free rate was 74.6% in the Optilume group and 26.8% in the control group, resulting in an estimated difference of 44.4% using multiple imputation ($p<0.0001$). At 12 months, 83.2% of Optilume patients remained free from repeat intervention, compared to 21.7% in the control group ($p<0.0001$).

stat. significant differences favouring Optilume

Optilume demonstrated superior urinary function improvements compared to the control group. At 6 months, the maximum flow rate (Qmax) increased by 4.78 ml/s ($p=0.0031$) in favour of Optilume, and at 12 months, Qmax remained higher (15.5 vs. 8.0 ml/s). International Prostate Symptom Score (IPSS) and post-void residual (PVR) also improved more with Optilume, while the control group worsened. Erectile function (IIEF) showed no difference compared to baseline at 6 months in both groups but improved with Optilume at 12 months while it declined in controls. Periprocedural pain, from discharge until 30 days post-procedure, decreased similarly in both groups. Quality of life (QoL) scores improved more with Optilume, while the control group remained closer to baseline. Patient satisfaction was not reported.

superior improvement with Optilume of urinary function (Qmax) at 6 m

IPSS, PVR, Omax, IIEF and QoL at 12 m had better results with Optilume

Safety

In ROBUST III, no device- or procedure-related serious complications occurred up to 3 months post-procedure. The 2-year follow-up data showed that AEs were slightly lower with Optilume (73% vs. 81%), while serious AEs non-related to the device or procedure were similar (14% vs. 17%). Device-related AEs were higher in the Optilume group (35% vs. 8%), but serious device-related AEs were rare (1% UTI in Optilume group, none in control). Procedure-related AEs were comparable (13% in each arm), but serious procedure-related AEs were more frequent in the control group (4% vs. 1%). Severe AEs (CTCAE ≥ 3) occurred at similar rates (33% vs. 27%), but grade 5 events occurred only in the Optilume group (3%).

ROBUST III: no device/ procedure-related serious AEs at 3 m;
serious AEs at 2 yrs: comparable

In ROBUST I (5-year follow-up), 9% of patients experienced serious AEs, but none of them were device- or procedure-related. ROBUST II (3-year follow-up) showed a higher serious AE rate (38%), with only 6% being treatment-related. A third study (30-day follow-up) reported no complications, confirming short-term safety.

long-term safety: ROBUST I at 5 yrs and ROBUST II at 3 yrs

No deaths in ROBUST I, one in ROBUST II, and two in the Optilume group in ROBUST III (2.5% difference, 95% CI -2.6; 7.7) occurred, all unrelated to treatment.

mortality: 3 treatmentunrelated deaths

Drug-related adverse events were not measured in any of the studies.

Upcoming evidence

Currently, there are no ongoing RCTs in the pipeline. One study, BALDIKA, which compares DCB to DVIU, initiated and sponsored by the German Federal Joint Committee, is already in planning, with the primary completion date unknown.

no ongoing RCTs

Discussion

Optilume DCB is proposed as an alternative for men with short bulbar urethral strictures who have failed multiple endoscopic treatments and wish to avoid urethroplasty. However, its added benefit over DVIU, dilation, or urethroplasty remains unproven. ROBUST III, the only RCT, did not separate results for dilation and DVIU and lacked a urethroplasty control. While it showed significant short-term improvements in stricture-free rates (RR 2.78; $p<0.0001$) and Qmax (+4.78 mL/s; $p=0.0031$) in favour of Optilume, long-term effectiveness is uncertain. PVR improved in the Optilume group but worsened in controls, and IPSS scores indicated better symptom relief with Optilume. Safety data showed no SAEs at 3 months in ROBUST III, but earlier single-arm trials (ROBUST I and II) reported SAEs in 9–38% of patients within 3 years, with 0% to 6% attributed to the device or procedure.

inconclusive evidence demonstrates short-term benefit with Optilume

long-term effect remains unproven

safety profile is good

The certainty of evidence remains very low to low due to methodological limitations. The high crossover rate (50% by 12 months) and lack of blinding after 6 months raise concerns about potential bias. Missing data handling for key endpoints (IPSS, Qmax, PVR, QoL) was unclear, and most outcomes were reported descriptively without between-group comparisons. Generalisability is limited as the study included pre-dilation (not standard practice) and a mixed-treatment control group. The unclear effect of paclitaxel versus balloon dilation further complicates the interpretation of the results. Additionally, the study population may not reflect typical patients with recurrent bulbar strictures, as most had multiple prior endoscopic treatments and shorter strictures than those seen in urethroplasty candidates.

very low to low certainty evidence due to:

methodological concerns with ROBUST III and external validity issues

Conclusion

Very low to low certainty evidence indicates that Optilume DCB has some short-term benefit over a mixed comparator of DVIU and dilation. The long-term durability of positive effectiveness results is uncertain, necessitating further high-quality comparative studies. The safety profile has been proven favourable in both the short and long term. Head-to-head comparisons to uncoated balloon dilation, DVIU and urethroplasty are needed to know how these procedures compare. It is recommended that a re-evaluation be conducted once the BALDIKA study data becomes available.

short-term benefit, long-term effectiveness unproven, favourable safety profile

re-evaluation

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Harnröhrenstriktur bei Männern

Harnröhrenstrikturen bei Männern sind Verengungen der Harnröhre, die eine obstruktive Miktionsstörung mit Auswirkungen auf den gesamten Harntrakt verursachen können. Unbehandelt können sie zu Komplikationen führen – dazu zählen wiederkehrende Harnwegsinfektionen, Harnverhalt und Nierenbeeinträchtigung. Bei einer Harnröhrenstriktur handelt es sich um eine relativ häufige Erkrankung mit erheblichen Auswirkungen auf die körperliche Gesundheit und die Lebensqualität. Im Jahr 2001 betrug die Prävalenzrate der Harnröhrenstriktur in den USA 895 pro 100.000 Männer. Entsprechende europäische epidemiologische Daten sind nicht verfügbar, und auch die genaue Anzahl der betroffenen Patienten in Österreich ist nicht bekannt. 2022 wurden allerdings in Österreich 1.988 Harnröhrenoperationen bei Männern durchgeführt. Diese Bewertung betrachtet die Evidenz zu Behandlungsoptionen für erwachsene Männer mit symptomatischen Rezidivstrikturen der anterioren Harnröhre bis zu einer Länge von 3 cm.

epidemiologische Daten nicht verfügbar für Europa + Österreich

Rezidivstrikturen der anterioren Harnröhre bis zu 3 cm

Das therapeutische Management umfasst laut der Europäischen Gesellschaft für Urologie (EAU) endoskopische Behandlungen (Dilatation und interne Urethrotomie) oder eine offene chirurgische Behandlung (Urethroplastik). Die Dilatation/Urethrotomie ist vor allem bei kurzstreckigen (<2 cm) erstmaligen bulbären Strikturen empfohlen. Wiederholte endoskopische Behandlungen nach mehreren Rückfällen sollten vermieden werden, wenn die Urethroplastik eine valide Option darstellt. Dies begründet sich darin, dass die Rezidivrate von der Länge der Striktur abhängig ist und bessere Ergebnisse nur bei kurzstreckigen Strikturen der bulbären Harnröhre erwartet werden können. Zudem ist die Anzahl der durchgeführten endoskopischen Verfahren ein negativer prädiktiver Faktor für das Versagen einer nachfolgenden Urethroplastik.

Therapieoptionen:
Dilatation
Urethrotomie
Urethroplastik

Ist eine Urethroplastik keine Option und wurden mindestens zwei endoskopische Behandlungen erfolglos durchgeführt, kann die Dilatation mit einem medikamentenbeschichteten Ballon (Paclitaxel, drug-coated balloon, DCB) eine therapeutische Alternative für kurzstreckige (<3 cm) bulbäre Strikturen darstellen.

medikamenten (Paclitaxel)-beschichteter Ballon (DCB) zur Dilatation

Beschreibung der Technologie

Optilume DCB

Der Optilume-Harnröhren-DCB ist derzeit der einzige verfügbare medikamentenbeschichtete Ballon (DCB) für die transurethrale Behandlung von Harnröhrenstrikturen. Der Ballon ist mit Paclitaxel, einem antiproliferativen Wirkstoff, beschichtet und zur Dilatation der anterioren Harnröhre bei erwachsenen Männern zugelassen.

seit 2023 in der EAU-Leitlinie

weniger invasiv

für Rezidivstrikturen

Der Harnröhren-DCB wurde 2023 als neuartige Technologie in die Leitlinie der Europäischen Gesellschaft für Urologie (EAU) aufgenommen. Im Vergleich zu Standardverfahren (Dilatation, Urethrotomie, Urethroplastik) bietet er eine weniger invasive Behandlungsoption. Ziel ist es, die Lücke zwischen wiederholten endoskopischen Eingriffen und der offenen Urethroplastik zu schließen. Der Harnröhren-DCB kann sowohl allein als auch in Kombination mit anderen endourologischen Verfahren eingesetzt werden.

Methoden

Adaptation und Update eines EUnetHTA Berichtes

Diese Bewertung ist eine nationale Adaptation und Update eines EUnetHTA Joint Clinical Assessments (JCA). JCAs sind wissenschaftliche Berichte auf EU-Ebene, die die Mitgliedstaaten der Europäischen Union in ihren nationalen HTA-Prozessen unterstützen.

systematische Literaturrecherche und Handsuche

Im Dezember 2024 wurde eine systematische Literaturrecherche in drei Datenbanken (Medline, Embase, Cochrane) durchgeführt. Ergänzend erfolgte eine Handsuche in PubMed, um relevante Studien zu identifizieren, die nach dem Suchzeitraum des JCA veröffentlicht wurden. Nach Deduplikation blieben 34 Zitate übrig. Die Handsuche ergab keine zusätzlichen Treffer.

Qualitätsbewertung der Studien

Vertrauenswürdigkeit der Evidenz nach GRADE

Die Studienauswahl, die Datenextraktion und die Bewertung der methodischen Qualität der Studien wurden von zwei Autorinnen unabhängig voneinander durchgeführt. Bei Unstimmigkeiten wurde eine dritter Autor zur Entscheidungsfindung hinzugezogen. Die Bewertung der eingeschlossenen randomisierten kontrollierten Studien (RCTs) erfolgte mit dem Cochrane Risk of Bias Tool v.2 (RoB2). Die Vertrauenswürdigkeit der Evidenz wurde nach dem GRADE-Bewertungsschema (Grading of Recommendations, Assessment, Development and Evaluations) eingestuft.

Klinische Wirksamkeit

entscheidungsrelevante Wirksamkeitsendpunkte

Zur Bewertung der klinischen Wirksamkeit wurden folgende Endpunkte als *entscheidungsrelevant* definiert: Harnfunktion, Behandlungserfolg, anatomischer Erfolg und gesundheitsbezogene Lebensqualität. Der Behandlungserfolg sowie der anatomische Erfolg wurden als Strikturfreiheitsrate und Freiheit von wiederkehrenden Strikturen definiert.

Sicherheit

entscheidungsrelevanter Sicherheitsendpunkt

Zur Bewertung der Sicherheit wurden schwerwiegende unerwünschte Ereignisse als *entscheidungsrelevanter Endpunkt* definiert.

Ergebnisse

Verfügbare Evidenz

Wirksamkeitsbewertung: 1 RCT (n=127); Sicherheitsbewertung: 3 einarmige Studien (n=86)

Für die Wirksamkeitsbewertung wurde eine RCT (ROBUST III, n=127) herangezogen. Für die Bewertung der Sicherheit lagen zusätzlich drei einarmige Studien vor (ROBUST I und II, Alhamdani et al., n=86).

ROBUST III: Optilume DCB + Vordilatation vs Dilatation/Urethrotomie ohne Vordilatation, Cross-over Design

ROBUST III war eine vom Hersteller gesponserte, multizentrische Studie, die in den USA und Kanada durchgeführt wurde. Die Studie verglich Optilume DCB mit einer Kontrollgruppe, die entweder eine Dilatation oder Urethrotomie erhielt. In der Optilume-Gruppe erfolgte zunächst eine Vordilatation, gefolgt von der Anwendung des Optilume DCB. Die Kontrollgruppe erhielt verschiedene endoskopische Behandlungen ohne Vordilatation. Das Studiendesign beinhaltete ein Cross-over nach sechs Monaten, wobei ein früherer Wechsel bei medizinischer Notwendigkeit möglich war.

ROBUST I & II: Langzeitsicherheitsdaten

Zwei einarmigen Studien berichten Langzeitsicherheitsdaten: ROBUST I, bei der alle Patienten eine Vordilatation erhielten umfasst einen Beobachtungszeitraum von bis zu fünf Jahren. ROBUST II erstreckt sich über drei Jahre, wobei ein Drittel der Patienten eine Vordilatation erhielt. Eine dritte einarmige Studie weist eine sehr kurze Nachbeobachtungszeit von 30 Tagen auf.

Klinische Wirksamkeit

stat. signifikante Unterschiede zugunsten Optilume

Nach sechs Monaten waren 74,6 % der Patienten in der Optilume-Gruppe strikturfrei, verglichen mit 26,8 % in der Kontrollgruppe. Dies entspricht einer statistisch signifikanten Differenz von 44,4 % (p<0,0001, unter Verwendung der multiplen Imputation fehlender Daten). Nach zwölf Monaten waren 83,2 % der Optilume-Patienten frei von wiederholten Eingriffen, gegenüber 21,7 % in der Kontrollgruppe (p<0,0001).

signifikant bessere Ergebnisse in der Harnfunktion (Qmax) mit Optilume nach 6 Monaten

bessere Ergebnisse mit Optilume bei IPSS, PVR, Omax, IIEF und Lebensqualität (QoL) nach 12 Monaten

Optilume zeigte im Vergleich zur Kontrollgruppe signifikant bessere Ergebnisse in der Harnfunktion. Der maximale Harnfluss (Qmax) stieg nach sechs Monaten um 4,78 ml/s zugunsten von Optilume an (p=0,0031) und blieb auch nach 12 Monaten höher als in der Kontrollgruppe (15,5 vs. 8,0 ml/s). Der Internationaler Prostata-Symptom-Score (IPSS) und das Post-Void-Restvolumen (PVR) verbesserten sich ebenfalls stärker mit Optilume, während sie sich in der Kontrollgruppe verschlechterten. Die erektile Funktion (IIEF) zeigte in beiden Gruppen nach sechs Monaten keinen Unterschied, verbesserte sich jedoch mit Optilume nach 12 Monaten, während sie in der Kontrollgruppe nachließ. Die Schmerzreduktion nach dem Eingriff bis zu 30 Tagen war in beiden Gruppen ähnlich. Die Lebensqualität verbesserte sich stärker mit Optilume, während die Kontrollgruppe näher am Ausgangswert blieb. Angaben zur Patientenzufriedenheit wurden nicht berichtet.

Sicherheit

ROBUST III: keine schwerwiegenden produkt-/verfahrensbedingten UE nach 3 Monaten

schwerwiegende UE nach 2 Jahren vergleichbarIn ROBUST III traten innerhalb der ersten drei Monate nach dem Eingriff keine schwerwiegenden geräte- oder verfahrensbedingten Komplikationen auf. Die Zwei-Jahres-Nachbeobachtung zeigte eine insgesamt geringere Rate unerwünschter Ereignisse (UE) in der Optilume-Gruppe (73 % vs. 81 %). Schwerwiegende nicht produkt- oder verfahrensbezogene UE traten in beiden Gruppen mit ähnlicher Häufigkeit auf (14 % vs. 17 %). Gerätebezogene UE waren in der Optilume-Gruppe häufiger als in der Kontrollgruppe (35 % vs. 8 %), während schwerwiegende produktbezogene UE selten auftraten (1 % Harnwegsinfektionen in der Optilume-Gruppe, keine in der Kontrollgruppe). Verfahrensbezogene UE traten in beiden Gruppen mit gleicher Häufigkeit auf (13 % je Arm), jedoch waren schwerwiegende verfahrensbezogene UE in der Kontrollgruppe häufiger (4 % vs. 1 %). Schwere UE (CTCAE ≥3) traten in beiden Gruppen mit ähnlicher Häufigkeit auf (33 % vs. 27 %). Grad-5-Ereignisse wurden ausschließlich in der Optilume-Gruppe berichtet (3 %).

Langzeitdaten: ROBUST I nach 5 Jahren und ROBUST II nach 3 Jahren

In ROBUST I (fünf-Jahres-Nachbeobachtung) erlitten 9% der Patienten schwerwiegende UE, jedoch waren keine davon geräte- oder verfahrensbedingt. ROBUST II (drei-Jahres-Nachbeobachtung) zeigte eine höhere Rate an schwerwiegenden UE (38%), von denen nur 6% behandlungsbedingt waren. Eine dritte Studie (30-Tage-Nachbeobachtung) berichtete über keine Komplikationen und bestätigte damit die kurzfristige Sicherheit.

Sterblichkeit: 3 behandlungsunabhängige Todesfälle

In ROBUST I gab es keine Todesfälle, in ROBUST II wurde ein Todesfall berichtet, und in ROBUST III traten zwei Todesfälle in der Optilume-Gruppe auf (2,5 % Unterschied, 95 % KI -2,6; 7,7). Alle Todesfälle waren nicht behandlungsbedingt.

Medikamentenbezogene unerwünschte Ereignisse wurden in keiner der Studien erfasst.

