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JCAMD001 Assessment Report – OPTILUME ® URETHRAL DRUG-COATED BALLOON

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Disclaimers

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This Joint Clinical Assessment (JCA) report is a pilot produced while the JCA report and submission dossier templates were still in development, and it was used for further fine-tuning of these templates.

Participants

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The work in EUnetHTA 21 is a collaborative effort. While the agencies in the Assessment Team actively wrote the joint clinical assessment (JCA) report, the entire EUnetHTA 21 consortium was involved in its production throughout various stages. This means that the Committee for Scientific Consistency and Quality (CSCQ)

reviewed and discussed several drafts of the deliverable. Afterwards the Consortium Executive Board (CEB) endorsed the final deliverable before publication.

Conflict of Interest

All authors, co-authors, CSCQ members, CEB members and external experts involved in the production of this JCA have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA 21 declaration of interest form. Conflict of interest was evaluated following the EUnetHTA 21 Procedure Guidance for handling declarations of interest form (https://eunethta.eu/doi).

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Please contact the EUnetHTA 21 Secretariat (EUnetHTA@zinl.nl) if you have enquiries about this JCA.

List of abbreviations

Abbreviation	Meaning
AE	Adverse event
AIHTA	Austrian Institute for Health Technology Assessment
atm	Standard atmosphere (measure of pressure)
BPH	Benign prostatic hyperplasia
CE	Conformité Européenne
CEB	Consortium Executive Board
CI	Confidence interval
ClinROM	Clinician-reported outcome measure
CSCQ	Committee for Scientific Consistency and Quality
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
Fr	French
HAS	Haute Autorité de Santé
HCP	Healthcare professional
HR	Hazard ratio
HTD	Health technology developer
IFU	Instructions for use
IIEF	International Index of Erectile Function
IPSS	International Prostate Symptom Score
JCA	Joint clinical assessment
LE	Level of evidence
LUT	Lower urinary tract
MD	Mean difference
NA	Not applicable
ND	No data
NEC	Not elsewhere classifiable
PerfO	Performance outcome
PICO	Population, Intervention, Comparator, Outcome
PROM	Patient-reported outcome measure
PVR	Postvoid residual volume
Qmax	Maximum flow rate
QoL	Quality of life
RCT	Randomised controlled trial
RD	Risk difference
RoB	Risk of bias
SAP	Statistical analysis plan
SD	Standard deviation
SSCP	Summary of Safety and Clinical Performance
UDI-DI	Unique Device Identification-Device Identifier
UEMO	European Union of General Practitioners
UTI	Urinary tract infection
VAS	Visual Analogue Scale

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1 GENERAL INFORMATION

The aim of this joint clinical assessment (JCA) is to assess the relative clinical effectiveness and safety of the Optilume urethral drug-coated balloon (DCB) medical device in the target patient population against relevant comparators. In accordance with the requirements of EUnetHTA 21 members, the target patient population and relevant comparators were defined before the start of the assessment in the assessment scope according to a Population, Intervention, Comparator, Outcome (PICO) framework. The assessment scope is presented in Section 3.

The assessment was based on the submission dossier submitted by the health technology developer (HTD) of this medical device, Laborie Medical Technologies.

1.1 Assessment team

The assessment team consists of assessors from Haute Autorité de Santé (HAS) and co-assessor from the Austrian Institute for Health Technology Assessment (AIHTA).

1.2 Overview of procedural steps

The procedural steps and corresponding dates for the JCA are listed in **Table 1**.

Table 1. Procedural steps for the joint clinical assessment of the Optilume urethral drug-coated balloon

	Start date	End date
Project duration	**4 October 2022**	**6 June 2023**
Receipt of the letter of intent from the HTD	4 October 2022	
Scoping phase	**4 October 2022**	**21 November 2022**
PICO survey	13 October 2022	26 October 2022
PICO consolidation	27 October 2022	21 November 2022
Sharing of the consolidated PICO with the HTD	**22 November 2022**	
Receipt of the submission dossier	9 January 2023	
Check for formal completeness of the submission dossier	10 January 2023	20 January 2023
Final dossier (completed with the missing elements, CSR received)	1 March 2023	
Assessment phase	**30 January 2023**	**29 May 2023**
First draft of the assessment	30 January 2023	15 March 2023
CSCQ review of the first draft	15 March 2023	24 March 2023
Second draft of the assessment	25 March 2023	25 April 2023
CSCQ validation review of the second draft	26 April 2023	5 May 2023
Medical editing and HTD fact checking	22 May 2023	26 May 2023
Final assessment	26 May 2023	30 May 2023
CEB review	19 May 23	30 May 2023
CEB endorsement	31 May 2023	
Publication of the assessment report	**1 June 2023**	**6 June 2023**

Source: EUnetHTA 21 Secretariat.
Abbreviations: CEB=Consortium Executive Board; CSCQ=Committee for Scientific Consistency and Quality; CSR=clinical study report; HTD=health technology developer; PICO=Population, Intervention, Comparator, Outcome.

1.3 Stakeholder and external expert involvement

Stakeholders were consulted early in the JCA scoping process to support the development of the PICO questions. Input from patients and clinical experts was subsequently used to support the development of the PICO questions.

Table 2. Contributors to the joint clinical assessment

Contributor	Patient or healthcare professional	Organisation or individual	Type and timing of involvement
Stakeholders	Patients and healthcare professionals	European Association of Urology, the Netherlands European Union of General Practitioners, Belgium Bundesverband Prostatakrebs Selbsthilfe e.V., Germany	Participated in the open call for input during the scoping process. Completed an online submission.
Expert	Clinical expert	Dr. Stefan Schleibner, independent medical advisor in the field of regulatory affairs, health technology assessment, reimbursement and pricing, Germany	Provided written input during the scoping process.

Source: EUnetHTA 21 Secretariat.

Stakeholder organisations were invited to provide input via an online questionnaire during the scoping process. Three stakeholder organisations made submissions. Stakeholder organisations represented healthcare professionals working in the therapeutic area of urology, general practitioners and patients with prostate cancer. It must be noted that the disease for the assessment scope was urethral stricture and not prostate cancer, and the latter is the focus of the patient organisation that participated in the open call. However, there is no specific patient organisation for urethral stricture. Two of the stakeholder organisations were Europe-wide and one was a national organisation.

The aim of the public call for involvement was to identify patients and clinical experts. No patient was identified for this JCA. One clinical expert was identified and was involved during the scoping process. The clinical expert had clinical experience with the disease and/or clinical experience with the technology under evaluation. The clinical expert had no conflict of interest.

Submissions from the stakeholder organisations, including details of their funding, are included in Appendix A.

2 BACKGROUND

2.1 Overview of the health condition

In males, a urethral stricture is a narrowing of the anterior urethra lumen due to chronic fibrosis of the urethral mucosa and surrounding spongiosum tissue.

2.1.1 Epidemiology of the health condition

Urethral stricture is a relatively common disease among men, with an average annualised incidence rate of 229 per 100,000 males over the period 1992–2000 in the USA.[1] The rate of urethral stricture disease increases sharply after the age of 55 years [1]. Corresponding European epidemiological data could not be found. The anterior urethra is most frequently affected (approx. 92%), in particular the bulbar urethra (approx. 47%) and the penile urethra (approx. 31%) [2].

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) [2, 3].

2.1.2 Characterisation of the health condition

Urethral strictures may be characterised by their location, tightness and length.

The anterior urethra is made up of three segments (from proximal to distal):

- The bulbar urethra (segment fixed to the pelvic floor);
- The penile urethra (segment passing through the pendulous portion and glans penis);
- The segment including the fossa navicularis and the meatus.

These different segments may be involved in strictures at varying frequency, as mentioned above.

The European Association of Urology (EAU) guidelines [4] on anterior strictures provide a classification of urethral strictures according to location (meatal, penile, bulbar or penobulbar) and tightness (**Table 3**).

[1] 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 [1].

Table 3. 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 significant 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 [4].
Abbreviations: Fr=French (unit of measure of the outer diameter of a catheter; 1 Fr = 0.33 mm).

The EAU guidelines do not provide a formal classification of urethral strictures based on length and report that the length of a "short" bulbar stricture is poorly defined. However, according to these guidelines, bulbar strictures are considered short when measuring less than 2 cm and long when measuring more than 2 cm. The guidelines also state 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 on the patient's anatomy and the stricture location within the bulbar urethra [4].

2.1.3 Management of the health condition

From a functional perspective, urethral stricture has the effect of obstructing the lower urinary tract (LUT). This condition adversely impacts physical health and quality of life (QoL). Left untreated, strictures can lead to serious complications such as recurrent urinary tract infections, urinary retention and eventual renal impairment [4].

The management of anterior urethral strictures in males may differ between countries. However, while not endorsed by EUnetHTA 21, the 2022 EAU guidelines[2] present different options for the management of this health condition, as detailed in **Table 4**.

Table 4. 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	**DVIU with "cold-knife"** commonly performed as a first-line treatment under general or spinal anaesthesia; the stricture is incised **DVIU 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
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 [4].
Abbreviations: DVIU=direct vision internal urethrotomy; Fr=French (unit of measure of the outer diameter of a catheter; 1 Fr = 0.33 mm.

[2] The 2023 EAU guidelines update [5] has introduced the drug-coated balloon dilation as one of the several strategies for post-dilation/ direct vision internal urethrotomy.

The EAU guidelines on urethral strictures recommend the following strategies for management of anterior urethral strictures [4] that are of interest in the context of this JCA.

Considering that "direct vision internal urethrotomy (DVIU) performs poorly in penile strictures" and that it "might provoke venous leakage from the corpora cavernosa with a subsequent risk of erectile dysfunction" (level of evidence (LE) 1b[3]), the EAU recommends against using DVIU for penile strictures (strong recommendation[4]).

As "increased stricture length is associated with higher risk of failure of DVIU" (LE 1b[3]), the EAU recommends against using "DVIU/dilation as solitary treatment for long (> 2 cm) segment strictures" (strong recommendation[4]).

Considering that "in selected patients with a primary, single, short (<2 cm) and nonobliterative bulbar stricture, a 5-year stricture-free rate of up to 77% can be expected" (LE 3[3]), the EAU recommends performing "DVIU/dilatation for a primary, single, short (<2 cm) and nonobliterative stricture at the bulbar urethra" (weak recommendation[4]).