Laufende Studien

Es gibt keine laufenden RCTs. Eine Erprobungsstudie (BALDIKA), die DCB mit DVIU vergleicht, ist in Vorbereitung, wobei das voraussichtliche Abschlussdatum noch unbekannt ist.

keine laufenden RCTs

Diskussion

Optilume DCB wird als Behandlungsalternative für Männer mit kurzstreckigen bulbären Harnröhrenstrikturen vorgeschlagen, die bereits mehrere erfolglose endoskopische Eingriffe hatten und eine Urethroplastik vermeiden möchten. Ein Zusatznutzen gegenüber DVIU, Dilatation oder Urethroplastik ist jedoch nicht belegt. Das einzige verfügbare RCT (ROBUST III) differenzierte nicht zwischen Dilatation und DVIU und schloss keine Kontrollgruppe mit Urethroplastik ein. Obwohl die Studie eine signifikant höhere Strikturfreiheitsrate (RR 2,78; p<0,0001) und eine Verbesserung des maximalen Harnflusses (Qmax: +4,78 mL/s; p=0,0031) unter Optilume zeigte, bleibt die Langzeitwirksamkeit ungewiss. Das Post-Void-Restvolumen (PVR) verbesserte sich in der Optilume-Gruppe, während es sich in der Kontrollgruppe verschlechterte. Die IPSS-Werte deuteten auf eine bessere Symptomlinderung mit Optilume hin. Hinsichtlich der Sicherheit wurden in ROBUST III innerhalb der ersten drei Monate keine schwerwiegenden unerwünschten Ereignisse (UE) beobachtet. Einarmige Langzeitstudien (ROBUST I und II) berichteten jedoch über UE bei 9–38 % der Patienten innerhalb von drei Jahren, von denen 0–6 % als geräte- oder verfahrensbedingt eingestuft wurden.

unzureichende Evidenz zeigt einen kurzfristigen Nutzen mit Optilume

langfristige Effekte bleiben unbewiesen

gutes Sicherheitsprofil

Die Vertrauenswürdigkeit der Evidenz bleibt aufgrund methodischer Limitationen bei ROBUST III und Fragen zur externen Validität sehr gering bis gering. Die hohe Crossover-Rate (50% nach 12 Monaten) und das Fehlen einer Verblindung nach 6 Monaten schränken die Aussagekraft der Daten erheblich ein. Die Handhabung fehlender Daten für wichtige Endpunkte (IPSS, Qmax, PVR, QoL) war unklar und die meisten Ergebnisse wurden beschreibend, ohne statistische Gruppenvergleiche berichtet. Die Generalisierbarkeit ist eingeschränkt, da die Studie eine Vordilatation (keine Standardpraxis) und eine heterogene Kontrollgruppe einschloss. Der Effekt von Paclitaxel im Vergleich zur reinen Ballondilatation bleibt unklar, was die Interpretation zusätzlich erschwert. Zudem könnte die Studienpopulation nicht repräsentativ für typische Patienten mit wiederkehrenden bulbären Strikturen sein, da die meisten Teilnehmenden bereits mehrfache endoskopische Vorbehandlungen hatten und ihre Strikturen kürzer waren als jene, die üblicherweise für eine Urethroplastik in Frage kommen.

sehr geringe bis geringe Vertrauenswürdigkeit der Evidenz aufgrund von:

methodischen Schwächen von ROBUST III

und

eingeschränkte externe Validität

Schulssfolgerung

Die verfügbare Evidenz weist darauf hin, dass Optilume DCB kurzfristig einen Nutzen gegenüber einer gemischten Vergleichsgruppe aus Urethrotomie und Dilatation bieten könnte. Der langfristige Behandlungserfolg ist jedoch ungewiss, sodass weitere hochwertige Vergleichsstudien erforderlich sind. Das Sicherheitsprofil zeigte sich sowohl kurz- als auch langfristig vorteilhaft. Die Vertrauenswürdigkeit der Evidenz ist jedoch sehr gering bis gering. Direkte Vergleiche mit unbeschichteter Ballondilatation, Urethrotomie und Urethroplastik sind notwendig. Es wird empfohlen, eine Re-Evaluirung durchzuführen, sobald die BALDIKA-Studiendaten verfügbar sind.

kurzfristiger Nutzen, langfristige Wirksamkeit ungewiss

gutes Sicherheitsprofil

Re-Evaluierung

1 Background

1.1 Overview of the disease, health condition and target population[1]

Harnröhrenstriktur bei Männern

Urethral stricture in males is the disease in the scope of this assessment. In males, urethral stricture is a narrowing of the anterior urethra lumen due to chronic fibrosis of the urethral mucosa and surrounding spongiosum tissue [1].

häufige Erkrankung: Inzidenz 229 per 100.000, Prävalenz 895 per 100.000 in den USA, keine europäischen Daten gefunden,

Österreich 2022: 1.988 Harnröhreneingriffe

Urethral stricture is a relatively common disease among men, with an average annualised incidence rate of 229 per 100,000 males from 1992–2000 in the USA[2]. The rate of urethral stricture disease increases sharply after the age of 55 years [1]. In 2001, the prevalence rate of urethral stricture among male Medicare beneficiaries in the USA was 895 per 100,000 people (Confidence Interval [CI] 873-916). The data of this study also demonstrate an increase in incidence rate with rising age [2]. The anterior urethra is most frequently affected (approx. 92%), in particular the bulbar urethra (approx. 47%) and the penile urethra (approx. 31%) [3]. Corresponding European epidemiological data could not be found. In 2022, the number of urethral operations performed on males in Austria amounted to 1,988 cases [4].

Ätiologie: iatrogen, idiopathisch, entzündlich, traumatisch

Urethral stricture disease has several aetiologies, including iatrogenic, idiopathic, inflammatory and traumatic causes, which vary according to geographic location and socioeconomic conditions. In well-resourced countries, the most frequent aetiologies are iatrogenic (resulting from urethral manipulations related to catheterisation, hypospadias repair, transurethral surgery, radiotherapy, prostate adenomectomy or prostatectomy) and idiopathic. Strictures can also occur as a result of trauma associated with pelvic fractures or an infection (untreated gonorrhoea and chlamydia, balanitis xerotica obliterans and lichen sclerosus) [3, 5].

EAU-Leitlinie 2024: keine formale Klassifikation nach Länge: < 2 cm = „kurz", > 2 cm = „lang", Definition bleibt uneinheitlich

The latest guideline from 2024 of the European Association of Urology (EAU) [6] on anterior strictures provides a classification of urethral strictures according to location (meatal, penile, bulbar or penobulbar) and tightness (see Table 1-1). The guideline does not provide a formal classification of strictures based on length and indicates that the definition of a "short" bulbar stricture remains ambiguous. However, according to the guideline, bulbar strictures are classified as short if they measure less than 2 cm and long if they exceed 2 cm. The guideline also states that, in general, "short bulbar strictures" are those amenable to stricture excision and subsequent tension-free anastomotic repair. The limit is usually approximately 2–3 cm but can be longer, depending

[1] This section addresses the following assessment elements:

A0002 – What is the disease or health condition in the scope of this assessment?

A0003 – What are the known risk factors for urethral stricture?

A0004 – What is the natural course of urethral stricture?

A0005 – What is the burden of disease for patients with urethral stricture?

A0006 – What are the consequences of urethral stricture for the society?

A0007 – What is the target population in this assessment?

A0023 – How many people belong to the target population?

[2] On the basis of the number of "physician office visits for males with urethral stricture listed as any diagnosis" out of a sample of 1,460,899 for 1992, 1994, 1996, 1998 and 2000 from the National Ambulatory Medical Care Survey.

on the patient's anatomy and the stricture location within the bulbar urethra [6]. To date, there are no specific guidelines for diagnosing and treating urethral strictures in German-speaking countries [7].

EAU-Klassifikation nach Verengung (tightness)

Table 1-1: European Association of Urology classification according to the degree of urethral narrowing for male patients with a normal functioning bladder

Category	Description	Urethral lumen	Degree
0	Normal urethra on imaging	–	–
1	Subclinical strictures	Urethral narrowing but ≥16 Fr	Low
2	Low-grade strictures	11–15 Fr	
3	High-grade or flow-limiting strictures	4–10 Fr	High
4	Nearly obliterative strictures	1–3 Fr	
5	Obliterative strictures	No urethral lumen (0 Fr)	

Source: European Association of Urology guidelines on urethral strictures [6].

Abbreviations: Fr=French (unit of measure of the outer diameter of a catheter; 1 Fr = 0.33 mm).

keine lebensbedrohliche Erkrankung, aber beeinträchtigt QoL

Urethral stricture is not a life-threatening disease. From a functional perspective, urethral stricture obstructs the lower urinary tract (LUT). This condition adversely impacts physical health and quality of life (QoL). Untreated, urethral strictures may result in serious complications such as recurrent urinary tract infections, urinary retention and eventual renal impairment [6].

Zielgruppe: Männer mit Rezidivstrikturen ≤ 3 cm der anterioren Harnröhre

The target population of this assessment comprises adult men with bothersome urinary symptoms associated with recurrent anterior urethral stricture with a maximum of 3 cm in length. There is no information regarding the exact number of patients in Austria with this size of urethral stricture.

1.2 Current clinical practice[3]

Diagnostik laut EAU-Leitlinie

According to the EAU guideline, a comprehensive diagnostic evaluation of urethral stricture encompasses clinical history and examination, urinalysis (+/- culture), uroflowmetry and post-void residual (PVR) assessment, radiography, and endoscopy [6].

Therapieoptionen laut EAU-Leitlinie 2024

DCB-Dilatation erst seit 2023 in EAU-Leitlinie aufgenommen

The 2024 EAU guideline [6] presents different options for the management of this health condition, as detailed in Table 1-2. It was not until 2023 that drug-coated balloon (DCB) dilation was incorporated into the guideline as a strategy for either post-dilation or post-direct vision internal urethrotomy (DVIU) [8].

[3] This section addresses the following assessment elements:

A0024 – How urethral stricture currently diagnosed according to published guidelines and in practice?

A0025 – How is urethral stricture currently managed according to published guidelines and in practice?

Table 1-2: European Association of Urology guidelines on management of anterior urethral strictures in males

Type of treatment	Management of anterior urethral strictures in males
Conservative	**Observation** in patients with asymptomatic incidental strictures >16 Fr. **Long-term suprapubic catheter** in patients with radioinduced bulbomembranous strictures.
Endoluminal treatment	**Direct vision internal urethrotomy (DVIU)** ■ with "cold-knife" commonly performed as a first-line treatment under general or spinal anaesthesia; the stricture is incised. ■ with "hot-knife": laser urethrotomy and plasmakinetic (bipolar) urethrotomy are considered alternative techniques to cold-knife DVIU. **Single dilation** performed in the office under local anaesthesia: the urethral mucosa at the stricture site is stretched and the scarring is disrupted. **Post-dilatation/DVIU** to prevent wound contraction, improve the stricture-free rate and time to stricture recurrence after dilatation or DVIU ■ Intermittent self-dilation ■ Intralesional injections ■ Urethral stents are aimed to oppose wound contraction after dilatation or DVIU. Stent insertion is a short procedure under local or spinal anaesthesia. Urethral stents are classified as permanent or temporary. ■ *Drug-coated balloon dilatation* after standard dilatation, or DVIU, aims to reduce scar formation based on its antimitotic action.
Open repair	**Urethroplasty**: stricture excision and subsequent tension-free anastomotic repair is generally performed for "short bulbar strictures" (2–3 cm).

***Source**: European Association of Urology guidelines on urethral strictures [6].*

***Abbreviations**: DVIU=direct vision internal urethrotomy; Fr=French (unit of measure of the outer diameter of a catheter; 1 Fr = 0.33 mm.*

EAU-Empfehlungen

In the context of this assessment, the following treatment strategies are of interest from the EAU guideline [6]:

- DVIU is not recommended for penile strictures due to poor outcomes and risk of erectile dysfunction (level of evidence (LE) 1b[4], strong recommendation[5]).
- DVIU/dilation is not recommended as a solitary treatment for long (>2 cm) segment strictures due to higher failure rates (LE 1b, strong recommendation).
- DVIU/dilation may be used for primary, single, short (<2 cm) and non-obliterative bulbar stricture with a 5-year stricture-free rate of up to 77% (LE 3, weak recommendation).
- Repetitive dilatations/DVIU (>2) should be avoided if urethroplasty is a viable option due to lack of long-term freedom of recurrence and increased stricture complexity (LE 1b, strong recommendation).
- Due to higher anatomic patency rates (at 6 months) and lower risk of retreatment (at 1 year) with drug (paclitaxel)-coated balloon dilation compared to standard dilatation/DVIU for short (< 3 cm) bulbar strictures that recur after at least two failed endoscopic treatments, paclitaxel-coated balloon dilatation is recommended for this patient group, but only when urethroplasty is not an option (LE 1b, weak recommendation).
- Intralesional injections should be used only in the context of a clinical trial (LE 1a, weak recommendation).
- Temporary stents after DVIU/dilatation can delay recurrence at the bulbar urethra compared to DVIU/dilatation alone but should only be used if urethroplasty is not viable (LE 1b, weak recommendation).

EAU: keine Evidenz für Überlegenheit von Dilatation oder DVIU

Rezidivrate variiert stark bei Dilatation und DVIU

The EAU acknowledges a lack of evidence supporting the superiority of dilation over DVIU (or vice versa). Consequently, the indications for single dilatation are considered equivalent to those for DVIU [6]. However, studies report widely varying stricture recurrence rates (8% to 77% for DVIU and 36% to 92% for dilation) [9, 10], raising questions about whether these interventions can truly be considered interchangeable until further evidence is available.

1.3 Features of the intervention[6]

Optilume® medikamentenbeschichtetes DCB zur Behandlung der Harnröhrenstriktur

Currently, only one drug-coated balloon (DCB) is available for treating urethral stricture: the Optilume® urethral DCB. This device is a urethral balloon pre-coated with the antiproliferative drug paclitaxel. The comparators in the

[4] Level of evidence graded by the EAU according to a classification system modified from the Oxford Centre for Evidence-Based Medicine: Levels of Evidence (March 2009). LE 1b: based on an individual RCT with a narrow confidence interval; LE 3: based on case series.

[5] The EAU rate the strength of their recommendations as "strong" or "weak" on the basis of six key elements: 1) the overall quality of evidence graded according to levels of evidence (see note above); 2) the magnitude of the effect (individual or combined effects); 3) the certainty of the results (precision, consistency, heterogeneity and other statistical or study-related factors); 4) the balance between desirable and undesirable outcomes; 5) the impact of patient values and preferences on the intervention; and 6) the certainty of those patient values and preferences.

[6] This section addresses the following assessment elements:

scope of this assessment are urethroplasty, urethrotomy and dilation, which are well-established surgical procedures. Drug-coated balloon dilation was only included in the EAU guideline in 2023 and is considered a novel technology [8]. According to the health technology developer (HTD), the claimed benefit of Optilume is that it is less invasive than urethroplasty and can bridge the gap between repeated endoscopic treatments and open urethroplasty. This makes Optilume a viable option for men with short bulbar urethral strictures who have failed multiple endoscopic management but wish to avoid urethroplasty.

Charakteristika der Technologie

The characteristics of Optilume DCB are presented in Table 1-3, and a schematic figure of the device is displayed in Figure 1-1.

Table 1-3: Characteristics of the medical device under assessment

Device trade name	**Optilume**
Manufacturer	Laborie Medical Technologies
Device description according to the EMDN	U0399: Devices for urinary tract dilation – other
Risk class of the device	Class III
Function of the device	Therapeutic

B0001 – What is Optilume DCB, urethrotomy, dilation and urethroplasty?

A0001 – For which health conditions, and for what purposes is Optilume DCB used?

A0020 – For which indications has Optilume DCB received marketing authorisation or CE marking?

B0002 – What is the claimed benefit of Optilume DCB in relation to urethrotomy, dilation or urethroplasty?

B0003 – What is the phase of development and implementation of Optilume DCB, urethrotomy, dilation and urethroplasty?

B0004 – Who administers Optilume DCB, and in what context and level of care is it provided?

B0008 – What kind of special premises are needed to use Optilume DCB?

B0009 – What supplies are needed to use Optilume DCB?

A0021 – What is the reimbursement status of Optilume DCB?

A0011 – How much is Optilume DCB utilised?