As "repetitive dilatations/DVIU have no long-term freedom of recurrence and increase stricture complexity" (LE 1b), the EAU recommends against performing "repetitive (>2) DVIU/dilatations if urethroplasty is a viable option" (strong recommendation[4]).

In addition, the EAU considers that "at present, there is a lack of evidence to support the claim that dilatation is superior to DVIU (or vice versa) and therefore, the indications for single dilatation are the same as for DVIU. Repetitive dilatation/DVIU with curative intent should be avoided, as no long-term freedom of recurrence can be expected and because of the significant risk of increasing stricture length and complexity and prolonging the time to urethroplasty (which has better patency rates)" [4].

Stricture recurrence rates for endoscopic procedures vary considerably between 8% and 77% for DVIU and between 36% and 92% for dilatation. Moreover, endoscopic procedures lead to progressively worse outcomes over time, with a failure rate of almost 100% after three treatments [6, 7].

2.2 Characterisation of the health technology

The Optilume urethral drug-coated balloon (DCB) is a urethral balloon that is precoated with an antiproliferative medicinal product (paclitaxel).

2.2.1 Characteristics of the health technology

The characteristics of the medical device under assessment are presented in **Table 5**.

[3] 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.

[4] 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.

Table 5. Characteristics of the health technology under assessment

<table>
<tr><td>Device trade name</td><td>Optilume</td></tr>
<tr><td>Name of manufacturer</td><td>Laborie Medical Technologies</td></tr>
<tr><td>Device description according to the EMDN</td><td>U0399: Devices for urinary tract dilation – other</td></tr>
<tr><td>Risk class of the device</td><td>Class III</td></tr>
<tr><td>Function of the device</td><td>Therapeutic</td></tr>
<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>OPTBDL7000C</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>OPTBDL7001C</td><td>18</td><td>5</td><td>12</td><td>3.299</td></tr>
<tr><td>OPTBDL7002C</td><td>24</td><td>3</td><td>12</td><td>2.639</td></tr>
<tr><td>OPTBDL7003C</td><td>24</td><td>5</td><td>12</td><td>4.398</td></tr>
<tr><td>OPTBDL7004C</td><td>30</td><td>3</td><td>10</td><td>3.299</td></tr>
<tr><td>OPTBDL7005C</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 with 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 for the treatment of 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 of the device</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 result in inhibition of urothelium hyperplasia and therefore stricture recurrence.</td></tr>
</table>

Source: Submission dossier.
Abbreviations: atm=atmosphere; CE=Conformité Européenne; DCB=drug-coated balloon; EMDN=European Medical Device Nomenclature; Fr=French.

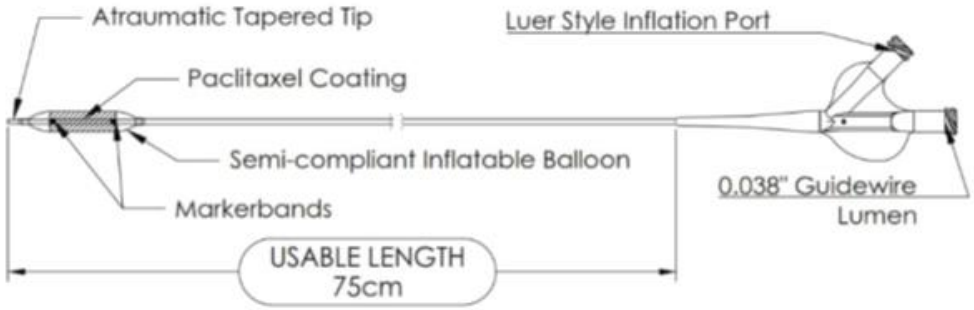

Figure 1. The Optilume urethral drug-coated balloon.
Source: Submission dossier.

2.2.2 Requirements/instructions for use

The characteristics of use of the Optilume urethral DCB are described in **Table 6**.

Table 6. Characteristics of the use of the Optilume urethral drug-coated balloon

Specific feature of the device	To administer a medicinal product (paclitaxel)
Description of (surgical) procedures, services and organisational aspects associated with use of the device	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.
Suggested profile and training for users as outlined in the SSCP or IFU	According to the 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.

Source: Submission dossier.
Abbreviations: DCB=drug-coated balloon; IFU=instructions for use; SSCP=summary of safety and clinical performance.

2.2.3 Regulatory status of the technology

Regulatory information on the medical device under assessment is provided in **Table 7**.

Table 7. Regulatory information on the health technology under assessment

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

Further regulatory information is included in the submission dossier.[5]

[5] https://www.eunethta.eu/d5-4/

3 RESEARCH QUESTION AND SCOPE

The JCA is performed against the parameters chosen after identification of the assessment scope via a survey of member states, a consolidation process and subsequent endorsement by the CSCQ. The consolidated assessment scope including the PICO questions is presented in **Table 8**.

Table 8: Assessment scope including the consolidated PICO questions

Description of PICO elements	PICO 1	PICO 2	PICO 3
Population	According to the intended use: Men aged ≥18 yr with bothersome urinary symptoms associated with recurrent anterior urethral strictures ≤3 cm in length.	The same as for PICO 1	The same as for PICO 1
Intervention	According to the intended use: * The Optilume urethral drug-coated balloon catheter is used as a dilation balloon for a single, tandem or diffuse anterior urethral stricture ≤3 cm in length or used as an adjunctive therapy with other dilation devices and/or procedures.	The same as for PICO 1	The same as for PICO 1
Comparator	Urethrotomy [a]	Dilation	Urethroplasty
Outcomes	The following outcomes are assessed across all PICO questions: – 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, including a description of each AE included in the following categories: • Any 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		
* The other dilation devices and/or procedures used with the Optilume DCB will have to be specified in the description of the procedure used in the clinical study/studies in the "Characteristics of the studies included" section of the health technology developer's submission dossier, if relevant.			
[a] Urethrotomy and direct vision internal urethrotomy (DVIU) are used indistinctly in the report.			

Source: EUnetHTA 21 Committee for Scientific Consistency and Quality.
Abbreviations: AE=adverse event; DCB=drug-coated balloon; PICO=Population, Intervention, Comparator, Outcome; PROM=patient-reported outcome measure.

4 RESULTS

This section 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 are identified, taking into account the strengths and limitations of the available evidence.

4.1 Information retrieval

An assessment of the appropriateness of the sources and the search strategies is provided in Appendix B. The studies included in the assessment were compiled using the following information.

Sources provided by the HTD in the dossier were as follows:

- List of HTD-sponsored studies on the Optilume DCB (as of 1 March 2023).
- Bibliographic search for the Optilume DCB (last search on 12 January 2023).
- Searches in study registers and study result databases for the Optilume DCB (last search on 12 January 2023).

The assessment team verified the completeness of the studies included by searching study registries and bibliographic databases on Optilume DCB (last search on 14 December 2022); Appendix B lists the search strategies used.

No additional relevant study was identified via the supplementary searches conducted by the assessment team.

4.1.1 Resulting list of studies included, overall and by PICO question

The HTD did not provide any study individually addressing the PICO 1, PICO 2 or PICO 3 question (**Table 9**).

Table 9. Studies included: list of relevant studies used for the assessment

Study reference/ID Study information	Study for marketing authorisation/CE marking of the technology under assessment	Sponsored or third-party study of the technology under assessment	Documentation available from the submission dossier
PICO 1			
No evidence provided by the health technology developer.			
PICO 2			
No evidence provided by the health technology developer.			
PICO 3			
No evidence provided by the health technology developer.			

Source: Submission dossier.
Abbreviations: CE=Conformité Européenne.

However, three studies from the clinical development programme for the intervention under assessment were provided by the HTD and are presented in Section 4.4. The first study is an

RCT (ROBUST III) comparing the Optilume DCB to urethrotomy or dilation (without any separate analysis for the comparators). The other two are single-arm studies considered for safety outcomes only. The ROBUST I study has 4-year follow-up data; the ROBUST II study has 3-year follow-up data.

Table 10 lists studies that were included by the HTD in the submission dossier but that were not considered relevant for the assessment.

Table 10. List of studies excluded: studies included by the health technology developer but not used in the joint clinical assessment report

Study reference/ID	Reason for exclusion
The OPEN RCT	Study did not include use of the Optilume DCB. RCT comparing DVIU and urethroplasty.
Steenkamp, 1997	Study did not include use of the Optilume DCB. RCT comparing DVIU and dilation.
Heyns, 1998	Study did not include use of the Optilume DCB. RCT comparing DVIU and dilation.
Jordan, 2013	Study did not include use of the Optilume DCB. RCT comparing a Memokath TW44 stent and DVIU.
Hoy, 2013	Study did not include use of the Optilume DCB. Single-arm study on urethroplasty.
Cecen, 2014	Study did not include use of the Optilume DCB. RCT comparing DVIU and laser urethrotomy.
Azab, 2020	Study did not include use of the Optilume DCB. RCT comparing DVIU and an Amplatz renal dilator.
Elkady, 2019	Study did not include use of the Optilume DCB. RCT comparing two types of urethroplasty.
Isen, 2015	Study did not include use of the Optilume DCB. Single-arm study on DVIU.
Guo, 2010	Study did not include use of the Optilume DCB. Single-arm study on laser urethrotomy.
Pansadoro, 1996	Study did not include use of the Optilume DCB. Single-arm study on DVIU.
Santucci, 2010	Study did not include use of the Optilume DCB. Single-arm study on DVIU.
Algadagossi, 2014	Study did not include use of the Optilume DCB. RCT comparing two types of urethroplasty.
Erickson, 2014	Study did not include use of the Optilume DCB. Single-arm study on urethroplasty.

Source: Submission dossier.
Abbreviations: DCB=drug-coated balloon; DVIU=direct vision internal urethrotomy; HTD=health technology developer; RCT=randomised controlled trial.

4.2 Characteristics of the studies included

No study individually addressed the PICO 1, PICO 2 or PICO 3 question.

4.3 Study results on relative effectiveness and relative safety

4.3.1 Results for the patient population: men aged ≥18 years with bothersome urinary symptoms associated with recurrent anterior urethral strictures ≤3 cm in length

4.3.1.1 Outcomes for PICO 1

The HTD did not provide any study addressing the PICO 1 question, and in particular for urethrotomy as the comparator. No study could be identified to address this PICO question in the search conducted by the assessment team.

4.3.1.2 Outcomes for PICO 2

The HTD did not provide any study addressing the PICO 2 question, and in particular for dilation as the comparator. No study could be identified to address this PICO question in the search conducted by the assessment team.

4.3.1.3 Outcomes for PICO 3

The HTD did not provide any study to address the PICO 3 question, and in particular for urethroplasty as the comparator. No study could be identified to address this PICO question in the search conducted by the assessment team.

4.4 Results from the main studies from the clinical development programme for the intervention under assessment

Table 11 lists relevant studies provided by the HTD from the clinical development programme for the intervention under assessment that were considered to be outside the assessment scope.

Table 11. List of relevant studies from the clinical development programme for the intervention under assessment

Study reference/ID Study information	Study for marketing authorisation/CE marking of the technology under assessment	Sponsored[a] or third-party study of the technology under assessment	Documentation available
Direct comparison: Optilume DCB versus dilation or DVIU			
ROBUST III [b] RCT	Yes [c]	Sponsored	• CSR for the 2-year results (RP1076-001 Rev C, 27 October 2022) • Protocol PR1076-001 version J (13 May 2020) [d] • Registry entry: NCT03499964 [8] • Publication: [9] [e,f]
Uncontrolled interventional studies			
ROBUST I [b] Single-arm study	No information	Sponsored	• CSR for the 4-year results (DSC016-004 Rev H, 19 October 2021) • Registry entry: NCT03014726 [10] • Publications: 3-year results [11], 2-year results [12] and 1-year results [13]
ROBUST II [b] Single-arm study	No information	Sponsored	• CSR for 3-year results (RP1032-004 Rev D, 15 June 2022) • Registry entry: NCT03270384 [14] • Publication: 1-year results [15]

[a] Study sponsored by the HTD.
[b] In the following tables, the study is referred to using this abbreviated form.
[c] This study was designed for US market approval.
[d] From ClinicalTrials.gov.
[e] 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 were found in the literature search [16, 17].
[f] Additional information was submitted by the HTD as part of a German health technology assessment process (national report from 3 May 2023 [18]).

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

Study design and study populations

Table 12 lists characteristics of studies from the clinical development programme for the intervention under assessment.

Table 12. Characteristics of studies from the clinical development programme for the intervention under assessment

Study reference/ID	Study type	Study population	Study arms (number of patients randomised/included)	Study duration, data cutoffs and locations	Study endpoints
ROBUST I	Prospective, interventional uncontrolled study (single-arm study)	Males aged ≥18 years Visual confirmation of stricture via cystoscopy or urethrogram Single-lesion anterior urethral stricture or bladder neck contracture <2 cm At least 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	N = 53	• Study duration: 5 years • Start date: November 2016 • Primary completion date: October 2018 • Estimated study completion date: April 2023 • Location: Latin America, 4 study sites	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
ROBUST II	Prospective, interventional uncontrolled study (single-arm study)	Males aged ≥18 years Visual confirmation of stricture via cystoscopy or urethrogram Single-lesion anterior urethral stricture <3 cm >2 prior diagnoses and treatments of urethral stricture (including self-catheterisation, dilation and/or DVIU but no prior urethroplasty) Significant LUT symptoms IPSS >13 Urethral lumen diameter <12 Fr on urethrogram Able to complete validated questionnaire independently Qmax <15 ml/s, guidewire must be able to cross the lesion	N = 16	• Study duration: 5 years • Start date: October 25, 2017 • Primary completion date: November 1, 2019 • Estimated study completion date: June 2024 • Location: USA, 5 study sites	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

ROBUST III	Prospective, interventional RCT [b], patient-blinded, parallel, with superiority objective + adaptive sample size with a nonrandomised pharmacokinetics study arm.	Adult males with anterior strictures ≤12 Fr and ≤3 cm, ≥2 prior endoscopic treatments, IPSS ≥11 and Qmax <15 ml/s [c]	Optilume DCB (N = 79) Standard-of-care endoscopic management as determined by the treating physician, including rigid rod dilation, DVIU, balloon dilation or a combination [d] (N = 48): – Dilation (N = 36) – DVIU (N=12) Pharmacokinetics study arm (N = 15) [e]	• Study duration: 5 years • Start date: October 2018 • Estimated completion date: December 2025 • Data cutoff: December 2020 (planned interim analysis) • 22 centres in North America	Primary: stricture-free rate at 6 months [f] Other [a]: all-cause mortality; composite of specific device- or procedure-related serious complications at 3 months [g]; freedom from repeat intervention at 1 year; Qmax, IPSS, PVR, IPSS-QoL and IIEF over time; periprocedural pain and adverse events

[a] Only if included in the PICO.
[b] Randomisation was planned as 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.
[c] Participants with previous urethroplasty, hypospadias repair, lichen sclerosis or unresolved confounding aetiologies were excluded.
[d] The control arm as defined in the 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.
[e] The pharmacokinetics arm is not relevant for the joint clinical assessment and is not presented in any further tables.
[f] Proportion of participants in whom a 16 Fr flexible cystoscope or a 14 Fr catheter could be atraumatically passed through the treated area.
[g] Composite of specific device- or procedure-related serious complications including urethral fistula, unresolved de novo stress urinary incontinence and urethral rupture.

Source: Refer to Table 11.
Abbreviations: DCB=drug-coated balloon; DVIU=direct vision internal urethrotomy; Fr=French; IIEF=International Index of Erectile Function; IPSS=International Prostate Symptom Score; LUT=lower urinary tract; N: number of included patients; PROM=patient-reported outcome measure; PVR=postvoid residual volume; Qmax=maximum urinary flow rate; QoL=quality of life; RCT=randomised controlled trial.

Table 13 describes the interventions in studies from the clinical development programme for the intervention under assessment.

Table 13. Characteristics of interventions in studies from the clinical development programme for the intervention under assessment.

Study reference/ID	Study intervention	Study comparator
ROBUST I	Predilation with an uncoated balloon and/or DVIU + Optilume DCB	Not applicable
ROBUST II	Predilation with an uncoated balloon, rigid rods or DVIU + Optilume DCB or Optilume DCB without predilation	Not applicable
ROBUST III	Predilation with an uncoated balloon and/or DVIU to ≥20 Fr + Optilume DCB (24 Fr, 30 Fr or 36 Fr)	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

Source: Clinical study reports.
Abbreviations: DCB=drug-coated balloon; DVIU=direct vision internal urethrotomy.

Table 14 provides information on observation time points in the studies from the clinical development programme for the intervention under assessment.

Table 14. Observation time points in studies from the clinical development programme for the intervention under assessment (including planned follow-up duration)

Study reference/ID Outcome category	Planned follow-up
ROBUST I **(3-year results)**	
Composite of specific device- or procedure-related serious complications Safety events	3 months 5 years
ROBUST II **(1-year results)**	
Safety: rate of device-related serious complications Safety: change in IIEF Safety events	3 months 3 months 5 years
ROBUST III **(1-year results)**	
Stricture-free rate Composite of specific device- or procedure-related serious complications Freedom from repeat intervention Qmax and PVR IPSS and IPSS-QoL IIEF	6 months 3 months 12 months 1, 3, 6, 12 months 1, 3, 6, 12 months 1, 3, 6, 12 months

Source: Clinical study reports.
Abbreviations: IIEF=International Index of Erectile Function; IPSS=International Prostate Symptom Score; PVR=postvoid residual volume; Qmax=maximum urinary flow rate; QoL=quality of life.

No mean or median observation period was reported for any outcome in any of the studies.

Table 15 describes studies from the clinical development programme for the intervention under assessment.

Table 15. Population characteristics of studies from the clinical development programme for the intervention under assessment

Study reference/ID Relevant study arms (number of patients randomised/included)	Population analysed
Direct comparison: Optilume DCB versus dilation or DVIU	
ROBUST III Optilume DCB (N = 79) Dilation or DVIU (N = 48)	Men aged ≥18 years with bothersome urinary symptoms associated with recurrent anterior urethral strictures ≤3 cm in length
Uncontrolled interventional studies	
ROBUST I Optilume DCB (N = 53)	Men aged ≥18 years with bothersome urinary symptoms associated with recurrent anterior urethral strictures ≤3 cm in length
ROBUST II Optilume DCB (N = 16)	Men aged ≥18 years with bothersome urinary symptoms associated with recurrent anterior urethral strictures ≤3 cm in length

Source: Clinical study reports.
Abbreviations: DCB=drug-coated balloon; DVIU=direct vision internal urethrotomy; N: number of randomised patients.

The patient population for the ROBUST III study corresponds to the unique patient population defined in the assessment scope (PICO 1, PICO 2, and PICO 3). **Table 16** lists the characteristics of patients in the ROBUST III study.

Table 16. Baseline patient characteristics in the ROBUST III study

Study reference/ID Characteristics and category	Study intervention	Study comparator
ROBUST III (1-year results)	**Optilume DCB (N = 79)**	**Dilation or DVIU (N = 48)**
Age (years)		
Mean ± SD	59 ± 16	61 ± 16
Median (range)	61 (25–87)	63 (23–86)
Ethnicity, n/N (%)		
Black or African American	9/78 (12)	6/48 (13)
White	65/78 (83)	39/48 (81)
Other [a]	4/78 (5)	3/48 (6)
Hispanic or Latino	3/78 (4)	3/48 (6)
Not Hispanic or Latino	75/78 (96)	45/48 (94)
Body mass index(kg/m^2)		
Mean ± SD	31 ± 7 [b]	29 ± 7
Median (range)	30 (20–58)	27 (15–48)
Baseline stricture characteristics		
Stricture aetiology, n/N (%)		
Iatrogenic	21/78 (27)	16/47 (34)
Idiopathic	42/78 (54)	22/47 (47)
Inflammatory	1/78 (1)	2/47 (4)
Traumatic	14/78 (18)	7/47 (15)
Prior pelvic radiation	9/79 (11)	6/48 (13)
Anatomic location, n/N (%)		
Bulbar	71/79 (90)	45/47 (96)
Penile	8/79 (10)	2/47 (4)
Stricture measurements, mean ± SD		
Length (cm)	1.63 ± 0.76	1.72 ± 0.73
Diameter (mm)	2.46 ± 0.96	2.33 ± 0.88
Prior dilations		
Mean ± SD	3.2 ± 1.7	4.3 ± 7.5 [c]
Median	3	3
Number ≥5 overall (%)	13/79 (17)	10/48 (21)
Study discontinuation, n/N (%)	11/79 (14) [d]	27/48 (56) [e]

[a] Pacific Islander, Asian or Native American.
[b] Body mass index was only reported for 77 patients in this group.
[c] One individual in the dilation or DVIU group had 53 prior dilations; the mean number is 3.3 when excluding this patient.
[d] Reasons for study discontinuation: 1 death, 6 treatment failures, 2 withdrawal of consent, 1 adverse event and 1 lost to follow-up.
[e] Reasons for study discontinuation: 24 crossed over to the other arm, 2 treatment failures and 1 withdrawal of consent.