<table>
<tr><td>Models of the device/reference numbers</td><td>The device is CE-marked for three different diameters and two different lengths.
<table>
<tr><th>Product number</th><th>Description</th><th>Diameter (Fr)</th><th>Length (cm)</th><th>Rated burst pressure (atm)</th><th>Paclitaxel dose (mg)</th></tr>
<tr><td>OPT-BDL7000C</td><td rowspan="6">Optilume DCB and inflation device</td><td>18</td><td>3</td><td>12</td><td>1.979</td></tr>
<tr><td>OPT-BDL7001C</td><td>18</td><td>5</td><td>12</td><td>3.299</td></tr>
<tr><td>OPT-BDL7002C</td><td>24</td><td>3</td><td>12</td><td>2.639</td></tr>
<tr><td>OPT-BDL7003C</td><td>24</td><td>5</td><td>12</td><td>4.398</td></tr>
<tr><td>OPT-BDL7004C</td><td>30</td><td>3</td><td>10</td><td>3.299</td></tr>
<tr><td>OPT-BDL7005C</td><td>30</td><td>5</td><td>10</td><td>5.498</td></tr>
</table>
The Optilume DCB catheter and the inflation device are supplied sterile (ethylene oxide sterilisation) for single use only in a double-pouch packaging system contained in a single unit box. It should be stored at room temperature in a dry location.</td></tr>
<tr><td>Intended purpose of the device</td><td>The Optilume urethral DCB catheter is intended to treat strictures in the anterior urethra in adult males.</td></tr>
<tr><td>Indication and target population</td><td>The Optilume urethral DCB catheter is used to treat men aged ≥18 years with bothersome urinary symptoms associated with recurrent anterior urethral stricture. It is designed to be used as a dilation balloon for a single, tandem, or diffuse anterior urethral stricture of ≤3 cm in length or used as an adjunctive therapy with other dilation devices and/or procedures.</td></tr>
<tr><td>Contraindications and/or restrictions for use and/or limitations</td><td>The Optilume urethral DCB catheter is contraindicated for use in:
Patients with known hypersensitivity to paclitaxel or structurally related compounds;
Patients with lesions that cannot be crossed with a 0.038-inch guidewire.</td></tr>
<tr><td>Description of the device, including its constituents</td><td>The Optilume urethral DCB is a coaxial catheter compatible with a 0.038-inch (0.97 mm) guide and a flexible cystoscope with two lumens and an atraumatic bevelled tip. The distal end of the catheter is equipped with a semicompliant inflatable balloon that is coated with paclitaxel and excipients. The device has two radiopaque marks that indicate the useful length of the balloon (Figure 1).</td></tr>
<tr><td>Mode of action</td><td>The Optilume urethral DCB exerts radial force to dilate narrow urethral segments when introduced and inflated in the stricture area and circumferentially delivers an antiproliferative medicinal product (paclitaxel) to the inner urethral wall during the procedure. It has been reported that paclitaxel inhibits the proliferation and migration of smooth muscle cells and fibroblasts, and the secretion of extracellular matrix. The combination of these effects may inhibit urothelium hyperplasia and, therefore, stricture recurrence.</td></tr>
</table>

***Source**: Submission dossier, EUnetHTA JCA [11].*
***Abbreviations**: atm=atmosphere; CE=Conformité Européenne; DCB=drug-coated balloon; EMDN=European Medical Device Nomenclature; Fr=French.*

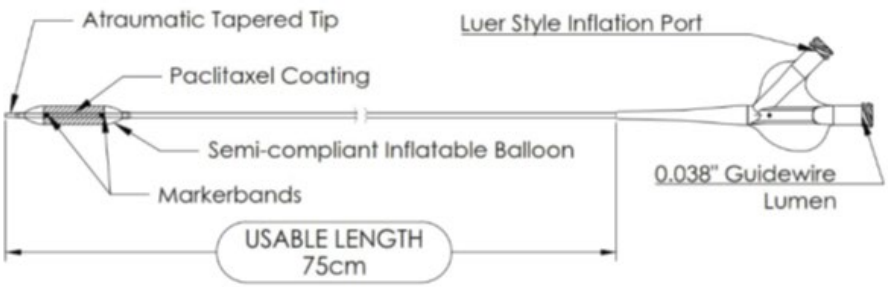

Figure 1-1: Schematic figure of Optilume DCB

Geräteeigenschaften, organisatorische Aspekte, Anforderungen an Benutzerprofile und Schulungen

The Optilume urethral DCB procedure can be performed via rigid or flexible cystoscopy. Fluoroscopy may be used at the time of the procedure to assess or confirm the stricture length and location. The Optilume urethral DCB is passed over a guidewire under direct vision and positioned along the length of the urethral stricture. It is then inflated using normal saline or sterile water with a pressure inflation device. The Optilume urethral DCB is left in situ across the urethral stricture for a minimum of 5 minutes to facilitate drug uptake. The Optilume urethral DCB is then deflated and removed. A catheter may be inserted and left in place for a few days at the discretion of the clinician. According to the instructions for use (IFU), Optilume urethral DCB balloon catheters are intended for use by physicians trained and experienced in techniques for balloon catheter dilation. The procedure follows the established urological practice for urethral dilation. It can be performed under direct visualisation in a hospital setting or in an outpatient setting under local anaesthesia or conscious sedation [11].

Regulatory and reimbursement status

Regulatorischer- und Erstattungsstatus

Regulatory information on Optilume urethral DCB is provided in Table 1-5.

Table 1-4: Regulatory information on Optilume urethral drug-coated balloon

UDI-DI	08530950081110L6
Name, identification number and country of notified body	Polskie Centrum Badad I Certyfikacji S.A., 1434, Poland
Date of initial CE marking	14/01/2021
Expiry date of current certificate	27/05/2024
Date and reference of the expert panel opinion	Not applicable

***Source**: Submission dossier, EUnetHTA JCA [11]*

***Abbreviations**: CE=Conformité Européenne; UDI-DI=Unique Device Identification-Device Identifier*

im Leistungskatalog: Urethroplastik, Urethrotomie, und Dilatation

Urethroplasty (JE010), urethrotomy (JE530) and dilation (JE520) are fully reimbursable interventions in Austria; however, the use of the Optilume DCB is not included in the in the Austrian hospital benefit catalogue (*LKF, leistungsorientierte Krankenanstenfinanzierung*).

geschätzte jährliche Nutzung in Österreich: 200–1.000 Eingriffe

According to information provided by the submitting hospital, the estimated number of annual utilisation of Optilume DCB in Austria is between 200 and 1,000 procedures.

2 Objectives and Scope

2.1 PICO question

PIKO-Frage

Is the drug (paclitaxel)-coated urethral balloon catheter used as a dilation balloon for a single, tandem or diffuse anterior urethral stricture equal to or less than 3 cm or used as adjunctive therapy with other dilation devices or procedures in men ≥ 18 years as effective and safe as or safer than urethrotomy or dilation alone or urethroplasty concerning treatment success, anatomical success, health-related quality of life, urinary function as well as serious adverse events?

2.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarised in Table 2-1.

Table 2-1: Inclusion criteria

Population	Men aged ≥18 yrs with bothersome urinary symptoms associated with recurrent anterior urethral strictures ≤3 cm in length. *ICD-10 code*: N35.9 - Urethral stricture, unspecified, N35.8 - Other urethral stricture *MeSH term*: C12.050.351.968.767.700.700, C12.200.777.767.700.700, C12.950.767.700.700
Intervention	Urethral drug-coated balloon catheter used as a dilation balloon for a single, tandem or diffuse anterior urethral stricture ≤3 cm in length or used as adjunctive therapy with other dilation devices and/or procedures. *MeSH term*: E02.148.947 [urinary catheterisation]
Control	Urethrotomy[a] OR Dilation OR Urethroplasty *MeSH term*: E05.284 [dilation], E04.950.774 [urologic surgical procedures], E04.502 [minimally invasive surgical procedures] [a] Urethrotomy and direct vision internal urethrotomy (DVIU) are used indistinctly in the report. *Rationale*: The control interventions were defined in the EUnetHTA PICO survey and consolidation of survey results. All member states were invited to indicate which control interventions are of interest to their health systems. These interventions are common clinical practices defined in the relevant EAU guideline. Their level of usage depends on the local circumstances, financial considerations, and the surgeon's discretion.
Outcomes	*Rationale*: Outcomes (provided below) were defined in the EUnetHTA PICO survey and consolidation of survey results. All member states were invited to indicate which outcomes are of interest to their health systems. These outcomes were validated and ranked by an Austrian clinical expert.
Efficacy	■ All-cause mortality ■ Urinary function (lower urinary tract symptoms related to stricture) measured using: International Prostate Symptom Score, postvoid residual urine volume, maximum flow rate. ■ Erectile function measured using: International Index of Erectile Function ■ Pain ■ Treatment success preferably measured as: stricture-free rate, recurrence rate, reintervention or time to treatment failure (preferably at a minimum of 6 months, 1 year, 2 years and in the long term). ■ Anatomical success preferably measured in terms of stricture tightness. ■ Health-related quality of life (generic and disease- or population-specific measures), any other patient-centred outcome and health status measured using PROMs.

Safety	■ Any adverse events (AEs) and device-related AEs, including but not limited to perioperative and postoperative complications, urinary tract infection, urinary retention, incontinence, erectile dysfunction ■ Drug-related AEs ■ Serious adverse events
Study design	
Efficacy	Randomised controlled trials Prospective non-randomised controlled trials
Safety	Randomised controlled trials Prospective non-randomised controlled trials Prospective case-series

***Source**: EUnetHTA JCA [11].*
***Abbreviations**: AE=adverse event; DCB=drug-coated balloon; PICO=Population, Intervention, Comparator, Outcome; PROM=patient-reported outcome measure.*

3 Methods

nationale Adaption & Aktualisierung der EUnetHTA-Bewertung „JCAMD001 – Optilume Urethral DCB"

Einreichungsdossier des Herstellers (Laborie Medical Technologies)

Stakeholder-Beteiligung: Patienten, klinische Experten & Organisationen

EUnetHTA-Bewertung: Überprüfung des Einreicherdossiers, ergänzende Literaturrecherche, Studiencharakteristika und Ergebnisse, RoB-Bewertung und Stärke + Limitationen der Evidenz

eingeschlossene Studien der EUnetHTA-Bewertung

This assessment is a national adaptation and update of the European Network for Health Technology Assessment (EUnetHTA) joint clinical assessment (JCA) "JCAMD001 Assessment Report – Optilume Urethral Drug-Coated Balloon" [11], which had the aim to assess the relative clinical effectiveness and safety of the Optilume urethral DCB medical device. The target patient population and relevant comparators were defined before the assessment started in the scope according to a Population, Intervention, Comparator, Outcome (PICO) framework. The assessment was based on the submission dossier submitted by the health technology developer (HTD) of this medical device, Laborie Medical Technologies.

Stakeholders (patients, clinical experts and stakeholder organisations) were consulted early in the JCA scoping process to support the development of the PICO questions. Submissions via an online questionnaire from the stakeholders and organisations, including details of their funding, are included in Appendix A of the EUnetHTA JCA [11].

The EUnetHTA JCA [11] describes findings from the systematic information retrieval, characterises the studies included and presents results on the relative effectiveness and relative safety of the health technology under assessment versus the comparators defined in the PICO questions. Factors that may affect the degree of certainty of the relative effects were identified, taking into account the strengths and limitations of the available evidence.

In the EUnetHTA process, while the HTD conducts the initial systematic information retrieval, the assessment team verifies the completeness of the included studies. For this JCA, the verification process included searching study registries and bibliographic databases for Optilume DCB. The assessment team's supplementary searches did not identify any additional relevant studies.

The included studies and corresponding references used in the EUnetHTA JCA [11] are presented in Table 3-1.

Table 3-1: Studies included in the EUnetHTA JCA

Study reference/ID	Study information (purpose, sponsoring)	Available documentation
Direct comparison: Optilume DCB versus dilation or DVIU		
ROBUST III [b]	Study was designed for marketing authorisation (U.S. market approval) Sponsored by the HTD	Clinical study report (CSR) for the 2-year results (RP1076-001 Rev C, 27 October 2022) [12] Protocol PR1076-001 version J (13 May 2020) [13] Registry entry: NCT03499964 [14] Publication: [15][a, b]
Single-arm studies		
ROBUST I [b]	Sponsored by the HTD	CSR for the 4-year results (DSC016-004 Rev H, 19 October 2021) [16] Registry entry: NCT03014726 [17] Publications: 3-year results [18], 2-year results [19] and 1-year results [20]

ROBUST II [b]	Sponsored by the HTD	CSR for 3-year results (RP1032-004 Rev D, 15 June 2022) [21] Registry entry: NCT03270384 [22] Publication: 1-year results [23]
a A letter to the Editor requesting separate analyses for the comparators used in the Elliott study and a reply to this letter from the HTD was found in the literature search [24, 25]. b Additional information was submitted by the HTD as part of a German health technology assessment process (national report from 3 May 2023 [26]).		

Source: *Submission dossier, EUnetHTA JCA [11].*

Abbreviations: *CSR=clinical study report; DVIU=direct vision internal urethrotomy; HTD=health technology developer; RCT=randomised controlled trial.*

3.1 Research questions

Assessment elements from the EUnetHTA Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customised to the specific objectives of this assessment.

EUnetHTA Core Model®

3.2 Clinical effectiveness and safety

3.2.1 Systematic literature search

In this national adaptation and update, the systematic literature search was conducted on the 09.12.2024 in the following databases:

systematische Literatursuche in drei Datenbanken

- Medline via Ovid
- Embase
- The Cochrane Library

The systematic search was limited to the period from January 2023 to December 2024, as it was an update. After deduplication, overall, 34 citations were found. The specific search strategy employed can be found in the Appendix.

Furthermore, to identify ongoing and unpublished studies, a search was conducted in three clinical trial registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) on January 9, 2025, yielding seven potentially relevant hits.

Suche nach laufenden Studien

The HTD of the product was contacted but did not submit any new publications.

insgesamt 34 Publikationen identifiziert

By hand-search, no additional citations were found, resulting in 34 hits overall.

3.2.2 Flow chart of study selection

Literaturauswahl

Overall, 34 hits were identified. The references were screened by two independent researchers (JE, JP), and a third researcher was involved in case of disagreement to solve the differences. The selection process is displayed in Figure 3-1.

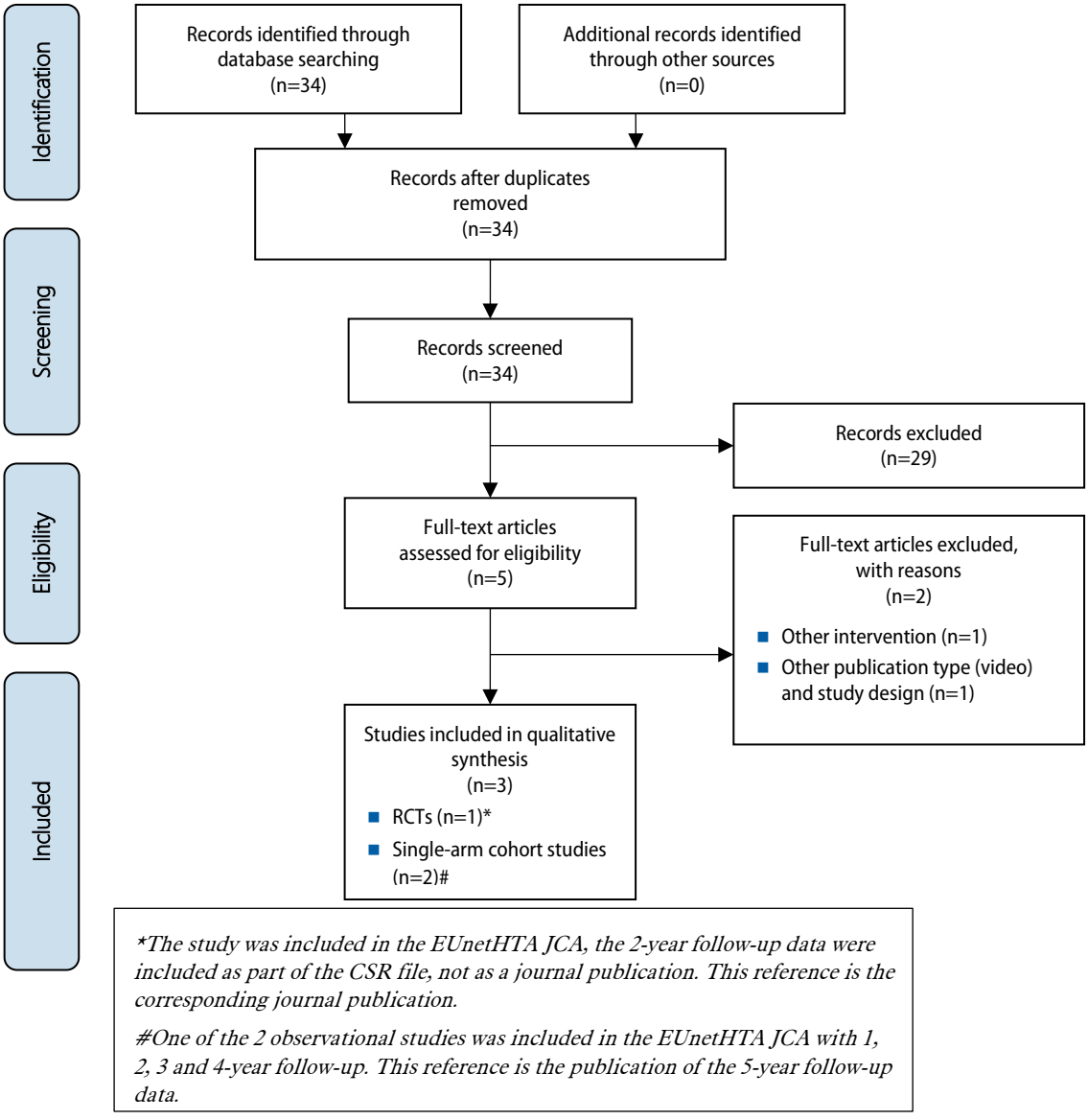

Figure 3-1: Flow chart of study selection (PRISMA Flow Diagram)

3.2.3 Analysis

Datenextraktion und Kontrolle

Data from the EUnetHTA JCA [11] and the studies identified in the update search were extracted into data extraction tables based on the research question (see Appendix Table A 1 and Table A 2).

Bewertung der Studienqualität und Verzerrungsrisiko

For both the EUnetHTA JCA [11] and this adaptation and update assessment, data accuracy was validated by an independent second researcher. The risk of bias assessment from the EUnetHTA JCA was adopted, and no new assessment was required. In the JCA, two researchers independently conducted risk of bias assessments using the Cochrane RoB 2.0 tool [27] (see Table A 3), with any differences resolved through consensus. The original documentation of the detailed risk of bias assessments can be found in the EUnetHTA JCA.

Single-arm trials were classified as having a high risk of bias according to the HTA guideline "*Validity of clinical studies*" [28], which was issued by the HTA Coordination Group pursuant to the HTA Regulation, and were therefore not subject to further assessment.

3.2.4 Synthesis

Evidenzsynthese mittels GRADE

The questions were answered in plain text format with reference to GRADE evidence tables that are included in Appendix Table A 4. The results were summarized in the Summary of findings table (Table 5-1). The GRADE and Summary of findings tables present the critical outcomes only.

4 Results: Clinical effectiveness and Safety

4.1 Outcomes

4.1.1 Outcomes effectiveness

kritische Endpunkte für eine Empfehlung: Harnfunktion, Behandlungserfolg, anatomischer Erfolg, gesundheitsbezogene QoL

The following outcomes were defined as *critical* to derive a recommendation:

- Urinary function
- Treatment success
- Anatomical success
- Health-related quality of life

Treatment success was defined as the freedom from repeat intervention and stricture-free rate, anatomical success was defined as the stricture-free rate in this assessment.

Further outcomes defined as *important* to derive a recommendation include erectile function and pain.

Details about the single outcomes, their measurement instruments and how to interpret them are detailed in the Appendix (Table A 5).