Source: Clinical study report.
Abbreviations: DCB=drug-coated balloon; DVIU=direct vision internal urethrotomy; N=number of randomised patients; n=number of patients; SD=standard deviation.

There were no major differences in patient characteristics between the treatment groups in the ROBUST III study.

Table 17 lists the characteristics of patients in the noncomparative studies presented for the safety outcomes (ROBUST I and ROBUST II).

Table 17. Patient baseline characteristics in the ROBUST I and ROBUST II studies

Study reference/ID Characteristic and category	ROBUST I (4-year results)	ROBUST II (3-year results)
Age (years), mean ± SD	51 ± 15	64 ± 16
Ethnicity, n/N (%)		
Black or African American	8 /53 (15)	ND
Hispanic or Latino	44/53 (83)	ND
Other	1/ 53 (2)	ND
Baseline stricture characteristics		
Stricture aetiology, n/N (%)		
Iatrogenic	24/53 (45)	2/16 (13)
Idiopathic	2/53 (4)	11/16 (69)
Traumatic	27/53 (51)	3/16 (19)
Anatomic location, n/N (%)		
Bulbar	ND	ND
Penile	ND	ND
Stricture measurements, mean ± SD		
Length (cm)	0.9 ± 0.5	2.1 ± 0.7
Diameter (mm)	2.47 ± 1.97	2.3 ± 0.9
Pretreatments [a], n (%)		
Uncoated balloon	31 (59)	ND
DVIU	8 (15)	ND
DVIU + uncoated balloon	14 (26)	ND
Direct DCB dilation	ND	10 (63)
Predilation with uncoated balloon or DVIU	ND	6 (37)
Direct DCB dilation with postdilation	ND	0 (0)
Number of previous endoscopic treatments, mean ± SD	ND	4.1 ± 4.9
Number of previous endoscopic treatments, n (%)		
1	30 (57)	ND
2	13 (25)	ND
3	8 (15)	ND
4	2 (4)	ND
Study discontinuation, n (%)	ND	ND

[a] 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.

Source: Clinical study reports.
Abbreviations: DCB=drug-coated balloon; DVIU=direct vision internal urethrotomy; N=number of patients included; n=number of patients; ND=no data; SD=standard deviation.

4.4.1 Relative effectiveness and safety results from the direct comparison: Optilume DCB versus dilation or DVIU

4.4.1.1 Available outcomes in the ROBUST III study

Table 18 provides an overview of the endpoints available in the ROBUST III study of the direct comparison: Optilume DCB vs. dilation or DVIU.

Table 18. Matrix of outcomes in the ROBUST III study for direct comparison of the Optilume DCB versus dilation or DVIU

Outcomes defined in the PICO questions	Study reference/ID ROBUST III
All-cause mortality	Yes [a]
Urinary function (LUT symptoms related to stricture) (IPSS)	Yes
Urinary function (LUT symptoms related to stricture) (PVR)	Yes
Urinary function (LUT symptoms related to stricture) (Qmax)	Yes
Erectile function (IIEF)	Yes
Pain	Yes [b]
Treatment success (stricture-free rate at 6 months) [c]	Yes
Treatment success (freedom from repeat intervention at 1 year)	Yes
Anatomical success (stricture-free rate at 6 months) [c]	Yes
Health-related QoL (generic and disease- or population specific measures), any other patient centred outcome and health status measured via patient-reported outcome measures (IPSS-QoL)	Yes
Any AEs and device-related AEs including but not limited to: perioperative and postoperative complications, urinary tract infection, urinary retention, incontinence and erectile dysfunction	Yes
Drug-related AEs [d]	No
Serious AEs	Yes

[a] From the clinical study report only.
[b] Periprocedural pain (reported in the clinical study report only).
[c] Proportion of participants in whom a 16 Fr flexible cystoscope or a 14 Fr catheter could be atraumatically passed through the treated area.
[d] Refers to AEs related to the drug only (and not to the device).

Source: Refer to Table 11.
Abbreviations: AE=adverse event; DCB=drug-coated balloon; DVIU=direct vision internal urethrotomy; IIEF=International Index of Erectile Function; IPSS=International Prostate Symptom Score; LUT=lower urinary tract; PICO=Population, Intervention, Comparator, Outcome; PVR=postvoid residual volume; Qmax: maximum flow rate; QoL=quality of life.

The outcomes reported are presented in brief in **Table 19**.

Table 19. Outcomes reported and their measurement instruments

Outcome (concept)	Outcome measurement instrument/ Type of outcome measurement 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:

Outcome (concept)	Outcome measurement instrument/ Type of outcome measurement instrument	Outcome measurement instrument definition/ Interpretation
		• 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: Clinical study report.
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.

4.4.1.2 Risk of bias

Table 20 summarises the risk-of-bias (RoB) assessment for the ROBUST III study conducted by the assessment team at the outcome level using the Cochrane RoB 2.0 method. These assessments were based on the ROBUST III publication [9], on publicly available evidence from ClinicalTrials.gov, in particular study protocol #PR1076-001 version J of 13 May 2020, and on the clinical study report (CSR) RP1076-001 Rev C of 27 October 2022.

Seven different outcomes or groups of outcomes were assessed. Six outcomes were assessed as single outcomes:

- The stricture-free rate at 6 months;
- The rate of freedom from repeat intervention at 12 months;
- The change in Qmax at 6 months;
- Qmax measured over time (at 30 days and 3, 6 and 12 months);
- PVR measured over time (at 30 days and 3, 6 and 12 months); and
- 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.

The other outcomes assumed to have similar RoB were grouped according to the way they were collected and analysed:

- IPSS, IPSS-QoL, IIEF (at 30 days and 3 and 6 months) and periprocedural pain were grouped, as they are all self-reported PROMs assessed using administered questionnaires with prespecified response formats.

Detailed reports on the seven assessments are provided in Appendix D.

Table 20. Risk of bias (randomised controlled trial at study outcome level; Cochrane RoB 2.0)

Domain	Bias arising from randomisation 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	Comments
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	Patients were blinded to the treatment until 6 months. After this 6-month time point we assume that the risk of bias for these outcomes will be higher.
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 imputation 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.

Domain	Bias arising from randomisation 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	Comments
[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.							

Source: Appendix D.
Abbreviations: CI=confidence interval; CSR=clinical study report; IIEF=International Index of Erectile Function; IPSS=International Prostate Symptom Score; PVR=postvoid residual volume; Qmax=maximum flow rate; QoL=quality of life.

The overall risk of bias is considered high for all outcomes in the ROBUST III study.

4.4.1.3 Health outcome results

Table 21 presents relative effectiveness results for the stricture-free rate from the ROBUST III study and **Table 22** lists the sensitivity analysis results for this outcome. **Table 23, Table 24** and **Table 25** present relative effectiveness results for the other outcomes in ROBUST III.

Table 21. Relative effectiveness results (dichotomous outcome) from direct comparison: Optilume DCB versus dilation or DVIU

Time point Outcome Study reference/ID	Optilume DCB		Dilation or DVIU		Optilume DCB vs. dilation or DVIU	
	N	Patients with event, n (%)	N	Patients with events, n (%)	RD [95% CI] p value	Hypothesis testing
6 months						
Stricture-free rate [a]						
ROBUST III	67 [b]	50 (74.6)	41 [b,c]	11 (26.8)	44.4 [d] [27.6; 61.1] p < 0.0001	S-P-C
Reading the "Hypothesis testing" columns: 1. statistical significance: S=statistically significant against the alpha level specified in the study SAP, NS = non-significant, NO = nominal p-value. 2. Prespecification: P=statistical test was prespecified according to the study SAP, NP = Not prespecified. 3. Multiple hypothesis testing: C=appropriate control for multiplicity according to the study SAP and clinical study report, NC = not controlled.						
[a] Proportion of participants in whom a 16 Fr flexible cystoscope or a 14 Fr catheter could be atraumatically passed through the treated area. [b] Data were missing for 12/79 (15%) patients in the Optilume DCB group and 7/48 (15%) patients in the dilation or DVIU group for this outcome (missing cystoscopy). [c] Some 12/48 (25%) patients from the control group crossed over to the Optilume DCB group. These patients were considered a failure for this endpoint. [d] Estimated difference using multiple imputation of missing data.						

Source: Clinical study report.
Abbreviations: CI=confidence interval; DCB=drug-coated balloon; DVIU=direct vision internal urethrotomy; Fr=French; N=number of patients considered in the analysis for calculation of the effect estimation; n: number of patients with event; RD=risk difference; SAP=statistical analysis plan.

As prespecified in the ROBUST III study protocol, a sensitivity analysis was conducted using the methods detailed in **Table 22** to assess the impact of the handling of missing data in the primary analysis for the stricture-free rate.

Table 22. 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.
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.

Results from the sensitivity analysis have the same directionality as for results from the primary analysis.

Table 23. Relative effectiveness results (time-to-event outcomes) from direct comparison: Optilume DCB versus dilation or DVIU

Time point	Optilume DCB		Dilation or DVIU		Optilume DCB versus dilation or DVIU		
Outcome Study reference/ID	**N**	**Median time to event [95% CI] Patients with event (%)**	**N**	**Median time to event [95% CI] Patients with event (%)**	**HR [95% CI] p value**	**Log-rank test p value**	**Hypothesis testing [a]**
1 year							
Freedom from repeat intervention rate							
ROBUST III	79	83.2 [a,b]	48	21.7 [a,b]	ND	p <0.0001 [c]	NO-NP-NC [d]

Reading the "Hypothesis testing" columns:
1. Statistical significance: S = statistically significant against the alpha level specified in the study SAP, NS = non-significant, NO=nominal p value.
2. Prespecification: P=statistical test was prespecified according to the study SAP, NP = Not prespecified.
3. Multiple hypothesis testing: C = appropriate control for multiplicity according to the study SAP and clinical study report, NC = not controlled.