4.1.2 Outcomes safety

und schwerwiegende unerwünschte Ereignisse (UE)

The following outcomes were defined as *critical* to derive a recommendation:

- Serious adverse events

Further outcomes that were defined as *important* to derive a recommendation are:

- Any adverse events and device-related adverse events including but not limited to peri-and post-operative complications, urinary tract infection (UTI), urinary retention, incontinence, erectile dysfunction
- Drug-related adverse events and
- All-cause mortality

4.2 Included studies

Übersicht der einbezogenen Studien

An overview of the included studies (of the EUnetHTA JCA and the newly identified references in bold font) and available documentation is presented in Table 4-1.

Table 4-1: Summary of included studies and available documentation

Study reference/ID	Available documentation
Direct comparison: Optilume DCB versus dilation or DVIU	
ROBUST III	CSR for the 2-year results (RP1076-001 Rev C, 27 October 2022) [12] Protocol PR1076-001 version J (13 May 2020) [13] Registry entry: NCT03499964 [14] Publication: 1-year results [15], **2-year results [29]**
Single-arm studies	
ROBUST I	CSR for the 4-year results (DSC016-004 Rev H, 19 October 2021) Registry entry: NCT03014726 [17] Publications: **5-year results [30]**, 3-year results [18], 2-year results [19] and 1-year results [20]
ROBUST II	CSR for 3-year results (RP1032-004 Rev D, 15 June 2022) Registry entry: NCT03270384 [22] Publication: 1-year results [23]
Alhamdani et al. 2024	Publication: [31]

Source: *Submission dossier, EUnetHTA JCA [11] and own search*
Abbreviations: *CSR=clinical study report; DVIU=direct vision internal urethrotomy; HTD=health technology developer; RCT=randomised controlled trial.*

4.2.1 Included studies on effectiveness

1 Studie: ROBUST III, ein multizentrisches, Hersteller gesponsertes RCT mit 127 Patienten

Optilume DCB versus Behandlungsstandard (endourologisches Verfahren: DVIU oder Dilatation)

Design zum Überlegenheitsbeweis

One RCT, the ROBUST III (NCT03499964) study was included in the effectiveness assessment. The assessment utilised data from this study, including the clinical study report (CSR) with 2-year follow-up data, two publications (1-year [15] and 2-year study results [29]) and the study protocol [13]. The RCT was a prospective, interventional RCT that included 127 patients (79 in the intervention arm and 48 in the control arm) with a short follow-up duration (6 months) for outcomes with prespecified hypothesis testing. Study sites span 22 centres across North America, including the U.S. and Canada. It was sponsored by Urotronic Inc. The study evaluates the efficacy and safety of predilation with an uncoated balloon and/or DVIU, followed by the application of the Optilume DCB. The comparator group received standard-of-care endoscopic management, which varied according to the treating physician's discretion and could include rigid rod dilation, DVIU, uncoated balloon dilation, or combinations of these methods, but pre-dilation was not performed. The randomisation was planned at a 2:1 allocation to treatment versus control, stratified by investigational centre and prior radiation treatment and the number of prior dilation treatments using randomly permuted blocks. There is no specific information on the concealment of the allocation sequence. The study was designed with the primary objective of demonstrating superiority.

The primary effectiveness endpoint was stricture-free rate at 6 months. Stricture-free rate was defined as the proportion of participants in whom a 16 Fr flexible cystoscope or a 14 Fr catheter could be atraumatically passed through the treated area. The study protocol prespecified a statistical analysis using a two-sample continuity corrected Chi-square test with a two-sided significance level of 0.05. To maintain control over type-I error while accounting for the interim sample size re-estimation, a weighted Z score approach was applied, as outlined in both the study protocol and clinical study report. The study protocol prespecified a sensitivity analysis to evaluate how missing data in the primary analysis affected the stricture-free rate results. The detailed methods for this analysis are provided in the Appendix (Table A 6). The primary safety endpoint was a composite of specific device- or procedure-related serious complications at 3 months, which was analysed with descriptive statistics and nominal 95% confidence interval.

primärer Wirksamkeitsendpunkt: die Strikturfreiheitsrate nach 6 Monaten

primärer Sicherheitsendpunkt: die Rate an erheblichen produkt-/prozedur-bezogenen Komplikationen nach 3 Monaten

Freedom from repeat intervention rate at 6 months and change in Qmax at 6 months were secondary endpoints in the study. A hierarchical testing strategy was prespecified in the study protocol: endpoints were tested in a predefined sequential order, meaning that subsequent endpoints were only tested if the primary endpoint showed statistical significance, thereby controlling the overall type I error rate. For the freedom from repeat intervention rate the statistical test was prespecified and controlled for multiplicity at 6-month, but no formal hypothesis testing was planned at the 12-month follow-up. The results were described via Kaplan-Meier analysis. Change in Qmax was reported as the mean difference (MD) in change from baseline between the two groups. The MD was estimated using multiple imputation of missing data. The estimated MD without multiple imputation of missing data was not provided for this outcome.

sekundäre Endpunkte: die Änderung der maximalen Harnflussrate und die Freiheit von Reintervention aufgrund des Wiederauftretens der Striktur nach 6 Monaten

Other endpoints encompassed urinary function, erectile function, pain, and other adverse events. Urinary function was measured by using various measurement instruments, including Qmax, IPSS, and PVR. Erectile function was measured by IIEF overall satisfaction score. Pain was measured by the VAS pain score. For IPSS, PVR, IIEF, IPSS-QoL and for pain formal hypothesis test was not planned, only descriptive statistics were used to present the results. In these outcomes, a failure-carried-forward analysis was undertaken. Assessment of mortality was not prespecified in the protocol and only descriptive statistics were used to report this outcome.

andere Endpunkte: Harnfunktion, erektile Funktion, Schmerzen, UE, Mortalität nicht als Endpunkt vordefiniert

Surgeons and study investigators were not blinded to the treatment, only the patients. According to the study protocol, patients could cross over to the Optilume arm after 6 months and, if medically necessary (recurrent stricture requiring intervention) even before 6 months. Authors reported that 25% (12/48) of patients from the control group crossed over to the Optilume group before 6 months. Patients who switched to the intervention arm within the first 6 months or underwent other treatments were classified as treatment failures in the primary endpoint analysis.

keine doppelte Verblindung

Crossover: geplant nach 6 Monaten, 25% früher erfolgt

There were no major differences in baseline characteristics between treatment groups in the study. The mean age was 59 years (SD 16) in the Optilume group and 61 years (SD 16) in the control group. Most patients had a bulbar stricture (90% vs. 96%). Mean stricture length was 1.63 cm (SD 0.76) in Optilume and 1.72 cm (SD 0.73) in the control group. Prior dilations averaged 3.2 (SD 1.7) vs. 4.3 (SD 7.5), though one control patient had 53 dilations. Excluding this outlier, the control group mean was 3.3.

keine wesentlichen Unterschiede in den Patientencharakteristika der Studiengruppen

Study characteristics and results of included studies are displayed in Table A 1.

4.2.2 Additional included studies on safety

1 RCT (ROBUST III) und 3 einarmige Studien für Sicherheitsbewertung

In addition to the RCT included for effectiveness results, three single-arm prospective studies were included for safety assessment. Two of these studies were part of the clinical development programme and sponsored by the HTD: ROBUST I [30, 32-34] and ROBUST II [35]. The HTD did not sponsor the third one [31] but the device was provided by them.

Vordilatation: 100% in ROBUST I, 63% in ROBUST II

primärer Endpunkt der einarmigen Studien: schwere Komplikationen

sekundäre Endpunkte: Striktur, Symptome, funktionale Ergebnisse

The ROBUST I trial (NCT03014726) was conducted across four centres in Latin America, enrolling 53 patients. This assessment utilised data from the CSR of the 4-year results [16], and publications of the 1- [33], the 2- [32], the 3- [34] and 5-year [30] study results. The intervention involved pre-dilation using an uncoated balloon or DVIU, followed by the application of Optilume DCB. Similarly, the ROBUST II trial (NCT03270384), conducted at five centres in the U.S., enrolled 16 patients. This assessment utilised data from the CSR of the 3-year results [21] and the publication of the 1-year results [35]. The study allowed multiple approaches, including pre-dilation with uncoated balloons or DVIU (37%), with 63% of patients receiving Optilume DCB without prior dilation. The third study [31] was an uncontrolled observational study conducted in Australia with 17 patients, where shallow DVIU with a cold knife was performed before Optilume DCB treatment. Across all studies, the primary endpoints focused on treatment-related serious complications, with secondary endpoints examining stricture recurrence, symptom improvement (e.g., IPSS, Qmax), and functional outcomes such as freedom from repeat intervention.

überwiegend mittelaltriger Patienten, unterschiedliche Strikturlängen: Ø 0.9 cm in ROBUST I, Ø 2.1 cm in ROBUST II, Ø 2-3 cm in Studie 3

Patients enrolled in these studies were predominantly middle-aged, with mean ages ranging from 51 years in ROBUST I to 64 years in ROBUST II. Stricture characteristics also varied. ROBUST I included the least severe patients with smaller strictures (mean 0.9 cm). ROBUST II had a mean length of 2.1 cm, while the third study [31] predominantly included patients with 2 and 3 cm strictures but also 12% of patients with even more extensive strictures.

vorherige endourologische Eingriffe

Most patients had undergone prior interventions before enrolment. In ROBUST I, 57% of patients had only one prior endoscopic treatment, 25% had two and 19% had three or more previous procedures. Patients in ROBUST II and Alhamdani et al. similarly had histories of multiple urethral procedures, including DVIU and dilation.

langfristige Nachbeobachtungen: 3 bis 5 Jahre

Follow-up durations were typically long, ranging from 3 years of the ROBUST II to 5 years of ROBUST I. Loss to follow-up varied between 10% and 22%.

Study characteristics and results of included studies are displayed in Table A 2.

4.3 Results

Morbidity[7],[8]

Stricture-free rate at 6 months and freedom from repeat intervention (anatomical and treatment success) at 12 months were reported in the ROBUST III study [12, 15, 29]. The data for this outcome was missing for 12 (15%) patients in the Optilume group and seven (15%) patients in the dilation or DVIU group (missing cystoscopy). Twelve (25%) patients from the control group crossed over to the Optilume group. These patients were considered failures for this endpoint. The risk difference was 44.4 (95% CI 27.6; 61.1), p<0.0001, meaning that there is a 44.4% difference in the proportion of patients who were stricture-free at the 6-month follow-up. This result was estimated based on using multiple imputations of missing data. A sensitivity analysis was conducted, which shows that the results have the same directionality as the results of the primary analysis.

Strikturfreiheitsrate nach 6 Monaten: 44,4% Risikounterschied (95% KI 27,6; 61,1), p<0,0001

fehlende Daten

Freedom from repeat intervention rate at 6 months was not reported. At 12 months the Kaplan-Meier curve shows that 83.2% of the Optilume patients remained free from repeat intervention, compared to 21.7% of the control group (log-rank p-value <0.0001). The two curves for observed survival did not cross each other during the follow-up period.

Freiheit von Reintervention aufgrund des Wiederauftretens der Striktur nach 12 Monaten: 83,2% vs 21,7% (Log-Rank p-Wert <0,0001)

Function[9],[10]

Urinary function, **erectile function**, and **periprocedural pain** were reported in ROBUST III [12, 15, 29] to answer this question.

Urinary function

The study reported a 4.78 ml/s difference in the **change of Qmax** from baseline to the 6-month follow-up between the Optilume and the control group, in favour of the Optilume group. Optilume patients (n=67) achieved a **MD of 4.78 ml**/s better than control patients (n=44) (90% CI 1.94; 7.61; **p=0.0031**). At 12-month follow-up, the **Qmax** was 15.5 (SD 9.0) in the Optilume group (n=65) versus 8.0 (SD 4.6) in the control group (n=42). The baseline values were 7.6 (SD 3.4) in the Optilume group (n=78) and 7.4 (SD 3.5) in the control group (n=47).

Qmax-Änderung nach 6 Monaten: MD 4,78 ml/s zugunsten Optilume (90% KI 1,94; 7,61); p=0,0031,
Qmax nach 12 Monaten: Verbesserung mit Optilume

Further urinary function measures were **IPSS** and **PVR**. From baseline 22.0 (SD 6.8) in the Optilume group (n=79) and 22.9 (SD 6.9) in the control group (n=47), the IPSS score decreased to 8.3 (SD 6.2) (n=71) at 6 months and to 9.0 (SD 7.1) (n=67) at 12 months in the Optilume group, and to 15.4 (SD 9.6) at 6 months (n=43) and 19.8 (SD 7.4) at 12 months (n=43) in the control group. The PVR values were 109.8 (SD 116.9) and 133.7 (SD 153.8) ml at baseline in the Optilume and the control group, respectively. This value decreased to 73.1 (SD 117.7) ml at 6 months and 94.6 (SD 121.8) ml at 12 months in the Optilume group, while in the control group this value increased to 141.4 (SD 194.1) at 6 months and increased further to 179.2 (SD 199.9) ml at 12 months.

IPSS: stärkere Verbesserung mit Optilume nach 6 Monaten, nach 12 Monaten blieb Optilume stabil, Kontrolle verschlechterte sich

PVR: Optilume-Gruppe verbesserte sich, Kontrolle verschlechterte sich

[7] **D0005** – How does Optilume DCB affect symptoms and findings (severity, frequency) of urethral stricture?

[8] **D0006** – How does Optilume DCB affect progression (or recurrence) of urethral stricture?

[9] **D0011** – What is the effect of Optilume DCB on patients' body functions?

[10] **D0016** – How does the use of Optilume DCB affect activities of daily living?

Erectile function

The **IIEF** overall satisfaction score increased from the baseline 5.8 (SD 2.9) in the Optilume group versus 6.0 (SD 3.2) in the control group to 6.5 (SD 2.8) versus 6.6 (SD 3.2), respectively at the 6-month follow-up. The score increased further in the Optilume group to 6.9 (SD 3.1) but decreased in the control group to 5.9 (SD 2.6) in the control group at the 12-month follow-up.

IIEF: nach 6 Monaten kein Unterschied, nach 12 Monaten verbesserte sich die Optilume-Gruppe, die Kontrollgruppe verschlechterte sich

Periprocedural pain

The **VAS pain score** was recorded before the procedure, before discharge, and 30 days after the procedure. The mean baseline score of 1.6 (SD 2.2) of the Optilume group increased to 2.5 (SD 2.2) at the time of discharge, but it decreased by the 30-day mark to 0.6 (SD 1.0). The control group showed a similar pattern, from baseline 1.8 (SD 2.3) to 2.1 (SD 2.2) at discharge and to 0.2 (SD 0.5) at 30-day follow-up.

Schmerzreduktion ähnlich in der Studiengruppen

Health-related quality of life[11],[12]

The **IPSS-QoL** subscore was used to assess quality of life. From baseline 4.5 (SD 1.3) the score decreased to 1.7 (SD 1.3) at 6 months and to 1.9 (SD 1.5) at 12 months in the Optilume group, meaning that the patients valued their quality of life better at the follow-ups compared to baseline. The control arm started from 4.7 (SD 1.2) points, and their score decreased to a lesser extent, to 3.4 (SD 1.8) at 6 months and 4.0 (SD 1.3) at 12 months.

QoL verbesserte sich deutlicher in der Optilume- als in der Kontrollgruppe

Patient satisfaction[13]

Patient satisfaction was not measured in the included study.

Patientenzufriedenheit wurde nicht berichtet

Patient safety[14],[15],[16],[17],[18]

The primary safety endpoint of the ROBUST III study [12, 15, 29] was the **composite of specific device-or procedure-related serious complications**, including urethral fistula, unresolved de novo stress urinary incontinence and urethral rupture at 3 months after the procedure. None of the patients in either study arm experienced any such event.

ROBUST III (RCT): erhebliche produkt-/prozedurbezogene Komplikationen nach 3 Monaten: 0 vs 0,

At the 2-year follow-up, the Optilume group had a slightly lower incidence of any AE at 73% compared to 81% in the control group. **Serious AEs** were reported at 14% for Optilume and 17% for the control group. Substantially more device-related AEs were noted in the Optilume group (35%) compared to the control group (8%). However, **device-related serious AEs** were minimal, with

(schwerwiegende) UE: weniger mit Optilume,

produktbezogene (S)UE: 1% mit Optilume

[11] **D0012** – What is the effect of Optilume DCB on generic health-related quality of life?

[12] **D0013** – What is the effect of Optilume DCB on disease-specific quality of life?

[13] **D0017** – Was the use of Optilume DCB worthwhile?

[14] **C0008** – How safe is Optilume DCB in comparison to urethrotomy, urethroplsty and dilation?

[15] **C0002** – Are the harms related to dosage or frequency of applying Optilume DCB?

[16] **C0004** – How does the frequency or severity of harms change over time or in different settings?

[17] **C0005** – What are the susceptible patient groups that are more likely to be harmed through the use of Optilume DCB?

[18] **C0007** – Are Optilume DCB, urethrotomy, urethroplsty and dilation associated with user-dependent harms?

one patient presenting UTI (1%) in the Optilume group and no patients in the control group.

Both treatments had similar rates of procedure-related AEs (13%), but **serious procedure-related AEs** were higher in the control group (4%) compared to Optilume (1%).

prozedurbezogene UE: keine Differenz, wenig davon schwerwiegend

The number of patients experiencing **severe AEs** (Common Terminology Criteria for Adverse Events, CTCAE grade ≥3) was comparable, with 33% in the Optilume group and 27% in the control group. Grade 4 events occurred in 4% of patients in both groups, while grade 5 events occurred only in the Optilume group (3%).

schwere UE (CTCAE ≥3 und Grad 4): keine Differenz
Grad 5: nur mit Optilume

Data on specific events show similar rates between groups, with urinary tract infections at 11% for Optilume and 10% for the control group and urinary retention at 9% and 8%, respectively. Urinary incontinence was reported only in the Optilume group (3%), and erectile dysfunction was reported only in the control group (2%).

Harnwegsinfekte, Harnverhalt: keine Differenz
Harninkontinenz, erektile Dysfunktion und Therapieabbruch wegen UE: minimal

Treatment discontinuation due to adverse events was minimal and only noted in the Optilume group (1%).

From the non-comparative studies, ROBUST I [16, 30, 32-34] provided comprehensive long-term safety data over 5 years. The aggregated AEs increased from 56 at 1 year to 93 at 5 years, of which 15 were treatment related. Six **serious AEs** occurred in five patients (9%), none of which were **device- or procedure-related**. Common complications included urinary tract infections (UTIs), peaking at 20.8% at 3 years before decreasing to 1% at 5 years, and urinary retention, which ranged from 8% at 1 year to 9% at 5 years. Severe AEs (CTCAE Grade ≥3) were rare, reported in 4–8% of patients over the follow-up period.

ROBUST I Langzeitdaten (5 Jahre):
9% schwerwiegende UE (keine produkt-/prozedurbezogen), schwere UE (CTCAE ≥3) sind minimal

ROBUST II [21, 35] with follow-ups at 3 months and 3 years, reported a higher proportion of patients experiencing AEs. At 3 months, 63% (10/16) of patients reported at least one AE, increasing to 81% (13/16) by 3 years. No treatment-related **serious AEs** were reported at 3 months, but this increased to 6% (1/16) by 3 years. In total, 11 **non-treatment-related SAEs** occurred in 6 patients (38%) in 3 years. **Severe AEs** included 1 Clavien-Dindo Grade 3a event (6%) and 2 Grade 3b events (6%). UTIs occurred in 12.5% of patients, and urinary retention was reported in 6% of patients at both 3 months and 3 years. Hematuria was observed in 19% of patients, and there was one case of mild bladder spasm. No incontinence or erectile dysfunction was reported.

ROBUST II Langzeitdaten (3 Jahre):
38% schwerwiegende UE, minimale produkt-/prozedurbezogenen UE

häufigste UE: Harnwegsinfekte, Harnverhalt, Hämaturie

In contrast, the third study [31] provided limited safety data, focusing only on perioperative and postoperative outcomes at 30 days. It reported no complications or urinary retention during this period, indicating a favourable short-term safety profile. However, long-term safety data, such as serious AEs or other AEs, were not reported, limiting comparisons with the other studies.

3. einarmige Studie: Kurzzeitdaten (30 Tage), keine Komplikationen oder Harnverhalt

None of the included studies reported drug-related adverse events.

arzneimittelbedingte UE wurde in keiner Studie berichtet

Mortality[19]

All-cause mortality was reported in the ROBUST III [12, 15, 29], II [21, 35], and I [16, 30, 32-34]studies. ROBUST I reported no deaths throughout the 5-year follow-up of the study. ROBUST II reported no deaths at 3 months. By the 3-year follow-up one patient died unrelated to the procedure. The ROBUST III study reported two deaths in the Optilume group and no deaths in the control group by 2-year follow-up, presenting a difference of 2.5% (95% CI; -2.6; 7.7; p-value not reported). The two deaths were unrelated to the use of Optilume DCB.

Mortalität
ROBUST I: 0,
ROBUST II: 1,
ROBUST III: 2 vs 0
Todesfälle in beiden Studien nicht produkt-/prozedurbedingt

[19] **D0001** – What is the expected beneficial effect of Optilume DCB on mortality?

5 Quality of evidence

Verzerrungsrisiko: hoch für alle Endpunkte

Hauptgründe: keine Verblindung, fehlende Daten, selektive Berichterstattung

Risk of bias for individual studies was assessed with the Cochrane Risk of Bias Tool 2.0 and is presented in Table A 3 in the Appendix. The risk of bias was assessed as high for all outcomes in ROBUST III [12, 15, 29]. Reasons for the high risk of bias included the lack of blinding in key clinician-reported outcomes, which raises concerns about potential measurement bias, particularly in assessments requiring subjective judgment. Furthermore, missing data concerns were evident for all outcomes except the composite of specific device- or procedure-related serious adverse events at 3 months. For the majority of these outcomes (change in Qmax, Qmax and PVR, IPSS, IPSS-QoL and IIEF), no measures were taken to control for this shortcoming (no sensitivity analysis, unclear data handling methods). Selective reporting bias was flagged for freedom from repeat intervention, Qmax, PVR, IPSS, IPSS-QoL, IIEF and pain. Freedom from repeat intervention was pre-specified for 6 months but the study did not report any p-value for this time point, only for the 12-month follow-up data. The other endpoints were measured at several time points that were not prespecified in the protocol and they were selectively reported in different study documents. Due to the crossover of control group for IPSS, IPSS-QoL, IIEF, and periprocedural pain, patients in the control group who crossed over (25%) were likely influenced by knowing their treatment assignment when answering self-administered questionnaires.

Vertrauenswürdigkeit der Evidenz nach GRADE

The strength of evidence was rated by two independent researchers (JE, JP) according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [36] for each endpoint individually. In case of disagreement, a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [36].

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table below and in the evidence profile in the Appendix in Table A 4.

Vertrauenswürdigkeit der Evidenz für Optilume DCB vs endourologisches Standardverfahren: sehr niedrig bis niedrig

Overall, the strength of evidence for the effectiveness and safety of Optilume DCB in comparison to standard of care endoscopic management (comprising of rigid rod dilation, DVIU, uncoated balloon dilation or a combination of rigid rod and uncoated balloon) very low to low. For the comparison of Optilume DCB and urethrotomy, Optilume and dilation and Optilume and urethroplasty no evidence is available.

Table 5-1: Summary of findings table of Optilume DCB

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with comparison	Risk with intervention				
Stricture-free rate at 6 months	268 per 1000	746 per 1000 (higher=better)	**RR 2.78** (1.98 to 3.58)	127 (1)	⨁⨁◯◯ Low	Optilume DCB increases the proportion of stricture-free patients (444 more stricture-free patients per 1,000). This means that patients with Optilume DCB intervention were 2.78 times more likely to be stricture-free than those in the control group at 6 months. This result was statistically significant (**p<0.0001**).
Freedom from repeat intervention rate at 12 months	See comment	See comment	HR: NR	127 (1)	⨁◯◯◯ Very low	The HR was not reported in the RCT. Kaplan-Meier curve was provided; the two lines did not cross each other during the follow-up period. The study protocol prespecified a statistical test for 6-month follow-up but not for the 12-month follow-up. Results were not reported for the 6-month follow-up.
Change in Qmax at 6 months (ml/s)	Mean value of 11.1 (SD 7.6) ml/s.	**MD 4.78** ml/s higher (higher=better)	Not estimable	127 (1)	⨁⨁◯◯ Low	The intervention led to a statistically significant improvement in Qmax, with a mean difference of 4.78 ml/s compared to the control (**p=0.0031**).
Qmax at 6 and 12 months (ml/s)	From baseline 7.4 (SD 3.5) to 11.1 (SD 7.6) at 6-month and 8.0 (SD 4.6) at 12 months.	From baseline 7.6 (SD 3.4) to 16.6 (SD 8.9) at 6-month and 15.5 (SD 9.0) at 12 months.	Not estimable	127 (1)	⨁◯◯◯ Very low	As the value of >15 ml/s is considered normal and the value <10 ml/s is considered abnormal, the result of the control group at 12 months might be a sign of recurrence. Only descriptive statistics were used to report this outcome.
PVR at 6 and 12 months (ml)	From baseline 133.7 (SD 153.8) to 141.4 (SD 194.1) at 6-month and to 179.2 (SD 199.9) at 12 months. (higher=worse)	From baseline 109.8 (SD 116.9) to 73.1 (SD 117.7) at 6-month and to 94.6 (SD 121.8) at 12 months. (higher=worse)	Not estimable	127 (1)	⨁◯◯◯ Very low	Optilume resulted in a decrease in PVR, while the control intervention resulted in an increase, meaning better outcomes at both the 6- and the 12-month follow-up with Optilume. Only descriptive statistics were used to report this outcome.

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with comparison	Risk with intervention				
IPSS at 6 and 12 months	From baseline 22.9 (SD 6.9) to 15.4 (SD 9.6) at 6 months and to 19.8 (SD 7.4) at 12 months. (higher score=worse)	From baseline 22.0 (SD 6.8) to 8.3 (SD 6.2) at 6 months and to 9.0 (SD 7.1) at 12 months. (higher score=worse)	Not estimable	127 (1)	⨁◯◯◯ Very low	The IPSS between 20-35 signals severe symptoms. Both groups started from the lower end of this range. The Optilume group achieved to get to the lower end of the moderately symptomatic (8-19) bracket, while the control intervention was at the higher end of the moderate category at both time points. Only descriptive statistics were used to report this outcome.
IPSS QoL at 6 and 12 months	From baseline 4.7 (SD 1.2) to 3.4 (SD 1.8) at 6 months and to 4.0 (SD 1.3) at 12 months. (higher score=worse)	From baseline 4.5 (SD 1.3) to 1.7 (SD 1.3) at 6 months and to 1.9 (SD 1.5) at 12 months. (higher score=worse)	Not estimable	127 (1)	⨁◯◯◯ Very low	In the Optilume group, the QoL score, which was initially close to the maximum of 6 (indicating a terrible quality of life as rated by the patient), decreased toward the most positive end of the scale (0 = delighted). In contrast, the control group's QoL score remained relatively unchanged and close to baseline. Only descriptive statistics were used to report this outcome.
Serious device- and procedure-related events at 3 months	0	0	Not pooled	127 (1)	⨁◯◯◯ Very low	No SAEs occurred in any of the study arms up to the 3-month follow-up.
Serious adverse events at 3 years	NA	ROBUST I: 9% ROBUST II: 38% device- or procedure-related: ROBUST I: 0 ROBUST II: 6%	Not pooled	69 (2)	⨁◯◯◯ Very low	9% to 38% of patients experienced SEAs within the follow-up period of 3 years of which 0% to 6% were related to the device or the procedure.

Abbreviations: DCB – drug-coated balloon, HR – hazard ratio, IPSS – International Prostate Symptom Score, MD – mean difference, PVR – post-void residual, RR – relative risk, SAE – serious adverse event

6 Discussion

Summary and interpretation of findings

According to HTD claims, Optilume DCB offers an alternative to a third or fourth dilation/DVIU for men with short bulbar urethral strictures who have already failed two or more endoscopic procedures and wish to avoid urethroplasty. However, the available evidence is insufficient to assess its superiority or non-inferiority over each of the already established interventions—DVIU, dilation or urethroplasty. While short-term benefits have been shown in comparison to a mixed control group of DVIU and dilation, the HTD's claim that these interventions are interchangeable, are not supported by clinical data. Consequently, it remains unclear whether Optilume is superior to both procedures or only one of them. Furthermore, no evidence directly compares Optilume DCB to urethroplasty, leaving its relative effectiveness unknown.

Optilume DCB als Alternative zur 3. oder 4. Dilatation/DVIU

unzureichende Evidenz um die Überlegenheit oder Nicht-Unterlegenheit gegenüber Dilatation, DVIU oder Urethroplastik zu beweisen

ROBUST III [12, 15, 29], the only comparative study, evaluated Optilume DCB in men with urethral strictures ≤3 cm against urethrotomy or dilation but did not report separate results for each comparison. The control arm included rigid rod dilation, uncoated balloon dilation, or DVIU, based on physician discretion. Additionally, three single-arm studies (ROBUST I [16, 30, 32-34], ROBUST II [21, 35], and Alhamdani et al. 2024 [31]) were included for safety outcomes.

Wirksamkeit: 1 RCT, aber keine getrennte Evidenz für Dilatation und DVIU,

Sicherheit: RCT + 3 einarmige Studien

In ROBUST III [12, 15, 29], significant short-term improvements were observed in stricture-free rates and urinary flow (Qmax) in favour of Optilume. At 6 months, patients treated with Optilume were 2.78 times more likely to be stricture-free (RR 2.78; $p<0.0001$), and Qmax improved by 4.78 mL/s on average ($p=0.0031$). By 12 months, Qmax in the control group dropped to below 10 mL/s, suggesting a higher risk of recurrence, while Optilume patients maintained better urinary flow. Additionally, PVR volume improved in the Optilume group and worsened in the control group, reinforcing a functional benefit in urinary emptying. Symptom relief, measured by IPSS, showed improvements in both groups, but Optilume patients achieved a lower (better) symptom severity category (IPSS 8.3-9.0 vs. 15.4-19.8 in controls). IPSS-QoL scores also decreased toward the "delighted" range with Optilume, whereas control patients remained close to baseline. The safety profile appeared favourable, with no SAEs at 3 months, but earlier trials (the non-comparative ROBUST I and II) reported SAEs in 9-38% of patients within 3 years, potentially due to differences in patient severity. Of these SAEs only 6% were due to the device or the procedure. Another small non-comparative study [31] with 30-day data confirms a low complication rate in the perioperative and early postoperative period.

Strikturfreiheit und Qmax: statistisch signifikanter Unterschied zugunsten Optilume

Harnfunktion stabil oder verbessert mit Optilume und verschlechtert in der Kontrollgruppe
schwerwiegende UE:

keine nach 3 Monaten (ROBUST III),
9–38% nach 3 Jahren (ROBUST I & II),
davon 6% produkt/prozedurbedingt

IQWiG-Bewertung: keine ausreichende Evidenz

DVIU als relevantester Vergleich für Deutschland

Verzerrungsrisiko, unsichere Ergebnisse

The Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG, "Institute for Quality and Efficiency in Health Care") first assessed this technology in 2021 [37] and has re-assessed it three times since then [38-40]. Authors reached the same conclusion as our report, namely that ROBUST III does not provide sufficient evidence to establish the benefit of urethral DCB compared to DVIU or dilation. They highlight the lack of separate evidence for each comparator and emphasize that DVIU is the most relevant comparator for the German context, making this evidence essential. Furthermore, they add that any attempt to analyse the study's data separately for each comparator would likely be inconclusive because treatment assignment was left to the treating physician's discretion, introducing potential selection bias. Without randomised allocation, the control groups are not structurally equivalent, making comparisons with the urethral DCB unreliable. Even if certain study centres used only one specific control intervention, the small sample sizes would still limit statistical power.

Internal and external validity

sehr niedrige und niedrige Vertrauenswürdigkeit der Evidenz

Despite positive signals of benefit based on the included studies, the available evidence does not permit a conclusion on comparative effectiveness and safety of Optilume DCB in comparison to dilation or DVIU. The overall certainty of evidence remains very low to low due to several methodological concerns.

methodische Schwächen:

hohe Crossover-Rate

keine Verblindung nach 6 Monaten

The study had a high crossover rate, significantly affecting patient-relevant endpoints. Control group patients were allowed to switch to the intervention arm if medically necessary due to stricture recurrence, leading to a substantial crossover rate, with 12 of 48 control patients switching before 6 months and 24 of 48 by the 12-month follow-up. Furthermore, the lack of blinding for both urologists and patients after 6 months raises concerns about treatment bias. Notably, all crossover patients were automatically classified as treatment failures, further compromising outcome reliability. For stricture-free rate and repeat intervention, the interpretation of cystoscopic findings and the decision to proceed with additional treatment could have been influenced by the treating urologist's awareness of treatment assignment, undermining the robustness of comparative effectiveness conclusions.

keine Angaben zum Umgang mit fehlenden Daten für IPSS, Qmax, PVR, IPSS-QoL, IIEF, Schmerzen

Datenanalyse: meist deskriptiv, fehlende Gruppenvergleiche für die Endpunkte

Another limitation is the handling of missing data, which was neither clearly explained nor systematically addressed. Only the 6-month stricture-free rate underwent a sensitivity analysis confirming the primary results. However, no details were provided on how missing data were handled for IPSS, Qmax, PVR, IPSS-QoL, IIEF, or pain, raising concerns about the reliability of these findings. Additionally, these study outcomes were reported only with descriptive statistics, and the study did not plan to analyse group differences; only within-group before-and-after comparisons were made. This approach may overestimate treatment effectiveness by not accounting for confounding factors or natural variability over time.

eingeschränkte Übertragbarkeit

Beyond internal validity concerns, there are other limiting factors that affect the generalisability of findings of ROBUST III to real-world clinical practice. The study was conducted in North America, where the applicable guideline is less strict regarding the use of DCB compared to the stricter limitations imposed by the EAU guideline. Additionally, the intervention in the study included pre-dilation with an uncoated balloon catheter before applying the drug-coated balloon dilator, which is not standard practice according to the Instructions for Use, potentially influencing the study's outcomes. Furthermore, in the control arm, the type and degree of endoscopic treatment were left to the surgeon's discretion. This difference potentially creates a confounding factor in the treatment arm, making it unclear whether the observed treatment effects at 6 months favouring Optilume is primarily due to the use of the balloon dilator, paclitaxel, or both.

Interventionsgruppe: Vordilatation mit unbeschichtetem Ballon

Verzerrungsrisiko: unklar, ob Effekt durch Ballondilatator, Paclitaxel oder beide verursacht wurde

eingeschränkte Anwendbarkeit: Studienpopulation nicht typisch für rezidivierende Harnröhrenstrikturen

The study also raises concerns about whether the results are applicable to a typical patient population with recurrent bulbar urethral strictures because most patients had undergone more than three prior endoscopic treatments, while Optilume is intended as a third-line treatment after stricture recurrence.

Additionally, the mean stricture length in the study population was 1.7 cm, which is likely shorter than the typical patient population presenting for bulbar urethroplasty after failed endoscopic treatment. This is partly due to the device design, as surgeons were instructed to select a balloon length that allowed for 0.5 to 1 cm overlap with normal urethra on either side of the stricture. Consequently, patients with a 3 cm bulbar urethral stricture required the maximal 5 cm balloon, which may limit the device's applicability to strictures of 3 cm or less in length [41].