[a] Only reported in the publication by Elliott et al. [9].
[b] Median time to event not provided.
[c] A Kaplan-Meier curve is provided in the paper by Elliott et al. [9]. The two curves for observed survival did not cross each other during follow-up.
[d] According to the protocol, the statistical test was prespecified and controlled for multiplicity at 6-month follow-up, but no formal hypothesis statistical test was planned at 12-month follow-up (ancillary endpoint). Results at 6 months are not reported in the paper. The clinical study report only shows the Kaplan-Meier curve, with no values at 6 months provided.

Source: Clinical study report.
Abbreviations: CI=confidence interval; DCB=drug-coated balloon; DVIU=direct vision internal urethrotomy; HR=hazard ratio; N: number of patients considered in the analysis for calculation of the effect estimate; ND=no data; SAP=statistical analysis plan.

Table 24. Relative effectiveness results (quantitative outcomes) from direct comparison: Optilume DCB versus dilation or DVIU

Time point Outcome Study reference/ID	Optilume DCB			Dilation or DVIU			Optilume DCB vs. dilation or DVIU	
	N	Value at baseline Mean ± SD Median (range)	Value at 6 months Mean ± SD Median (range)	N	Value at baseline Mean ± SD Median (range)	Value at 6 months Mean ± SD Median (range)	MD [a] [90% CI] [b] p value	Hypothesis testing
6 months								
Change in Qmax (ml/s)								
ROBUST III	67	7.6 ± 3.4 7.2 (0.0–14.9)	16.6 ± 8.9 15.0 (1.6–48.5)	44	7.4 ± 3.5 7.9 (0.0–14.5)	11.1 ± 7.6 9.8 (0.0–31.2)	+4.78 [c,d] [1.94; 7.61] p=0.0031	S-P-C

Reading the "Hypothesis testing" columns:
1. Statistical significance: S = statistically significant against the alpha level specified in the study SAP, NS = non-significant, NO=nominal p value.
2. Prespecification: P=statistical test was prespecified according to the study SAP, NP = Not prespecified.
3. Multiple hypothesis testing: C = appropriate control for multiplicity according to the study SAP and clinical study report , NC = not controlled.

[a] From the clinical study report only.
[b] The 95% CI was not provided in the clinical study report.
[c] Estimated MD using multiple imputation of missing data.
[d] The estimated MD without multiple imputation of missing data was not provided for this outcome.

Source: Clinical study report.
Abbreviations: CI=confidence interval; DCB=drug-coated balloon; DVIU=direct vision internal urethrotomy; MD=mean difference; SAP=statistical analysis plan; SD=standard deviation.

Table 25. Relative effectiveness outcomes (continuous) from direct comparison: Optilume DCB versus dilation or DVIU

Outcome Study reference	Optilume DCB			Dilation or DVIU			Optilume DCB vs dilation or DVIU
Values	**Baseline**	**6 months**	**1 year**	**Baseline**	**6 months**	**1 year**	**Effect [95% CI] p value**
Qmax (ml/s) [a]							
ROBUST III							
Mean ± SD	7.6 ± 3.4	16.6 ± 8.9	15.5 ± 9.0	7.4 ± 3.5	11.1 ± 7.6	8.0 ± 4.6	ND
Median (range)	7.2 (0.0–14.9)	15.0 (1.6–48.5)	13.5 (1.6–48.8)	7.9 (0.0–14.5)	9.8 (0.0–31.2)	7.6 (0.0–23.0)	
Number of patients	78	67	65	47	44	42	
IPSS [a]							
ROBUST III							
Mean ± SD	22.0 ± 6.8	8.3 ± 6.2	9.0 ± 7.1	22.9 ± 6.9	15.4 ± 9.6	19.8 ± 7.4	ND
Median (range)	22.0 (11–35)	8.0 (0–26)	8.0 (0–26)	22.0 (12–35)	14.0 (1–35)	18.0 (7–35)	
Number of patients	79	71	67	47	43	43	
PVR urine (ml) [a]							
ROBUST III							
Mean ± SD	109.8 ± 116.9	73.1 ± 117.7	94.6 ± 121.8	133.7 ± 153.8	141.4 ± 194.1	179.2 ± 199.9	ND
Median (range)	60.0 (0.0–557.0)	30.0 (0.0–634.0)	50.5 (0.0–546.0)	80.0 (0.0–703.0)	90.5 (0.0–999.0)	118.0 (0.0–999.0)	
Number of patients	77	67	66	47	44	43	
IPSS-QoL [a]							
ROBUST III							
Mean ± SD	4.5 ± 1.3	1.7 ± 1.3	1.9 ± 1.5	4.7 ± 1.2	3.4 ± 1.8	4.0 ± 1.3	ND
Median (range)	5.0 (1–6)	2.0 (0–5)	2.0 (0–5)	5.0 (2–6)	3.0 (0–6)	4.0 (1–6)	
Number of patients	79	71	67	47	43	43	
IIEF overall satisfaction							
ROBUST III							
Mean ± SD	5.8 ± 2.9	6.5 ± 2.8	6.9 ± 3.1	6.0 ± 3.2	6.6 ± 3.2	5.9 ± 2.6	ND
Median (range)	6.0 (2–10)	6.5 (2–10)	8.0 (2–10)	6.0 (2–10)	7.5 (2–10)	6.0 (2–10)	
Number of patients	72	68	59	46	30	14	
VAS pain score							
ROBUST III							
Mean ± SD	1.6 ± 2.2	2.5 ± 2.2 [b]	0.6 ± 1. 0 [c]	1.8 ± 2.3	2.1 ± 2.2 [b]	0.2 ± 0.5 [c]	ND

Median (range)	1.0 (0–8)	2.0 (0–9)	0.0 (0–6)	1.0 (0–8)	2.0 (0–8)	0.0 (0–2)
Number of patients	78	77	78	48	47	47

[a] Failure-carried-forward analysis.
[b] The time point is before discharge.
[c] The time point is 30 days after the procedure.

Source: Clinical study report.
Abbreviations: DCB=drug-coated balloon; DVIU=direct vision internal urethrotomy; IIEF=International Index of Erectile Function; IPSS=International Prostate Symptom Score; ND=no data; PVR=postvoid residual volume; Qmax=maximum flow rate; QoL=quality of life; SD=standard deviation; VAS=Visual Analogue Scale.

Only descriptive statistics were used to report these outcome data.

Table 26 presents relative safety outcomes from the ROBUST III study.

Table 26. Relative safety outcomes: direct comparison of the Optilume DCB versus dilation or DVIU

Time point Study reference/ID **Outcome**	Optilume DCB		Dilation or DVIU	
	N	Number of patients with event / randomised patients (%)	N	Number of patients with event / randomised patients (%)
3 months ROBUST III **Composite of specific device- or procedure-related serious complications** [a]	0	0/79 (0)	0	0/48 (0)
2 years ROBUST III				
All-cause mortality [b]	2	2/79 (3)	0	0/48 (0)
Any AE	182	58/79 (73)	89	39/48 (81)
Serious AEs	12	11/79 (14)	8	8/48 (17)
Device-related AEs	35	28/79 (35)	5	4/48 (8)
Device-related serious AEs	1 [c]	1/79 (1)	0	0/48 (0)
Procedure-related AEs	12	10/79 (13)	10	6/48 (13)
Procedure-related serious AEs	1 [d]	1/79 (1)	2 [e,f]	2/48 (4)
Severe AEs				
CTCAE grade ≥3	ND [h]	26 / 79 (33)	ND [h]	13 / 48 (27)
CTCAE grade 4 [g]	ND [h]	3 / 79 (4)	ND [h]	2 / 48 (4)
CTCAE grade 5 [g]	ND [h]	2 / 79 (3)	ND [h]	0 / 48 (0)
Treatment discontinuation due to AEs	1	1/79 (1)	0	0/48 (0)
Treatment interruption due to AEs	ND	ND	ND	ND
Suspected unexpected serious adverse reaction	0	0/79 (0)	0	0/48 (0)
Perioperative and postoperative complications [i]	6	12/79 (15)	13	3/48 (6)
Urinary tract infection	21	9/79 (11)	8	5/48 (10)
Urinary retention	9	7/79 (9)	4	4/48 (8)
Urinary incontinence	2	2/79 (3)	0	0/48 (0)
Erectile dysfunction	0	0/79 (0)	1	1/48 (2)

[a] Composite of specific device- or procedure-related serious complications including urethral fistula, unresolved de novo stress urinary incontinence and urethral rupture. Defined as the primary safety endpoint.
[b] Difference 2.5%, 95% CI [−2.6%; 7.7%]. The p value was not reported in the clinical study report.
[c] Urinary tract infection.
[d] Aspiration pneumonia.
[e] Sepsis.
[f] Aspiration/choking during crossover procedure.
[g] Calculated by the assessment team using data from the clinical study report.
[h] The number of events is not reported, only the number of patients experiencing the adverse event.
[i] Described in the clinical study report as "injury, poisoning and procedural complications".

Source: Clinical study report.
Abbreviations: AE=adverse event; CI=confidence interval; CTCAE=Common Terminology Criteria for Adverse Events; DCB=drug-coated balloon; DVIU=direct vision internal urethrotomy; N=number of events.

Details for all adverse events are provided in Appendix C.

4.4.2 Safety results from noncomparative studies

4.4.2.1 Safety outcomes available from the ROBUST I and ROBUST II studies

Table 27 provides an overview of the endpoints available in the studies presented for safety outcomes from noncomparative evidence.

Table 27. Matrix of outcomes in the ROBUST I and ROBUST II single-arm studies

Outcomes	**Study reference/ID** ROBUST I (4-year results)	**Study reference/ID** ROBUST II (3-year results)
Any adverse events and device-related adverse events including but not limited to: perioperative and postoperative complications, urinary tract infection, urinary retention, incontinence and erectile dysfunction	Yes [a]	Yes [a,b]
Drug-related adverse events	No [c]	No [c]
Serious adverse events	Yes	Yes

[a] Data for perioperative and postoperative complications were not recorded.
[b] Erectile dysfunction was not reported in the safety results but was reported in the efficacy results as part of the erectile symptom score.
[c] Data not recorded.

Source: Clinical study reports.