Evidence gaps

erforderliche RCTs zur Schließung der Evidenzlücke

To address the evidence gaps, not only an RCT with separate control groups for DVIU and dilation would be needed, but also an RCT comparing a drug-coated balloon to an uncoated balloon to determine whether the observed treatment effect is due to paclitaxel or simply the mechanical effect of dilation. Additionally, a randomised comparison between Optilume and urethroplasty could provide insights into whether this less invasive approach offers comparable long-term outcomes. However, such a study would be challenging, as urethroplasty is significantly more invasive with higher morbidity, making patient recruitment difficult.

Ongoing research

keine laufenden RCTs

eine Studie in Vorbereitung

No ongoing RCTs addressing these evidence gaps could be identified. Information was found about a planned RCT, ReBUS, which was cancelled due to a lack of financial support [38] and another comparative study, BALDIKA, which is initaiated and financed by the German "Federal Joint Committee" (Gemeinsamer Bundesausschuss, G-BA). The study aims to compare DCB to DVIU. The primary completion date is unknown [42].

Based on communication with the HTD, no new HTD-financed RCTs are being conducted or planned at the moment.

Limitations

begrenzte Übertragbarkeit auf die klinische Praxis und weitere Einschränkungen

Our assessment accurately summarizes the current evidence but is constrained by the limited quality and scope of available data. Key challenges include the ROBUST III trial's methodological weaknesses, lack of direct comparison with urethroplasty, short follow-up, and limited applicability to real-world clinical practice. Additionally, the lack of clarity on paclitaxel's contribution, missing data, and absence of ongoing research further limits the strength of conclusions.

Conclusion

Langzeitwirksamkeit ungewiss, allgemein als sicher angesehen

Vorsicht bei routinemäßigem Einsatz

To determine the true clinical value of Optilume DCB, high-quality, long-term RCTs with head-to-head comparison to uncoated balloon dilation, DVIU and urethroplasty are urgently needed. Until such data is available, the long-term clinical effectiveness of Optilume DCB remains uncertain, warranting caution in its widespread adoption. However, its safety profile is well documented, and the device is generally considered safe.

7 Evidence-based conclusion

In Table 7-1 the scheme for evidence-based conclusion is displayed, and the according choice is highlighted.

Table 7-1: Evidence based recommendations

	1	Strong evidence for added benefit in routine use.
	2a	Evidence indicates added benefit only in specific indications.
	2b	Less robust evidence indicating an added benefit in routine use or in specific indications
X	3	No evidence or inconclusive evidence available to demonstrate an additional benefit of the intervention of interest.
	4	Strong evidence indicates that intervention is ineffective and or harmful.

Reasoning:

Very low to low certainty evidence indicates that Optilume DCB has some short-term benefit over a mixed comparator of DVIUand dilation, and the long-term safety profile is favourable. The long-term durability of positive effectiveness results is uncertain, necessitating further high-quality comparative studies. Head-to-head comparisons to urethroplasty, DVIU and uncoated balloon dilation are needed to know how these procedures compare.

sehr niedrige/niedrige Vertrauenswürdigkeit der Evidenz,
kurzfristiger Nutzen,
langfirstige Wirksamkeit ungewiss,
gutes Sicherheitsprofil

A re-evaluation is recommended as soon as the BALDIKA trial has results.

Re-Evaluierung

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A 1: Optilume DCB: Results from randomised controlled trials

Author, year	**Elliott et al. 2022 [15]**	**Van Dyk et al. 2024 [29]**
Study name, trial register number	**ROBUST III, NCT03499964**	
Country	22 centres in North America (U.S., Canada)	
Sponsor	Urotronic Inc.	
Intervention/Product	Predilation with an uncoated balloon and/or DVIU to ≥20 Fr + Optilume DCB (24 Fr, 30 Fr or 36 Fr)	
Comparator	Standard-of-care endoscopic management as determined by the treating physician, including rigid rod dilation, DVIU, uncoated balloon dilation or a combination of rigid rod + uncoated balloon dilation[20] Pharmacokinetics study arm[21]	
Study design	RCT	
Number of patients	Optilume DCB (N = 79) vs Dilation or DVIU (N = 48)	
Study duration	5 years (start date: October 2018, estimated completion date: December 2025, data cutoff: December 2020 (planned interim analysis))	
Inclusion criteria	Male ≥ 18 yrs; visual confirmation of stricture via cystoscopy or urethrogram; single, tandem or diffuse anterior urethral stricture(s) ≤3.0 cm total length measured by retrograde urethrogram; ≥2 prior dilation treatments of the same stricture, including DVIU, but no prior urethroplasty; significant symptoms of stricture such as frequency of urination, dysuria, urgency, hematuria, slow flow, feeling of incomplete emptying, recurrent urinary tract infections; IPSS score ≥11; lumen diameter ≤ 12F by urethrogram; Qmax <15 ml/sec and guidewire must be able to cross the lesion	
Exclusion criteria	Previous urethroplasty, hypospadias repair, lichen sclerosis or unresolved confounding aetiologies.	
Study endpoints	Primary: stricture-free rate at 6 months Other[22]: all-cause mortality; composite of specific device- or procedure-related serious complications at 3 months; freedom from repeat intervention at 1 year; Qmax, IPSS, PVR, IPSS-QoL and IIEF over time; periprocedural pain and adverse events	
Age of patients (yrs)		
Mean ± SD	59 ± 16 vs 61 ± 16	
Median (range)	61 (25–87) vs 63 (23–86)	

[20] The control arm as defined in the Clinical Study Report (CSR). According to the CSR, "all three methods of dilation have been shown to be equivalent in terms of outcome and safety profile and therefore were considered interchangeable in this study. Physicians were able to use one or more of these methods to dilate the stricture as is his/her best practice to dilate the lesion". The "standard-of-care endoscopic management" group is referred to as the "dilation or DVIU" group in most of the text and tables hereafter.

[21] The pharmacokinetics arm is not relevant for the assessment and is not presented in any further tables.

[22] Listed only if outcome is included in the PICO.

Author, year	Elliott et al. 2022 [15]	Van Dyk et al. 2024 [29]
Study name, trial register number	ROBUST III, NCT03499964	
Ethnicity, n/N (%)		
Black or African American	9/78 (12) vs 6/48 (13)	
White	65/78 (83) vs 39/48 (81)	
Pacific Islander, Asia, or Native American	4/78 (5) vs 3/48 (6)	
Hispanic or Latino	3/78 (4) vs 3/48 (6)	
Not Hispanic or Latino	75/78 (96) vs 45/48 (94)	
Body mass index (kg/m2)		
Mean ± SD	31 ± 7[23] vs 29 ± 7	
Median (range)	30 (20–58) vs 27 (15–48)	
Stricture aetiology, n/N (%)		
Iatrogenic	21/78 (27) vs 16/47 (34)	
Idiopathic	42/78 (54) vs 22/47 (47)	
Inflammatory	1/78 (1) vs 2/47 (4)	
Traumatic	14/78 (18) vs 7/47 (15)	
Prior pelvic radiation	9/79 (11) vs 6/48 (13)	
Anatomic location, n/N (%)		
Bulbar	71/79 (90) vs 45/47 (96)	
Penile	8/79 (10) vs 2/47 (4)	
Stricture measurements, mean ± SD		
Length (cm)	1.63 ± 0.76 vs 1.72 ± 0.73	
Diameter (mm)	2.46 ± 0.96 vs 2.33 ± 0.88	
Prior dilations	3.2 ± 1.7 vs 4.3 ± 7.5[24]	
Mean ± SD	3 vs 3	
Median	13/79 (17) vs 10/48 (21)	
Number ≥5 overall (%)		
Follow-up (months)	12	24
Loss to follow-up, n/N (%)	At 3 months: 1/79 (1) vs 4/48 (8) At 6 months: 4/79 (5) vs 12/48 (25) At 12 months: 11/79 (14)[25] vs 27/48 (56)[26]	At 24 months: 26/79 (33) vs 42/48 (88)
Outcomes		
Efficacy, I vs C		

[23] BMI was reported for 77 patients in this group.

[24] One individual in the dilation or DVIU group had 53 prior dilations; the mean number is 3.3 when excluding this patient.

[25] Reasons for discontinuation: 1 death, 6 treatment failures, 2 withdrawal of consent, 1 adverse event and 1 loss to follow-up.

[26] Reasons for discontinuation: 24 crossed over to the other arm, 2 treatment failures and 1 withdrawal of consent.

Author, year	Elliott et al. 2022 [15]			Van Dyk et al. 2024 [29]
Study name, trial register number	ROBUST III, NCT03499964			
Stricture-free rate, n/N (%)	**At 6 months**: 50/67 (74.6) vs 11/41 (26.8), RD 44.4[27] [27.6; 61.1], p<0.0001			NA
Freedom from repeat intervention rate (%)	**At 12 months**: 83.2 vs 21.7, log-rank test p<0.0001			NA
Urinary function (Qmax, PVR and IPSS),[28] Mean ± SD Median (range)	**Qmax (ml/s)**: **At baseline (N=78 vs 47):** 7.6 ± 3.4 vs 7.4 ± 3.5 7.2(0.0–14.9) vs 7.9 (0.0–14.5) **At 6 months (N=67 vs 44):** 16.6 ± 8.9 vs 11.1 ± 7.6 15.0 (1.6–48.5) vs 9.8 (0.0–31.2) **MD at 6 months**: +4.78[29] [90% CI 1.94-7.61][30] p=0.0031 **At 12 months (N=65 vs 42):** 15.5 ± 9.0 vs 8.0 ± 4.6 13.5 (1.6–48.8) vs 7.6 (0.0-23.0)	**PVR (ml):** **At baseline (N=77 vs 47):** 109.8 ± 116.9 vs 133.7 ± 153.8 60.0 (0.0–557.0) vs 80.0 (0.0–703.0) **At 6 months (N=67 vs 44):** 73.1 ± 117.7 vs 141.4 ± 194.1 30.0 (0.0–634.0) vs 90.5 (0.0–999.0) **At 12 months (N=66 vs 43):** 94.6 ± 121.8 vs 179.2 ± 199.9 50.5 (0.0–546.0) vs 118.0 (0.0–999.0) **MD:** NR	**IPSS:** **At baseline (N=79 vs 47):** 22.0 ± 6.8 vs 22.9 ± 6.9 22.0 (11–35) vs 22.0 (12–35) **At 6 months (N=71 vs 43):** 8.3 ± 6.2 vs 15.4 ± 9.6 8.0 (0–26) vs 14.0 (1–35) **At 12 months (67 vs 43):** 9.0 ± 7.1 vs 19.8 ± 7.4 8.0 (0–26) vs 18.0 (7–35) **MD:** NR	NA
Erectile function (IIEF overall satisfaction), Mean ± SD Median (range)	**At baseline (N=72 vs 46)**: 5.8 ± 2.9 vs 6.0 ± 3.2 6.0 (2–10) vs 6.0 (2–10) **At 6 months (N=68 vs 30)**: 6.5 ± 2.8 vs 6.6 ± 3.2 6.5 (2–10) vs 7.5 (2–10) **At 12 months (N=59 vs 14)**: 6.9 ± 3.1 vs 5.9 ± 2.6 8.0 (2–10) vs 6.0 (2–10) **MD**: NR			NA

[27] Estimated risk difference using multiple imputation of missing data. Sensitivity analysis was conducted for this endpoint and results show the same direction as the results from the primary analysis. The sensitivity analysis can be found in Table A 6.

[28] Failure carried forward analysis for these data.

[29] Estimated MD using multiple imputation of missing data. The estimated MD without multiple imputation of missing data was not provided for this outcome. The MD was provided in the clinical study report only.

[30] A 95% CI was not provided in the report.

Author, year	Elliott et al. 2022 [15]	Van Dyk et al. 2024 [29]
Study name, trial register number	ROBUST III, NCT03499964	
Pain[31] (VAS pain score), Mean ± SD Median (range)	**At baseline (N=78 vs 48)**: 1.6 ± 2.2 vs 1.8 ± 2.3 1.0 (0–8) vs 1.0 (0–8) **At 6 months (N=77 vs 47)**:[32] 2.5 ± 2.2 vs 2.1 ± 2.2 2.0 (0–9) vs 2.0 (0–8) **At 12 months (N=78 vs 47)[33]**: 0.6 ± 1. 0 vs 0.2 ± 0.5 0.0 (0–6) vs 0.0 (0–2) **MD**: NR	NA
Health-related quality of life (IPSS-QoL),[34] Mean ± SD Median (range)	**At baseline (N=79 vs 47)**: 4.5 ± 1.3 vs 4.7 ± 1.2 5.0 (1–6) vs 5.0 (2–6) **At 6 months (N=71 vs 43)**: 1.7 ± 1.3 vs 3.4 ± 1.8 2.0 (0–5) vs 3.0 (0–6) **At 12 months (N=67 vs 43)**: 1.9 ± 1.5 vs 4.0 ± 1.3 2.0 (0–5) vs 4.0 (1–6) **MD**: NR	NA
Safety		
At 3 months		
Composite of specific device- or procedure-related serious complications, N/n (%)	0/79 (0) vs 0/48 (0)	
At 24 months		
All-cause mortality[35], n/N (%)	2/79 (3) vs 0/48 (0), RD 2.5%, 95% CI -2.6%; 7.7%, p-value: NR	
Any AE, events, n/N (%)	182, 58/79 (73) vs 89, 39/48 (81)	
SAE, events, n/N (%)	12, 11/79 (14) vs 8, 8/48 (8)	

[31] Reported in the clinical study report only.

[32] The time point is before discharge.

[33] The time point is 30 days after the procedure.

[34] Failure carried forward analysis.

[35] Reported in the clinical study report only.

Author, year	Elliott et al. 2022 [15]	Van Dyk et al. 2024 [29]
Study name, trial register number	ROBUST III, NCT03499964	
Device-related AEs, events, n/N (%)	35, 28/79 (35) vs 5, 4/48 (8)	
Device-related SAEs, events, n/N (%)	1 (urinary tract infection), 1/79 (1) vs 0, 0/48 (0)	
Procedure-related AEs, events, n/N (%)	12, 10/79 (13) vs 10, 6/48 (13)	
Procedure-related SAEs, events, n/N (%)	1 (aspiration pneumonia), 1/79 (1) vs 2 (sepsis and aspiration/choking during crossover procedure), 2/48 (4)	
Severe AEs, n/N (%)[36]	CTCAE Grade ≥3: 26/79 (33) vs 13/48 (27) CTCAE Grade 4: 3/79 (4) vs 2/48 (4) CTCAE Grade 5: 2/79 (3) vs 0/48 (0)	
Treatment discontinuation due to AEs, events, n/N (%)	1, 1/79 (1) vs 0, 0/48 (0)	
Suspected unexpected SAEs, n (%)	0 vs 0	
Perioperative and postoperative complications[37], events, n/N (%)	6, 12/79 (15) vs 13, 3/48 (6)	
Urinary tract infection, events, n/N (%)	21, 9/79 (11) vs 8, 5/48 (10)	
Unirnary retention, events, n/N (%)	9, 7/79 (9) vs 4, 4/48 (8)	
Urinary incontinence, events, n/N (%)	2, 2/79 (3) vs 0, 0/48 (0)	
Erectile dsyfunction, events, n/N (%)	0, 0/79 (0) vs 1, 1/48 (2)	

Abbreviations: AE – adverse event, CI – confidence interval, DVIU - Direct Vision Internal Urethrotomy, IPSS - International Prostrate Symptoms Score, N – number of patients considered in the analysis for calculation of the effect estimate, n – number of patients with the event, MD – mean difference, RD –risk difference, SAE – serious adverse event, SD – standard deviation

[36] Grade 4 and 5 data were calculated by the assessment team using the data from the clinical study report. The number of events was not reported, only the number of patients experiencing the adverse event.

[37] Described in the study report as "injury, poisoning and procedural complications".

Table A 2: Optilume DCB: Results from observational studies

Author, year	Virasoro et al. 2020 [33]	Mann et al. 2021 [32]	Virasoro et al. 2022 [34]	DeLong et al. 2024 [30]	DeLong et al. 2022 [35]	Alhamdani et al. 2024 [31]
Study name, trial register number	ROBUST I, NCT03014726				ROBUST II, NCT03270384	NR
Country	4 centres in Latin America				5 centres in U.S.	Australia
Sponsor	Urotronic				Urotronic	Urotronic
Intervention/Product	Predilation with an uncoated balloon and/or DVIU + Optilume DCB				Predilation with an uncoated balloon, rigid rods or DVIU + Optilume DCB or Optilume DCB without predilation	shallow DVIU with a cold knife + Optilume DCB[38]
Study design	Single-arm prospective study				Single-arm prospective study	Single-arm prospective study
Number of pts	53				16	17
Study endpoints	Primary: rate of treatment-related serious complication at 90 days after the procedure Other a: stricture recurrence rate at 90 days after the procedure, improvement in IPSS, Qmax, PVR, freedom from repeat intervention, functional success (reported as the percentage of subjects with IPSS improvement ≥50% without need for retreatment), IIEF				Primary: rate of device-related serious complications at 90 days Other a: change in IIEF at 90 days, stricture recurrence at 6 months, IPSS, anatomic success at 6 months, urethral stricture-specific PROM, Qmax, freedom from repeat intervention, IPSS responder rate (defined as the proportion of subjects with ≥50% improvement in IPSS without repeat treatment), anatomic success (ability to pass a 16 Fr flexible cystoscope through the treatment site), pain	Improvement in uroflow results or improvement in IPSS scores at 1, 6, 12, and 24 months, improvement in IPSS QOL scores at the same time points, rate of major device or procedure-related complications within 90 days
Inclusion criteria	Males ≥18 yrs; visual confirmation of stricture via cystoscopy or urethrogram; single-lesion anterior urethral stricture or bladder neck contracture <2 cm; ≥1 and <4 prior diagnoses and treatments of the same urethral stricture (including self-catheterisation, dilation and/or DVIU but no prior urethroplasty); significant LUT symptoms, IPSS >13; urethral lumen diameter <12 Fr by urethrogram; able to complete validated questionnaire independently; Qmax <10 ml/s				Male ≥ 18 yrs; visual confirmation of stricture via cystoscopy or urethrogram; single, tandem or diffuse anterior urethral stricture(s) ≤3.0 cm total length measured by retrograde urethrogram; ≥2 prior dilation treatments of the same stricture, including DVIU, but no prior urethroplasty; significant symptoms of stricture such as frequency of urination, dysuria, urgency, hematuria, slow flow, feeling of incomplete emptying, recurrent urinary tract infections; IPSS score ≥13; lumen diameter ≤ 12F by urethrogram; Qmax <12 ml/sec and guidewire must be able to cross the lesion	≥18 years old, urethral stricture > 2 cm and have undergone ≥ 2 prior interventions (DVIU or urethral dilatations) and have had recurrence and decided against urethroplasty, lumen diameter ≤12 F by urethrogram, QMax <15 mL/s at baseline and guidewire must be able to cross the lesion

[38] Predilation of the stricture was not performed as a standard practice prior to insertion of Optilume DCB in this cohort.

Author, year	Virasoro et al. 2020 [33]	Mann et al. 2021 [32]	Virasoro et al. 2022 [34]	DeLong et al. 2024 [30]	DeLong et al. 2022 [35]	Alhamdani et al. 2024 [31]
Study name, trial register number	ROBUST I, NCT03014726				ROBUST II, NCT03270384	NR
Exclusion criteria	Strictures>2.0 cm; >1 stricture; sensitivity to paclitaxel or on medication that may have negative interaction with paclitaxel; having a suprapubic catheter; previous urethroplasty within the anterior urethra; stricture due to bacterial urethritis or untreated gonorrhea; stricture dilated or incised within the last 3 months; abnormal prostate making catheterization difficult, urethral false passage or fistula; obstructive voiding symptoms not directly attributable to the stricture such as BPH at the discretion of the clinical investigator; previous radical prostatectomy; previous pelvic radiation; diagnosed kidney, bladder, urethral or ureteral stones or active stone passage in the past 6 months; use of alpha blockers, beta blockers, OAB (Overactive Bladder) medication, anticonvulsants, and antispasmodics where the dose is not stable; use of botox in the urethral area.				Strictures>3.0 cm; >1 stricture; sensitivity to paclitaxel or on medication that may have negative interaction with paclitaxel; having a suprapubic catheter; previous urethroplasty within the anterior urethra; stricture due to bacterial urethritis or untreated gonorrhea; stricture dilated or incised within the last 3 months; history of over active bladder or stress incontinence; previous radical prostatectomy; previous pelvic radiation; diagnosed kidney, bladder, urethral or ureteral stones or active stone passage in the past 6 months; presence of a penile implant, artificial urinary sphincter, or stent(s) in the urethra or prostate; known neurogenic bladder, sphincter abnormalities, or poor detrusor muscle function.	Stricture >6 cm; Hypersensitivity to TAXOL or interacting drugs; Solid tumours with neutrophil counts <8.0% or poor wound healing; Suprapubic catheter use before enrolment; Recent stricture dilation/incision; Untreated voiding issues, BPH, bladder neck contracture, or SUI; Radiation cystitis or recent genitourinary cancer; Recent/active urinary stones; Chronic renal failure on dialysis; New OAB or unstable medication doses; Dependence on urinary Botox or artificial urinary devices; Neurogenic bladder, sphincter abnormalities or poor detrusor function; Lichen sclerosis, BXO, or prior hypospadias repair; Uncured non-genitourinary cancer; Cognitive/psychiatric issues; Non-compliance with contraception or follow-up; Ongoing investigational drug/device use; Active urinary infection or uncontrolled diabetes; Neurological conditions affecting bladder function; Hematuria without benign cause.
Age of patients (yrs), Mean ± SD	51 ± 15				64 ± 16	61.6
Ethnicity, n/N (%) Black or African American Hispanic or Latino Other[a]	 8 /53 (15) 44/53 (83) 1/ 53 (2)				NR	NR

Author, year	Virasoro et al. 2020 [33]	Mann et al. 2021 [32]	Virasoro et al. 2022 [34]	DeLong et al. 2024 [30]	DeLong et al. 2022 [35]	Alhamdani et al. 2024 [31]
Study name, trial register number	ROBUST I, NCT03014726				ROBUST II, NCT03270384	NR
Stricture aetiology, n/N (%) Iatrogenic Idiopathic Traumatic	24/53 (45) 2/53 (4) 27/53 (51)				2/16 (13) 11/16 (69) 3/16 (19)	NR
Anatomic location, n/N (%) Bulbar Penile	NR NR				NR NR	12 1 (and 4 in the bladder neck)
Stricture measurements, mean ± SD Length (cm) Diameter (mm)	0.9 ± 0.5 2.47 ± 1.97				2.1 ± 0.7 2.3 ± 0.9	NR 2 cm: 8 patients 3 cm: 7 patients 4 cm: 1 patient 5 cm: 1 patient
Pretreatments[39], n (%) Uncoated balloon DVIU DVIU + uncoated balloon Direct DCB dilation Predilation with uncoated balloon or DVIU Direct DCB dilation with postdilation Number of previous endoscopic treatments, n (%)	31 (59) 8 (15) 14 (26) NR NR NR 1: 30 (57) 2: 13 (25) 3: 8 (15) 4: 2 (4)				NR NR NR 10 (63) 6 (37) 0 (0) mean ± SD: 4.1 ± 4.9	Mean number of prior urethral procedures: 7.7 <5: 8 (47) 5–10: 6 (35) 11–20: 1 (6) >20: 2 (12) Prior urethral surgery (excluding DVIU/dilation): 4 (24) Prior RTx: 4 (24)
Follow-up (months)	12 months	2 years	3 years	5 years	3 years[40]	4 years (median 30 months)
Loss to follow-up, n (%)	At 3 months: 2 At 12 months: 7	7	10	22	7	At 24 months: 5
Outcomes						
Safety						
All-cause mortality, n (%)	0	0	0	0	At 12 months: 0 At 3 years: 1	NR

[39] Pretreatments were reported in a different way. ROBUST I considered uncoated balloon, DVIU and the combination of these two, while ROBUST II considered DCB dilation, uncoated balloon or DVIU and DCB with postdilation.

[40] Clinical study report for the 3-year results. The publication by DeLong et al. reports 1-year follow-up data.

Author, year	Virasoro et al. 2020 [33]	Mann et al. 2021 [32]	Virasoro et al. 2022 [34]	DeLong et al. 2024 [30]	DeLong et al. 2022 [35]	Alhamdani et al. 2024 [31]
Study name, trial register number	ROBUST I, NCT03014726				ROBUST II, NCT03270384	NR
At least one AE, events, n/N (%)	56[41], NR Treatment-related: 12 events	Aggregated: 71, NR	Aggregated: 73, 35/53 (66) Treatment-related: 13 events	Aggregated: 93, NR Device-or procedure-related: 15 events	**At 3 months**: 21, 10/16 (63) **At 3 years**: 46, 13/16 (81)	NR
Serious AE, events, n/N (%)	**At 3 months:** treatment-related urinary SAEs: 0 **At 6 months:** myocardial infarction: 1 **At 12 months:** abdominal pain: 1	treatment-related urinary SAEs: 0 non-urinary SAEs (non-treatment or procedure-related): 6	6, 5/53 (9)	6, 5/53 (9) Device-or procedure-related: 0	**At 3 months**: 0, 0/16 (0) **At 3 years**: 11, 6/16 (38) treatment- or product-related: 1, 1/16 (6)	NR
Severe AEs	CTCAE severe: 2 events (4%)	CTCAE 6 events (8%)	Events: CTCAE grade ≥3: 3 CTCAE grade 3: 2 CTCAE grade 4: 1 CTCAE grade 5: 0	Events: CTCAE grade ≥3: 8 CTCAE grade 5: 0	Clavien-Dindo grade 3a: 1 event in 1 patient (6%) Clavien-Dindo grade 3b: 2 events in 1 patient (6%)	NR
Treatment discontinuation or interruption due to AEs	3 patients withdrew due to AE (BPH)				NR	NR
Perioperative and postoperative complications, events, n/N (%)	NR				NR	At 30 days: 0
Urinary tract infection, event (%)	8 (15)	(17)	(20.8)	1 (1)	2/16 (12.5) patients	NR
Urinary retention, events, n/N (%)	4 events (8)	4 events (6)	7 events (9.4)	6, 5/53 (9) 3 events (3)	**At 3 months**: 1, 1/16 (6)	At 30 days: 0
Incontinence, events, n/N (%)	At 3 months[42]: 0	NR	NR	NR	At 3 months[43]: 0	NR
Erectile dysfunction, events, n/N (%)	0	0	0	1, 1/53 (2)[44]	0	NR

[41] Virasoro et al. 2020 reported 52. Virasoro et al. 2022 reported 56 events.

[42] Incontinence was part of the composite primary safety endpoint and did not occur in any case during 3-month follow-up.

[43] Incontinence was part of the composite primary safety endpoint and did not occur in any case during 3-month follow-up.

[44] Reported in the clinical study report.

Author, year	Virasoro et al. 2020 [33]	Mann et al. 2021 [32]	Virasoro et al. 2022 [34]	DeLong et al. 2024 [30]	DeLong et al. 2022 [35]	Alhamdani et al. 2024 [31]
Study name, trial register number	ROBUST I, NCT03014726				ROBUST II, NCT03270384	NR
Other AEs	fever (12%), headache (8%), and dysuria (6%).	fever (8%), dysuria (7%), and headache (6%)	dysuria, fever, and urethral stricture (9.4% for each event).	Fever: 2 Dysuria: 3 Hematuria: 4 Orchitis: 1 Extravasation of contrast during retrograde urethrogram: 1	Hematuria: 2 events in 3/16 patients (19) Mild bladder spasm: 1 event	NR

Abbreviations: *DCB=drug-coated balloon; DVIU=direct vision internal urethrotomy; N=number of patients included; n=number of patients; NR=not reported; SD=standard deviation.*

Source: *Clinical study reports, clinical trials registry data, study protocols and publications [30-35]*

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers. In case of disagreement a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the AIHTA and in the Guidelines of EUnetHTA.

Table A 3: Risk of bias – study level (randomised studies)

Trial	Endpoints	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
ROBUST III	Stricture-free rate at 6 months	Low [a]	Low [b,c]	Low [d]	High [e]	Low [f]	High
ROBUST III	Freedom from repeat intervention rate at 12 months	Low [a]	Low [b,g]	Low [h]	High [e]	High [i]	High
ROBUST III	Change in Qmax at 6 months	Low [a]	Low [b,c]	High [j,k]	Low [l]	Low [f]	High
ROBUST III	Qmax at 30 days and 3, 6 and 12 months	Low [a]	High [b,m]	High [j]	Low [l]	High [n]	High
ROBUST III	PVR at 30 days and 3, 6 and 12 months	Low [a]	High [b,m]	High [j]	Some concerns [o]	High [n]	High
ROBUST III	Patient-reported outcomes at 30 days and 3 and 6 months: – IPSS – IPSS-QoL – IIEF (overall satisfaction) – Periprocedural pain	Low [a]	High [b,p]	High [k,q]	High [r]	High [n]	High
ROBUST III	Freedom from a composite of serious device- or procedure-related events (including urethral fistula, unresolved de novo stress urinary incontinence and urethral rupture) up to 3 months	Low [a]	High [b]	Low [s]	High [t]	Low [u]	High

a According to the protocol, randomisation was planned at 2:1 allocation to treatment versus control, stratified by investigational centre and by prior radiation treatment and number of prior dilation treatments using randomly permuted blocks. There is no specific information on the concealment of the allocation sequence.

b Some participants who experienced stricture recurrence requiring intervention were unblinded before 6 months: 12/48 (25%) patients in the control group crossed over. Surgeons and investigators were not blinded to the intervention over the entire study period.

c Intention-to-treat analysis with multiple imputations of missing data was prespecified and conducted.

d Data were missing for this outcome for 12/79 patients in the Optilume group and 7/48 in the control group (15% in each group). A sensitivity analysis comprising 5 subanalyses yielded results with the same directionality as for the primary analysis.

e The surgeons and investigators were not blinded to the intervention over the entire study period and the study authors note that this might have biased their interpretation of cystoscopic findings or the decision to proceed with repeat treatment. Therefore, assessment of this clinician-reported outcome may have been subject to measurement bias.

f Only one outcome measure was defined for the outcome and there is only one way in which the outcome measure can be analysed. Analysis reported in the CSR is consistent with what was planned in the protocol.

g While a Kaplan-Meier curve and a p value for a log-rank test are available, neither a difference in medians (point estimate and CI), nor a hazard ratio (point estimate and CI) is provided.

h According to the Kaplan-Meier curve, there was a low rate of loss to follow up in both groups for most of the follow-up period. However, during the last 20 days of follow-up, more patients are censored in the Optilume group than in the control group.

i A nominal p value is reported for this outcome at 12 months. Its analysis at 6 months was prespecified in the protocol, but group Kaplan-Meier estimates are only reported for 12 months in the publication. Several analyses are reported in the CSR (2 for 6 months) and in the publication (1 at 12 months).

j Data are missing data 12/79 (15%) patients in the intervention group and 4/48 (8%) in the control group.

k No sensitivity analysis was conducted for this outcome.

l Even though the measurement tool for this performance outcome is not detailed in the study, it can be assumed that, as in most routine care situations, uroflowmetry is carried out in a fully automatic way without any need for medical staff to read the results.

m The results for this outcome are only descriptive. There is no clear explanation for the handling of missing data (it was only stated in the CSR that failure-carried-forward analysis was performed).

n Analysis of this outcome was not prespecified in the protocol.

o There is no information on the methods used to assess PVR, which is a clinically reported outcome measure. The ultrasound method could imply some subjectivity from the assessor.

p Only descriptive statistics were used to report these outcomes. There is no clear explanation for the handling of missing IPSS data and no explanation for the handling of missing IIEF and periprocedural pain data.

q Data missing for 8/79 patients in the intervention group and 5/48 in the control group (10% in both groups) for IPSS and IPSS-QoL at 6 months. Data missing for 11/79 (14%) patients in the intervention group and 18/48 (38%) in the control group for IIEF at 6 months.

r Patients from the control group who crossed over (25%) are likely to have been influenced by the knowledge of their treatment assignment when answering these self-administered questionnaires.

s It can be assumed that this outcome is available for all or nearly all participants.

t Surgeons were not blinded to the type of treatment; this might have biased their assessment of the clinical status of the patient regarding the three components of this composite safety outcome.

u As prespecified in the protocol, only descriptive statistics were used to report this outcome.

Table A 4: Evidence profile: efficacy and safety of Optilume DCB in men aged ≥18 years with bothersome urinary symptoms associated with recurrent anterior urethral strictures ≤3 cm in length

Quality assessment							Summary of findings				
							Number of patients		Effect[a]		Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparison	Relative (95% CI)	Absolute (95% CI)	
Stricture-free rate at 6 months											
1 [15]	RCT	Serious[b]	Not serious	Serious[c]	Not serious	None	79	48	2.78 (1.98 to 3.58)	RD +44.4% (27.6 to 61.1 more) **p<0.0001***, #,$	⨁◯◯◯ Low
Freedom from repeat intervention rate at 12 months											
1 [15]	RCT	Very serious[b,d]	Not serious	Serious[c]	Serious[e]	None	79	48	HR: NR, p<0.0001	Not estimable	⨁◯◯◯ Very low
Change in Qmax at 6 months (ml/s)											
1 [15]	RCT	Very serious[b,f,g]	Not serious	Serious[c]	Not serious	None	79	48	Not estimable	MD +4.78 ml/s (90% CI 1.94 to 7.61) **p=0.0031***,#,$	⨁◯◯◯ Very low
Qmax at 6 months and 12 months (ml/s)											
1 [15]	RCT	Very serious[b,g]	Not serious	Serious[c]	Serious[h]	None	79	48	Not estimable	At 6 months I vs C: 16.6 (SD 8.9) vs 11.1 (SD 7.6) At 12 months I vs C: 15.5 (SD 9.0) vs 8.0 (SD 4.6)	⨁◯◯◯ Very low
PVR at 6 months and 12 months (ml)											
1 [15]	RCT	Very serious[b,g,i,j]	Not serious	Serious[c]	Serious[h]	None	79	48	Not estimable	At 6 months I vs C: 73.1 (SD 117.7) vs 141.4 (SD 194.1) At 12 months I vs C: 94.6 (SD 121.8) vs 179.2 (SD 199.9)	⨁◯◯◯ Very low
IPSS at 6 months and 12 months											
1 [15]	RCT	Very serious[b,g,i,k,l]	Not serious	Serious[c]	Serious[h]	None	79	48	Not estimable	At 6 months I vs C:	⨁◯◯◯ Very low

Quality assessment							Summary of findings				
							Number of patients		Effect[a]		Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparison	Relative (95% CI)	Absolute (95% CI)	
										8.3 (SD 6.2) vs 15.4 (SD 9.6) At 12 months I vs C: 9.0 (SD 7.1) vs 19.8 (SD 7.4)	
IPSS-QoL at 6 months and 12 months											
1 [15]	RCT	Very serious[b,g,i,k,l]	Not serious	Serious[c]	Serious[h]	None	79	48	Not estimable	At 6 months: 1.7 (SD 1.3) vs 3.4 (SD 1.8) At 12 months: 1.9 (SD 1.5) vs 4.0 (SD 1.3)	⨁◯◯◯ Very low
Serious device- or procedure related events at 3 months											
1 [15]	RCT	Serious[b]	Not serious	Serious[c,m]	Serious[h]	None	79	48	Not pooled	0 events vs 0 events	⨁◯◯◯ Low
2 [30, 32-35]	Single-arm	Serious[n]	Not serious	Serious[m,o]	Serious[h]	None	69	NA	Not pooled	ROBUST I: 0 ROBUST II: 0	⨁◯◯◯ Very low
Serious adverse events at 3 years											
2 [30, 32-35]	Single-arm	Serious[n]	Not serious	Serious[m,o]	Serious[h]	None	69	NA	Not pooled	At 3 years: ROBUST I: 6 events in 5/53 patients (9%) of which 0 was device- or procedure-related ROBUST II: 11 events in 6/16 patients (38%) of which 1 in 1/16 (6%) patient was device- or procedure-related	⨁◯◯◯ Very low