4.4.2.2 Risk of bias

No formal RoB assessment was conducted because the overall conclusion on the internal validity of single-arm studies is considered to be very limited, which is very unlikely to be changed by a formal RoB assessment.

4.4.2.3 Health outcome results

Table 28 presents the safety outcomes from the ROBUST I and ROBUST II studies.

Table 28. Safety outcomes for the Optilume urethral drug-coated balloon from noncomparative evidence (single-arm studies)

Outcome Study reference/ID	**N**	**Patients with event, n (%)**	**N**	**Patients with event, n (%)**	N	**Patients with event, n (%)**
Time frame		**3 months**		**3 years**		**4 years**
All-cause mortality						
ROBUST I		0		0		0
ROBUST II		0		1		NA
At least one AE						
ROBUST I	ND	ND	73	35/53 (66)	80	36/53 (68)
ROBUST II	21	10/16 (63)	46	13/16 (81)	NA	NA
Serious AEs						
ROBUST I	ND	ND	6	5/53 (9)	6	5/53 (9)
ROBUST II	0	0/16 (0)	11	6/16 (38)	NA	NA

Severe AEs						
ROBUST I						
CTCAE grade ≥3	ND	ND	3	ND	8	ND
CTCAE grade 3	ND	ND	2	ND	ND	ND
CTCAE grade 4	ND	ND	1	ND	ND	ND
CTCAE grade 5	ND	ND	0	ND	0	0
ROBUST II						
Clavien-Dindo grade 3a	1	1/16 (6)	ND	ND	NA	NA
Clavien-Dindo grade 3b	2	1/16 (6)	ND	ND	NA	NA
Treatment discontinuation due to AEs						
ROBUST I	ND	ND	ND	ND	ND	ND
ROBUST II	ND	ND	ND	ND	NA	NA
Treatment interruption due to AEs						
ROBUST I	ND	ND	ND	ND	ND	ND
ROBUST II	ND	ND	ND	ND	NA	NA
Suspected unexpected serious adverse reaction						
ROBUST I	0	0/53 (0)	0	0/53 (0)	0	0/53 (0)
ROBUST II	0	0/16 (0)	0	0/16 (0)	NA	NA
Perioperative and postoperative complications						
ROBUST I	ND	ND	ND	ND	ND	ND
ROBUST II	ND	ND	ND	ND	NA	NA
Urinary tract infection						
ROBUST I	ND	ND	ND	ND	12	11/53 (21)
ROBUST II	4	2/16 (13)	ND	ND	NA	NA
Urinary retention						
ROBUST I	ND	ND	ND	ND	6	5/53 (9)
ROBUST II	1	1/16 (6)	ND	ND	NA	NA
Incontinence						
ROBUST I	0 [a]	0/53 (0)	ND	ND	ND	ND
ROBUST II	0 [a]	0/16 (0)	ND	ND	NA	NA
Erectile dysfunction						
ROBUST I	ND	ND	ND	ND	1	1/53 (2)
ROBUST II	ND [b]	ND	ND	ND	NA	NA

[a] Incontinence was part of the composite primary safety endpoint and did not occur in any case during 3-month follow-up.
[b] Reported in the study as no negative impact on sexual function up to 1 year.

Source: Clinical study reports.
Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; N=number of events; NA=not applicable; ND=no data.

4.4.3 Summary table including the uncertainty of evidence

A summary table including the uncertainty of evidence is presented in **Table 29**.

Table 29. Uncertainty of evidence from the main studies from clinical development programme

Outcome	Design	Factors that may affect the certainty of evidence	Effect estimate p value
All outcomes	1 RCT	**Internal validity of individual studies** • ROBUST III is a prospective, interventional RCT that included 127 patients (79 in the intervention group vs 48 in the control group) with short follow-up duration (6 months) for outcomes with prespecified hypothesis testing. • The randomisation was planned at a 2:1 allocation to treatment vs control, stratified by investigational centre and by prior radiation treatment and number of prior dilation treatments using randomly permuted blocks (block size not reported). There is no specific information on the concealment of the allocation sequence. • Only the patients were blinded to the treatment. • The study was designed with a primary objective of demonstrating superiority. • There were no major differences in baseline characteristics between the treatment groups in the study. • The risk of bias was considered high for all outcomes. • Only descriptive statistics were used to report most of the outcomes apart from the stricture free rate, the freedom from repeat intervention rate at 12 months and the change in Qmax at 6 months. • Patients could cross over to the Optilume group after 6 months according to the study protocol and, if medically necessary (recurrent stricture requiring intervention) before 6 months. Some 25% (12/48) of patients from the control group crossed over to the Optilume group before 6 months. • There is no agreed single outcome measure that defines urethral stricture recurrence. **Applicability** • 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 study was conducted in North America, not in Europe. • Optilume treatment included predilation, 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 second-line treatment after stricture recurrence, but the majority of patients included in ROBUST III had more than 3 endoscopic treatments before the Optilume procedure. • The comparator for ROBUST III does not match any of the comparators defined in PICO 1, PICO 2 or PICO 3. • The comparator in the 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) which was a mix of the PICO 1 (urethrotomy) and PICO 2 (dilatation) comparators.	NA

		• No data were reported for the drug-related adverse events requested in the PICO question. All other outcomes were reported in this study. **Heterogeneity and inconsistency** No heterogeneity or inconsistency issue was raised as only 1 RCT was available and included for assessing the relative effectiveness and relative safety of Optilume.	
Stricture-free rate at 6 months		• Data for this outcome were missing for 12/79 (15%) patients in the Optilume group and 7/48 (15%) patients in the control group. • A sensitivity analysis comprising 5 different subanalyses yielded results with the same directionality as for the primary analysis. • Patients in the control group who crossed over to the Optilume group were considered a failure for this outcome. • The surgeons and investigators were not blinded to the intervention and the study authors noted that this might have biased their interpretation of cystoscopic findings or the decision to proceed with repeat treatment. Therefore, the assessment of this clinically reported outcome may have been subject to measurement bias.	RD for Optilume vs dilation or DVIU: 44.4% 95% CI [27.6; 61.1] p < 0.0001 *,#,$
Freedom from repeat intervention rate at 12 months	1 RCT	• A nominal p value is provided because analysis of this outcome was prespecified in the protocol at 6 months and not at 12 months, but Kaplan-Meier estimates for each group are only reported at 12 months in the publication. • No difference in the median time to event or hazard ratio was provided. • The surgeons and investigators were not blinded to the intervention over the entire study period and the study authors noted that this might have biased their interpretation of cystoscopic findings or the decision to proceed with repeat treatment. Therefore, the assessment of this clinically reported outcome may have been subject to measurement bias.	Optilume vs dilation or DVIU p < 0.0001
Change in Qmax (ml/s) at 6 months	1 RCT	• Only reported in the CSR. • The 95% CI for this effect measure was not provided in the CSR. • No sensitivity analysis was conducted for this outcome.	MD for Optilume vs dilation or DVIU: +4.78 ml/s 90% CI [1.94; 7.61] p = 0.0031 *,#,$
Qmax at 30 days and 3, 6 and 12 months	1 RCT	• Only descriptive statistics were used to report this outcome. • There is no clear explanation for handling of missing data.	NA
PVR at 30 days and 3, 6 and 12 months	1 RCT	• Only descriptive statistics were used to report this outcome. • There is no clear explanation for handling of missing data.	NA
IPSS at 30 days and 3 and 6 months	1 RCT	• Assessment of this outcome was not prespecified in the protocol. • Only descriptive statistics were used to report this outcome. • There is no clear explanation for handling of missing data.	NA

IPSS-QoL at 30 days and 3 and 6 months	1 RCT	• The protocol prespecified the assessment of the QoL outcome but did not indicate any measurement instrument or follow-up length. • Only descriptive statistics were used to report these outcomes. • There is no clear explanation for handling of missing data.	NA
IIEF (overall satisfaction) at 30 days and 3 and 6 months	1 RCT	• Assessment of this outcome was not prespecified in the protocol. • Only descriptive statistics were used to report this outcome. • There is no explanation for missing data.	NA
Freedom from a composite of serious device- or procedure related events including: – Urethral fistula – Unresolved de novo stress urinary incontinence – Urethral rupture up to 3 months	1 RCT	As prespecified in the protocol, only descriptive statistics were used to report this outcome.	NA
Periprocedural pain (VAS)	1 RCT	• Assessment of this outcome was not prespecified in the protocol. • Only descriptive statistics were used to report this outcome.	NA
All-cause mortality	1 RCT, 2 single-arm studies	• Assessment of this outcome was not prespecified in the protocols. • Only descriptive statistics were used to report this outcome.	NA
Other adverse events	1 RCT, 2 single-arm studies	Only descriptive statistics were used to report these outcomes.	NA
* Statistically significant according to a prespecified alpha level. # Prespecified analysis according to the statistical analysis plan (for individual studies) or the evidence synthesis protocol. $ Control for multiplicity.			

Source: Clinical study reports.
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; MD=mean difference; NA=not applicable; PICO=Population, Intervention, Comparator, Outcome; PVR=postvoid residual volume; Qmax=maximum flow rate; QoL=quality of life; RCT=randomised controlled trial; RD=risk difference; VAS=Visual Analogue Scale.

A version of this table using categories according to partial use of GRADE[6] is provided in Appendix E.

[6] EUnetHTA-GRADE-framework-paper.pdf

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6 SUMMARY REPORT

The Optilume urethral drug-coated balloon (DCB) is a urethral balloon coated with an antiproliferative medicinal product (paclitaxel).

It is intended for the treatment of strictures in the anterior urethra in adult males. 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.

In males, a urethral stricture is a narrowing of the anterior urethra lumen. It is a relatively common medical condition among men that adversely impacts physical health and quality of life. Left untreated, strictures can lead to serious complications such as recurrent urinary tract infections, urinary retention and eventual renal impairment.

The aim of this joint clinical assessment (JCA) was to assess the relative clinical effectiveness and safety of the Optilume urethral DCB medical device in the target patient population against relevant comparators defined before the start of the assessment in the assessment scope (Population, Intervention, Comparator, Outcome; PICO) and according to the requirements of EUnetHTA 21 members.

Stakeholders and external experts were consulted early in the JCA scoping process to support the development of the PICO question. Input was received from two healthcare professional organisations, one patient organisation and one clinical expert.

The consolidated assessment scope including the PICO questions is presented in **Table 30**.