***Abbreviations**: CI=confidence interval; CSR=clinical study report; DVIU=direct vision internal urethrotomy; IFU=instructions for use; IIEF=International Index of Erectile Function; IPSS=International Prostate Symptom Score; NA=not applicable; PICO=Population, Intervention, Comparator, Outcome; PVR=postvoid residual volume; Qmax=maximum flow rate; QoL=quality of life; RCT=randomised controlled trial; SAP: statistical analysis plan; VAS=Visual Analogue Scale.*

*Comments: a: Use of an * indicates statistical significance versus a pre-specified alpha level, use of a # indicates a pre-specified analysis according to the statistical analysis plan, use of a $ indicates control for multiplicity.*

b: There is no specific information on the concealment of the allocation sequence. Some participants were unblinded before the 6-month cut-off if they experienced recurrent stricture requiring intervention: 12/48 (25%) patients of the control group crossed over. Surgeons and investigators were not blinded to the intervention over the entire study period, which might have biased their interpretation of findings or the decision to proceed with repeat treatment. Therefore, the assessment of this clinically reported outcome may have been subject to measurement bias.

c: The RCT was conducted in North America. Optilume treatment encompassed a pre-dilation, which is not standard according to the IFU, it was done in the study only and it might have influenced the results. Optilume is proposed for third-line treatment after stricture recurrence, but the majority of patients included in the trial had more than 3 endoscopic treatments before having Optilume. The comparator in the study was standard of care endoscopic management as determined by the treating physician (rigid rod dilation, DVIU, balloon dilation or a combination) which was a mix of PICO 1 and PICO 2 comparators (urethrotomy and dilation). Additionally, there is no internationally agreed on single outcome measure, which defines stricture recurrence.

d: According to the Kaplan-Meier curve, for most of the follow-up, there is a low rate of loss-to-follow-up in both groups. However, during the last 20 days of follow-up, more patients were censored in the Optilume group than in the control group. The analysis of this outcome was prespecified in the protocol for 6 months, but the 12-month results are reported only (several analyses are reported in the CSR and in the publication).

e: Nominal p-value is reported. While a Kaplan-Meier curve is available, as well as a p-value of a log rank test, no difference in medians (point estimate and confidence intervals), nor a hazard ratio (point estimate and confidence interval), are provided.

f: Missing data for 12/79 (15%) patients in Optilume group and 4/48 (8%) in control group. No clear explanation for the handling of missing data for Qmax and PVR (it was stated only that a "failure carried forward" analysis was conducted).

g: No sensitivity analysis was conducted for this outcome.

h: Only descriptive statistics were used to report the outcome. No confidence interval was provided. The sample size is small and there is a lack of statistical power.

i: The analysis of the outcome was not pre-specified in the protocol.

j: There is no information on the methods used to assess PVR urine which is a clinically reported outcome. The ultrasound method could imply some subjectivity from the assessor.

k: Missing data for 8/79 patients in intervention group and 5/48 in control group: 10% in both groups for IPSS and IPSS-QoL at 6 months. No clear explanation provided for the handling of missing data.

l: Patients from control group who crossed over (25%) are likely to have been influenced by the knowledge of their treatment assignment when answering these self-administered questionnaires.

m: No data reported for the drug-related adverse events which were requested in the PICO question.

n: Single-arm observational study.

o: The single-arm prospective studies were conducted in Latin America and North America. Inclusion criteria were narrower than in the RCT, possibly resulting in more severe patients. Pre-dilation was carried out, which might have influenced the results.

Table A 5: Reported outcomes their measurement instruments

Outcome (concept)	Outcome measurement instrument/ Type of instrument	Outcome measurement instrument definition/ Interpretation
Urinary function	International Prostate Symptom Score/ PROM	A 7-item self-administered questionnaire to screen for, rapidly diagnose, track the symptoms of and suggest management for lower urinary tract symptoms of BPH. Scores range from 0 to 35, interpreted as follows: ■ 0–7: mildly symptomatic ■ 8–19: moderately symptomatic ■ 20–35: severely symptomatic
	PVR/ ClinROM	Quantity of urine (in ml) that remains in the bladder after urination. PVR is evaluated using ultrasound, a bladder scanner or a urinary catheter.
	Qmax/ PerfO	Maximum urinary flow rate measured in ml/s to assess the degree of obstruction in a patient with lower urinary tract symptoms. In men, Qmax >15 ml/s is considered normal and <10 ml/s abnormal.
Erectile function	International Index of Erectile Function/ PROM	A 15-item self-administered questionnaire for evaluation of male sexual function that includes 5 dimensions: ■ Erectile function (score 1–30 score) ■ Orgasmic function (score 1–10) ■ Sexual desire (score 2–10) ■ Intercourse satisfaction (score 0–15 score) ■ Overall satisfaction (score 2–10 score) For all domains, a higher score indicates less dysfunction.
Treatment success	Anatomical success, defined as the stricture-free rate/ ClinROM	The stricture-free rate was evaluated in ROBUST III as the proportion of patients in whom a flexible cystoscope (≥16 Fr) or 14 Fr rubber catheter could be atraumatically passed through the treated area. If at least one of the stated instruments is able to pass: subject is considered a success. If neither instrument can pass, the subject is considered a failure. Any subjects who have a second dilation procedure, pursue surgical intervention or otherwise seek alternative treatment for the target stricture before the visit window are considered treatment failures.
	Freedom from repeat intervention [a]/ ClinROM	Repeat intervention in ROBUST III study included repeated dilation of the study stricture with sounds, balloon dilation (including crossover treatment with Optilume DCB), DVIU and urethroplasty.
Health-related QoL	IPSS-QoL/ PROM	IPSS-QoL is an additional item on QoL in relation to urinary symptoms on the self-administered IPSS questionnaire. The score ranges from 0 (patient "delighted" with their QoL) to 6 (patient perceives their QoL as "terrible").
Periprocedural pain	Visual Analogue Scale (VAS) for pain/ PROM	A standardised VAS pain questionnaire was completed by the patients before the procedure and at the 30-day visit. The scale ranges from 0 (no pain) to 10 (worst possible pain).
[a] Also referred to as "time to treatment failure" in the ROBUST III study protocol.		

***Source**: EUnetHTA JCA [11]*

***Abbreviations**: BPH=benign prostatic hyperplasia; ClinROM=clinician-reported outcome measure; DCB=drug-coated balloon; DVIU=direct vision internal urethrotomy; Fr=French; PerfO=performance outcome; PROM=patient-reported outcome measure; Qmax=maximum flow rate; QoL=quality of life; VAS=Visual Analogue Scale.*

Table A 6: Sensitivity analysis for the stricture-free rate

Attribute	Analysis method	Optilume DCB N=79, n/N (%)	Dilation or DVIU N=48, n/N (%)	Risk difference, % [95% CI]
Missing data	Observed [a]	50/67 (74.6)	11/41 (26.8)	47.8 [28.7; 66.9]
Missing data	Worst case imputation [b]	50/79 (63.3)	18/48 (37.5)	25.8 [6.8; 44.8]
Missing data	Late cystoscopy as observed [c]	53/72 (73.6)	12/44 (27.3)	46.3 [27.9; 64.8]
Missing data	IPSS responder status at 6 months [d]	53/71 (74.6)	13/44 (29.5)	45.1 [26.4; 63.8]
Missing data	IPSS responder status at last visit [e]	58/79 (73.4)	16/47 (34.0)	39.4 [21.0; 57.8]

[a] Only observed values were used for this analysis.

[b] Including all patients randomised to the investigation group with missing data as failures and all patients randomised to the control group with missing data as successes.

[c] Carries back the next available cystoscopy results captured after the 6-month visit cutoff (240 days) if the 6-month cystoscopy is missing.

[d] Subjects missing 6-month cystoscopy with a documented improvement in IPSS ≥50% at 6 months are treated as a success and subjects with a documented improvement <50% as a failure. Subjects with missing IPSS data at 6 months are censored in this analysis.

[e] Subjects with missing 6-month cystoscopy and a documented improvement in IPSS ≥50% at their last visit before 6 months are treated as a success and subjects with a documented improvement <50% as a failure. Subjects with no measured IPSS results are censored in this analysis.

***Source**: Clinical study report, EUnetHTA JCA [11]*
***Abbreviations**: CI=confidence interval; DCB=drug-coated balloon; DVIU=direct vision internal urethrotomy; n/N=number of patients with overall endpoint success/number of randomised patients.*

Applicability table

Table A 7: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The population of the study was in line with the population defined in the assessment scope. The anatomic location of the anterior strictures was mainly bulbar in the study. The stricture length was on average 1.63 (SD 0.76) in the Optilume group versus 1.72 (SD 0.73) in the control group. The mean number of prior endoscopic treatments was 3.2 (SD 1.7) versus 4.3 (SD 7.5).
Intervention	Optilume treatment included pre-dilation, which is not standard according to the IFU; this step was only carried out in the study, and it might have influenced the results. Optilume is proposed for third-line treatment after stricture recurrence, but the majority of patients included in ROBUST III had more than 3 endoscopic treatments before the Optilume procedure. Any necessary pre-dilation should be performed using a method that is relevant to the Austrian healthcare context (internal urethrotomy or rigid rod dilation/bougienage). The fact that in the ROBUST III study, more than 90% of patients in the intervention group underwent pre-dilation using an uncoated balloon catheter only partially limits the study's applicability to the exploratory question, as the results can still be considered transferable.
Comparators	The comparator in the ROBUST III study was standard-of-care endoscopic management as determined by the treating physician. It included different procedures (rigid rod dilation, DVIU, balloon dilation or a combination), representing a mix of the PICO 1 (urethrotomy) and PICO 2 (dilatation) comparators. Hence, the ROBUST III trial comparators do not exactly match the comparators defined in the PICO. The PICO requested 3 comparators separately and the study applied two of these for the control arm indistinctly, results are reported for the whole control arm in a mixed manner.
Outcomes	No data were reported for the drug-related adverse events requested in the PICO question. All other outcomes were reported in this study. Long-term follow-up of the intervention versus comparator groups is lacking.
Setting	The ROBUST III study was conducted in North America, not in Europe. The clinical guidelines of the American Urological Association and the EAU overlap, but the EAU guideline sets stricter limitations on DCB use (only for ≥2 prior failed endoscopic treatments, if urethroplasty is not possible).

***Abbreviations**: DCB = drug-coated balloon; DVIU = direct vision internal urethrotomy; EAU = European Association of Urology; IFU = instructions for use; PICO = population-intervention-control-outcomes; SD = standard deviation*

List of ongoing trials

Table A 8: List of ongoing trials with Optilume DCB

Identifier/ Trial name	Patient population	Intervention	Control	Primary Outcome	Primary completion date	Sponsor
NCT05479422/ Optilume Registry for Treatment of Stricture of the Anterior Urethra	Anterior urethral stricture in males	Optilume DCB	NA	Responder rate at 12 months (i.e. ≥30% improvement in IPSS without repeat intervention)	August 2029	European Association of Urology Research Foundation
NCT05383274/ Optilume PoST AppRoval Clinical Evaluation of Andrology ParaMeters	Urethral stricture	Optilume DCB	NA	Average change in sperm concentration from baseline to 3-months, 3-months	September 2025	Urotronic, Inc.
BALDIKA	Urethral stricture	DCB	DVIU	IPSS improvement ≥6 points compared to baseline after 12 months, stricture-free rate within 12 months	NI	G-BA

***Abbreviations**: DCB – drug-coated balloon, DVIU – direct vision internal urethrotomy, G-BA – Gemeinsamer Bundesausschuss, IPSS - International Prostate Symptom Score, NA – not applicable, NI – no information*

Research questions

Table A 9: Health problem and Current use

Element ID	Research question
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for urethral stricture?
A0004	What is the natural course of urethral stricture?
A0005	What is the burden of disease for the patients with urethral stricture?
A0006	What are the consequences of urethral stricture for the society?
A0024	How is urethral stricture currently diagnosed according to published guidelines and in practice?
A0025	How is urethral stricture currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?

Table A 10: Description of the technology

Element ID	Research question
B0001	What is Optilume DCB, urethrotomy, DVIU and urethroplasty?
A0001	For which health conditions, and for what purposes is Optilume DCB used?
A0020	For which indications has Optilume DCB received marketing authorisation or CE marking?
B0002	What is the claimed benefit of Optilume DCB in relation to urethrotomy, DVIU or urethroplasty?
B0003	What is the phase of development and implementation of Optilume DCB, urethrotomy, DVIU or urethroplasty?
B0004	Who administers Optilume DCB, urethrotomy, DVIU and urethroplasty and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use Optilume DCB, urethrotomy, DVIU and urethroplasty?
B0009	What supplies are needed to use Optilume DCB, urethrotomy, DVIU and urethroplasty?
A0021	What is the reimbursement status of Optilume DCB?
A0011	How much are the technologies utilised?

Table A 11: Clinical effectiveness

Element ID	Research question
D0005	How does Optilume DCB affect symptoms and findings (severity, frequency) of urethral stricture?
D0006	How does Optilume DCB affect progression (or recurrence) of urethral stricture?
D0011	What is the effect of Optilume DCB on patients' body functions?
D0016	How does the use of Optilume DCB affect activities of daily living?
D0012	What is the effect of Optilume DCB on generic health-related quality of life?
D0013	What is the effect of Optilume DCB on disease-specific quality of life?
D0017	Was the use of Optilume DCB worthwhile?

Table A 12: Safety

Element ID	Research question
D0001	What is the expected beneficial effect of Optilume DCB on mortality?
C0008	How safe is Optilume DCB in comparison to urethrotomy, DVIU or urethroplasty?
C0002	Are the harms related to dosage or frequency of applying Optilume DCB?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of Optilume DCB?
C0007	Are Optilume DCB and urethrotomy, DVIU or urethroplasty associated with user-dependent harms?

Literature search strategies

Search strategy for Cochrane

Search Name: Balloon dilatation (with Optilume) for Urethral Strictures	
Search date: 09/12/2024	
ID	Search
#1	MeSH descriptor: [Urethral Stricture] explode all trees
#2	(urethra* NEAR (stricture* OR stenos*)) (Word variations have been searched)
#3	#1 OR #2
#4	MeSH descriptor: [Drug-Eluting Stents] explode all trees
#5	drug-coated (Word variations have been searched)
#6	(drug-eluting) (Word variations have been searched)
#7	#4 OR #5 OR #6
#8	balloon*
#9	#7 AND #8
#10	MeSH descriptor: [Paclitaxel] explode all trees
#11	(paclitaxel*) (Word variations have been searched)
#12	(Optilume*) (Word variations have been searched)
#13	(Lutonix*) (Word variations have been searched)
#14	(Stellarex*) (Word variations have been searched)
#15	(Biolux*) (Word variations have been searched)
#16	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#17	#3 AND #16
#18	#3 AND #16 with Cochrane Library publication date Between Jan 2023 and Dec 2024
#19	English:la
#20	German:la (Word variations have been searched)
#21	#19 OR #20
#22	#18 AND #21
#23	(conference proceeding):pt
#24	(abstract):so
#25	(((clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr))):so
#26	#23 OR #24 OR #25
#27	#22 NOT #26
Total hits: 1	

Search strategy for Embase

Search Name: Balloon dilatation (with Optilume) for Urethral Strictures		
Search date: 09/12/2024		
No.	Query Results	Results
#1	'urethra stenosis'/exp	13,771
#2	urethra* NEAR/3 (stricture* OR stenos*)	15,913
#3	#1 OR #2	15,913
#4	'drug-coated balloon'/exp	4,011
#5	'drug-eluting balloon catheter'/exp	651
#6	(coated OR eluting) NEAR/3 balloon*	6,436

#7	('drug-coated' OR 'drug-eluting') NEAR/3 balloon*	5,685
#8	'paclitaxel'/exp	145,966
#9	'surgical dilator'/exp	1,021
#10	optilume*	99
#11	lutonix*	333
#12	stellarex*	80
#13	biolux*	85
#14	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	150,892
#15	#3 AND #14	118
#16	#15 AND [2023-2025]/py	46
#17	#16 AND [2023-2025]/py AND ([english]/lim OR [german]/lim)	46
#18	#17 AND 'Conference Abstract'/it	27
#19	#17 NOT #18	19
Total hits: 19		

Search strategy for Medline via Ovid

Search Name: Ovid MEDLINE(R) ALL <1946 to December 02, 2024>	
Search date: 04/12/2024	
ID	Search
#1	Urethral Stricture*.mp. (8081)
#2	exp Urethral Stricture/ (5795)
#3	Urethral Stenos*.mp. (796)
#4	1 or 2 or 3 (8438)
#5	Drug-Coated Stent*.mp. (163)
#6	exp Drug-Eluting Stents/ (14194)
#7	Drug-Eluting Stent*.mp. (19694)
#8	5 or 6 or 7 (19740)
#9	Balloon*.mp. (130305)
#10	8 and 9 (7001)
#11	exp Paclitaxel/ (32263)
#12	Paclitaxel Coated Balloon*.mp. (537)
#13	Optilume.mp. (32)
#14	Lutonix.mp. (45)
#15	Stellarex.mp. (15)
#16	Biolux.mp. (50)
#17	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (160684)
#18	4 and 17 (172)
#19	limit 18 to yr="2023 - 2024" (21)
#20	limit 19 to (english or german) (20)
#21	remove duplicates from 20 (19)
Total hits: 19	

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Health Technology Assessment
GmbH