Table 30. Assessment scope including the consolidated PICO questions

Description of PICO elements	PICO 1	PICO 2	PICO 3
Population	According to the intended use: Men aged ≥18 years with bothersome urinary symptoms associated with recurrent anterior urethral strictures ≤3 cm in length.	The same as for PICO 1	The same as for PICO 1
Intervention	According to the intended use*: Optilume 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 an adjunctive therapy with other dilation devices and/or procedures.	The same as for PICO 1	The same as for PICO 1
Comparator	Urethrotomy [a]	Dilation	Urethroplasty
Outcomes	The following outcomes are assessed across all PICO question(s): – All-cause mortality – Urinary function (lower urinary tract symptoms related to stricture) measured using: International Prostatic Symptom Score, Post-Void Residual urine volume, maximum flow rate – Erectile function measured using: International Index of Erectile Function		

Description of PICO elements	PICO 1	PICO 2	PICO 3
	– 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 measure), any other patient-centred outcome and health status measured using PROMs - Safety, including a description of each adverse event included in the following categories: • Any 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 AEs		
* The other dilation devices and/or procedures used with the Optilume DCB will have to be specified in the description of the procedure used in the clinical study/studies in the "Characteristics of the studies included" section of the health technology developer's submission dossier, if relevant.			
[a] Urethrotomy and direct vision internal urethrotomy (DVIU) are used indistinctly in this report.			

Source: EUnetHTA 21 Committee for Scientific Consistency and Quality.
Abbreviations: AE=adverse event; DCB=drug-coated balloon; PICO=Population, Intervention, Comparator, Outcome; PROM=patient-reported outcome measure.

The three PICO questions only differed from each other in the comparator.

There was no evidence to address PICO 1, PICO 2 and PICO 3 separately. However, one RCT (ROBUST III) from the clinical development programme for the intervention under assessment is presented in the report. It addresses the assessment scope in terms of population, intervention and outcomes, but includes several comparators defined as standard endoscopic management by the treating physician, mixing the comparators from PICO 1 (urethrotomy) and PICO 2 (dilation).

In addition, two single-arm studies (ROBUST I and ROBUST II) with longer follow-up were included in the report for safety outcomes.

A summary-of-evidence table including the uncertainty of the evidence is presented in **Table 31**.

Table 31. Uncertainty of evidence from the main studies from the clinical development programme

Outcome	Design	Factors that may affect the certainty of evidence	Effect estimate p value
All outcomes	1 RCT	**Internal validity of individual studies** • ROBUST III is a prospective, interventional RCT that included 127 patients (79 in the intervention group vs 48 in the control group) with short follow-up duration (6 months) for outcomes with prespecified hypothesis testing. • The randomisation was planned at a 2:1 allocation to treatment vs control, stratified by investigational centre and by prior radiation treatment and number of prior dilation treatments using randomly permuted blocks (block size not reported). There is no specific information on the concealment of the allocation sequence. • Only the patients were blinded to the treatment. • The study was designed with a primary objective of demonstrating superiority. • There were no major differences in baseline characteristics between the treatment groups in the study. • The risk of bias was considered high for all outcomes. • Only descriptive statistics were used to report most of the outcomes apart from the stricture free rate, the freedom from repeat intervention rate at 12 months and the change in Qmax at 6 months. • Patients could cross over to the Optilume group after 6 months according to the study protocol and, if medically necessary (recurrent stricture requiring intervention) before 6 months. Some 25% (12/48) of patients from the control group crossed over to the Optilume group before 6 months. • There is no agreed single outcome measure that defines urethral stricture recurrence. **Applicability** • 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 study was conducted in North America, not in Europe. • Optilume treatment included predilation, 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 second-line treatment after stricture recurrence, but the majority of patients included in ROBUST III had more than 3 endoscopic treatments before the Optilume procedure. • The comparator for ROBUST III does not match any of the comparators defined in PICO 1, PICO 2 or PICO 3. • The comparator in the 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) which was a mix of the PICO 1 (urethrotomy) and PICO 2 (dilatation) comparators. • No data were reported for the drug-related adverse events requested in the PICO question. All other outcomes were reported in this study.	NA

		Heterogeneity and inconsistency No heterogeneity or inconsistency issue was raised as only 1 RCT was available and included for assessing the relative effectiveness and relative safety of Optilume.	
Stricture-free rate at 6 months		• Data for this outcome were missing for 12/79 (15%) patients in the Optilume group and 7/48 (15%) patients in the control group. • A sensitivity analysis comprising 5 different subanalyses yielded results with the same directionality as for the primary analysis. • Patients in the control group who crossed over to the Optilume group were considered a failure for this outcome. • The surgeons and investigators were not blinded to the intervention and the study authors noted that this might have biased their interpretation of cystoscopic findings or the decision to proceed with repeat treatment. Therefore, the assessment of this clinically reported outcome may have been subject to measurement bias.	RD for Optilume vs dilation or DVIU: 44.4% 95% CI [27.6; 61.1] p < 0.0001 *,#,$
Freedom from repeat intervention rate at 12 months	1 RCT	• A nominal p value is provided because analysis of this outcome was prespecified in the protocol at 6 months and not at 12 months, but Kaplan-Meier estimates for each group are only reported at 12 months in the publication. • No difference in the median time to event or hazard ratio was provided. • The surgeons and investigators were not blinded to the intervention over the entire study period and the study authors noted that this might have biased their interpretation of cystoscopic findings or the decision to proceed with repeat treatment. Therefore, the assessment of this clinically reported outcome may have been subject to measurement bias.	Optilume vs dilation or DVIU p < 0.0001
Change in Qmax (ml/s) at 6 months	1 RCT	• Only reported in the CSR. • The 95% CI for this effect measure was not provided in the CSR. • No sensitivity analysis was conducted for this outcome.	MD for Optilume vs dilation or DVIU: +4.78 ml/s 90% CI [1.94; 7.61] p = 0.0031 *,#,$
Qmax at 30 days and 3, 6 and 12 months	1 RCT	• Only descriptive statistics were used to report this outcome. • There is no clear explanation for handling of missing data.	NA
PVR at 30 days and 3, 6 and 12 months	1 RCT	• Only descriptive statistics were used to report this outcome. • There is no clear explanation for handling of missing data.	NA
IPSS at 30 days and 3 and 6 months	1 RCT	• Assessment of this outcome was not prespecified in the protocol. • Only descriptive statistics were used to report this outcome. • There is no clear explanation for handling of missing data.	NA
IPSS-QoL at 30 days and 3 and 6 months	1 RCT	• The protocol prespecified the assessment of the QoL outcome but did not indicate any measurement instrument or follow-up length. • Only descriptive statistics were used to report these outcomes. • There is no clear explanation for handling of missing data.	NA

IIEF (overall satisfaction) at 30 days and 3 and 6 months	1 RCT	• Assessment of this outcome was not prespecified in the protocol. • Only descriptive statistics were used to report this outcome. • There is no explanation for missing data.	NA
Freedom from a composite of serious device- or procedure related events including: – Urethral fistula – Unresolved de novo stress urinary incontinence – Urethral rupture up to 3 months	1 RCT	As prespecified in the protocol, only descriptive statistics were used to report this outcome.	NA
Periprocedural pain (VAS)	1 RCT	• Assessment of this outcome was not prespecified in the protocol. • Only descriptive statistics were used to report this outcome.	NA
All-cause mortality	1 RCT, 2 single-arm studies	• Assessment of this outcome was not prespecified in the protocols. • Only descriptive statistics were used to report this outcome.	NA
Other adverse events	1 RCT, 2 single-arm studies	Only descriptive statistics were used to report these outcomes.	NA

* Statistically significant according to a prespecified alpha level.
[#] Prespecified analysis according to the statistical analysis plan (for individual studies) or the evidence synthesis protocol.
[$] Control for multiplicity.

Source: Clinical study reports.
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; MD=mean difference; NA=not applicable; PICO=Population, Intervention, Comparator, Outcome; PVR=postvoid residual volume; Qmax=maximum flow rate; QoL=quality of life; RCT=randomised controlled trial; RD=risk difference; VAS=Visual Analogue Scale.

Appendix A Input from external experts

Input from stakeholder organisations and from clinical expert obtained via the open call for input are presented in this appendix.

Question	1	2	3
Please state the country where the HCP organisation/clinical society that you are representing is based	The Netherlands	Belgium	Germany
Please name the HCP organisation/clinical society you are representing	European Association of Urology	European Union of General Practitioners UEMO	
What role do you have in the organisation?	President/Vice President/ Board Member	Member with mandate to speak on behalf of organisation	I am a self employed medical consultant
How many members does your organisation have?	Approx 19 000 individual members	24 national medical Organisations	
How is your organisation funded?	See link for 2021: https://uroweb.org/european-medicine-agency-ema For 2020: As part of the evaluation for eligibility, the European Association of Urology has provided the following financial information (2020) to be assessed by the parameters as set by the European Medicine Agency: •Royalties EAU scientific journal: 26,08% – 50% non-industry – 50% industry •Membership fees 22.96% – 100% non-industry •Registration fees 9.12% – 100% non-industry •Results EAU meeting & education 33.15% – 100% industry •Accounting and management consulting 1.49% – 100% non-industry •Sold guidelines 1.98% – 100% non-industry •Other income 5.22% – 100% non-industry Overall proportion of industry and non-industry:46.19% vs 53.81% The following pharmaceutical companies provide funding to EAU: •Astellas Pharma Europe Ltd •Intuitive Surgical Sarl •Janssen Pharmaceutical N.V. •Bayer Consumer Care AG •GSK Services Unlimited •IPSEN innovation •BMS	Funding by annual cotisations coming from national medical organisations according the number of GPs / Family doctors. No industry funding. Ireland, UK, Belgium, NL, Luxemburg, Portugal, Spain, France, Italy, Switzerland, Germany, CZ, Slovenia, Slovakia, HR, HU, Austria, RO, Lituanua, Norway, Sweden, Finland, Serbia, Turkey. Budget: previsional 2023 More informations: secretariat@uemo.eu	No funding from medical industry during the last three years

	Bristol Myers Squibb •Ferring International Center S.A •Bayer Healthcare Pharmaceuticals, Inc. •Pfizer Inc. For 2019: As part of the evaluation for eligibility, the European Association of Urology has provided the following financial information (2019) to be assessed by the parameters as set by the European Medicine Agency: •Royalties EAU scientific journal: 8.33% – 50% non-industry – 50% industry •Membership fees 8.21% – 100% non-industry •Registration fees 42.36% – 100% non-industry •Results EAU meeting & education 40.22% – 100% industry •Accounting and management consulting 0.59% – 100% non-industry •Sold guidelines 0.22% – 100% non-industry •Other income 0.06% – 100% non-industry Overall proportion of industry and non-industry:44.79% vs 55.21% Funding Resources: The following pharmaceutical companies provide funding to EAU: •IPSEN innovation •Janssen Pharmaceutical N.V. •Karl Storz SE & Co. KG •Bayer •Olympus Europa SE & CO. KG •Intuitive Surgical Sarl •Astellas Pharma •Bristol-Myers Squibb •Boston Scientific •Cook Medical Europe Ltd.		
Please state the geographical spread of the organisation's membership		'+ Uk, Norway, Switzerland, Serbia, Turkey	
Please state the health condition(s) represented by the organisation and/or the remit of the organisation	All diseases in the field of Urology, Pediatric Urology, Renal Transplantation, and Andrology	Family medicine/general practice	
Population Please state relevant patient sociodemographic (e.g., age, ethnicity, socioeconomic status) and clinical baseline characteristics (e.g., severity of condition, comorbidities) which may contribute to differences in treatment outcomes or treatment preferences.	Male patients who suffer from significant lower urinary tract symptoms induced by a ureteral stricture. Lower urinary symptoms may include weak urine flow, dysuria, pollakisuria, recurrent urinary infection, residual post voiding urine and even urinary retention. The highest available evidence regarding optilume is obtained from the Robust III trial: Elliot et al. J Urol 2022; 207, 866-75 Key inclusion criteria were: -at least 2 prior (failed) endoscopic procedures -anterior urethral stricture (92% of	In general practice our patients are certainly in majority old men with BPH, less with recurent UTI. This technique could be useful in medical home for old persons or in palliative care units, if the use is simple and comfortable. Patients who need a dilatation are generally referred to the urologist. According to our numerous investigations of UEMO GPs practices around Europe, in some rural or remote areas the GP can	Primary or repeated urethral stricture Work status: company employed, self employed, retired Eligibility criteria: Age, concomitant diseases

What are the relevant eligibility criteria for treatment decisions made by HCPs?	included patients had a bulbar stricture; therefore, the results predominantly apply to the bulbar urethra and this device should only be endorsed for that part of the urethra only -stricture length ≤ 3cm (generally spoken „short" stricture) -stricture diameter ≤ 12Fr (generally spoken „high grade" stricture) -IPSS ≥11 (although not validated for urethral stricture disease, IPSS is often used for this condition; we can state that they included patients with moderate to severe LUTS -Q max <15ml/s (this is what you expect in a high grade stricture) Key exclusion criteria: -prior urethroplasty -hypospadias -Lichen sclerosus In summary the device has been tested in: Male adult patients with short, high-grade bulbar urethral stricture with moderate to severe LUTS and who underwent at least to endoscopic procedures but no prior urethroplasty.	have the possibility to make such medical acts when no specialist is at disposal. But such a technique needs a training. The technique can be	
Intervention Are there contextual factors, (e.g., prior, concurrent or subsequent treatments, training on administration, etc.) which may affect the safety and/or effectiveness of the intervention? Does the specific (professional) experience of the treating HCP or medical staff play a relevant role in the decision to use the intervention? Would the decision to use the intervention in clinical practice be affected by its route and/or frequency of administration? What would be relevant criteria for treatment discontinuation? Is there a specific time point at which you check the therapeutic effect?	Are there contextual factors, (e.g., prior, concurrent or subsequent treatments, training on administration, etc.) which may affect the safety and/or effectiveness of the intervention? Does the specific (professional) experience of the treating HCP or medical staff play a relevant role in the decision to use the intervention? Yes, any intervention should be performed by a certified urologist Would the decision to use the intervention in clinical practice be affected by its route and/or frequency of administration? Yes, the surgeon (urologist) should have sufficient experience in performing the respective procedure. What would be relevant criteria for treatment discontinuation? Is there a specific time point at which you check the therapeutic effect? 1/ Treatment discontinuation: -if pre-operatively, the stricture cannot be dilated or incised endoscopically, the procedure should be aborted -if after dilation/endoscopic incision, a false passage is present, the procedure should be aborted 2/ follow-up -> I propose to take over the follow-up protocol from the study which is not different to clinical practice -2-5 days (i.e. catheter removal) (-30 days: not really necessary) -3 months -6	Consider the intervention by the GP if no urologist at disposal but training is necessary. Certainly needs the experience of GP or trained doctor. Treatment discontinuation if allergy to the medicine involved, lesions (perforation), pain or recurent use	First line therapy versus repeated treatments Professional experience of the HCP/team Possibility of outclinic treatment Multiple repeated treatment would imply higher drug exposure There is a strong interest in definite "cure" after single intervention

Where does the intervention fit in the current treatment landscape?	months -12 months -annually until 5 years Where does the intervention fit in the current treatment landscape? The current treatment does NOT fit in the current treatment landscape according to the EAU guidelines. There there is a STRONG recommendations for this guideline: „Do not perform repetitive (>2) direct vision internal urethrotomy/dilatations if urethroplasty is a viable option.“ Nevertheless, repetitive DVIU/dilatations are still routinely performed by many urologists. The panel would only endorse the DCB dilatation for patients with recurrent bulbar strictures who are not fit to undergo urethroplasty or who refuse urethroplasty (this is also stated in the conclusion of the Robust III trial)		
Comparator(s) What is the standard of care in your country? Are you aware of the standard of care most commonly used in Europe? Are there different treatment options for different patient groups depending on severity, previous treatment, biomarker levels, etc.? What are the goals of current treatments? Are there contextual factors (e.g., prior, concurrent or subsequent treatments) which may affect the safety and/or effectiveness of the comparators? Would the decision to use comparators in clinical practice be affected by their route and/or frequency of administration?	What is the standard of care in your country? Are you aware of the standard of care most commonly used in Europe? The SOC for a recurrent short bulbar stricture is open urethroplasty. DVIU or dilatation can only be considered SOC for an untreated short bulbar stricture. In case of a short bulbar stricture treatment options should be discussed: One trial urethrotomy/dilatation or urethroplasty. Highest success rate with the last treatment. Are there different treatment options for different patient groups depending on severity, previous treatment, biomarker levels, etc.? -For short obliterative strictures or strictures with full thickness spongiofibrosis, the EAU guidelines recommend transecting excision and primary anastomosis -For short bulbar strictures not related to straddle injury, the EAU guidelines recommend non-transecting excision and primary anastomosis or free graft urethroplasty. -For longer strictures, the EAU guidelines recommend free graft urethroplasty. What are the goals of current treatments? To re-establish an open and not stenotic urethra and thus cure the existing lower urinary tract symptom. Are there contextual factors (e.g., prior, concurrent or subsequent treatments) which may affect the safety and/or effectiveness of the comparators? No, all existing techniques are safe and effective, but the new	Many old men in medical home can have an in situ remaining urethral catheter. Some can make self regular catheterism.	Surgical treatment with termino-terminal anastomosis is the recommended procedure However, repeated dilatation is preferred in clinical practise Comparison needs to be fair: Not single procedure against muli-modal treatment (i.e. pre-dilatation or DIVU followed by balloon dilatation and local chemotherapy)

	device offers a minimally invasive approach. Would the decision to use comparators in clinical practice be affected by their route and/or frequency of administration? Yes, the comparator in the Robust III trial is not the gold standard. The device should have been tested against open urehtroplasty and not against the (mal)practice of repetitive dilatations/DVIU		
Outcome(s) Please define relevant safety, efficacy and patient-centred outcomes (e.g., quality of life) which should be assessed. What safety and efficacy outcomes are used in clinical practice to inform clinical decisions regarding treatment and how are they measured? If surrogate outcomes (e.g., laboratory parameters) are relevant to the indication given, do you consider them to be clinically meaningful?	Possible intraoperative complications are: Bleeding, pain, infection, urinary retention, injury of the urethra; Possible late complications are recurrent formation of the stricture, obstruction and dislodgement of the device requiring further interventions. Anatomical succes at 6 months was 74.6% for DCB dilatation versus 26.8% for DVIU/dilatation. No serious device related adverse events were reported with DCB dilatation. Adverse events that were more frequent with DCB dilatation versus control were: hematuria and dysuria. Pacitaxel remained detectable in semen up to 6mo after procedure: contraception warranted in case of fertile partner What safety and efficacy outcomes are used in clinical practice to inform clinical decisions regarding treatment and how are these measured? Follow-up schedule mentioned above. Every follow-up visit should include: -history taking -Questionnaire evaluating LUTS and QoL Uroflow -Residual volume In case of obstructive symptoms or signs, further examinations with urethography or urethroscopy are needed. If surrogate outcomes (e.g., laboratory parameters, etc.) are relevant to the indication given, do you consider them to be clinically meaningful? Residual urine, Urine peak flow, Urine culture	Outcome seems first the comfort of the patient: self management of symptoms, more freedom, no pain.	Safety: Need for hospitalisation for any reason Efficacy: Bladder emptying without significant residual volume Most important: Long term patient reported outcome
If you have any further comments or remarks, please add them here	No further comments.	For the GP it is certainly a technique needing specialist competencies, but we are also the person where the patient come back if there is a problem. We have to discuss the options	All three clinical studies were performed in patients with recurrent urethral strictures; there are no reports on first line intervention. This would be very interesting (if

			not absolutely necessary) for real life use.

Input from patient organisation is provided in the following table.

Question	
Website of your organisation:	www.prostatakrebs-bps.de
Where have you sourced information on patients' experiences? If relevant, how did you gather information about the experiences of patients?	own individual experience, individual patient stories, leader of a patient support group, patient group helpline, one-to-one discussions with patients
How does urinary symptoms associated with urethral stricture affect patient's daily life?	male patients with prostate cancer may devellop urethral strictures some month after radical prostatectomy or some years after radiation therapy. the symptoms are very different, pain during urination, urinary retention etc.. treatment options are ur ethral dilation, urethrotomy etc. but often patients have recurrent urethral stricture.
How does urinary symptoms associated with urethral stricture affect carers?	partners of prostate cancer patients suffer especially when the patient is depressiv, incontinent or impotent etc.
Please provide your answer to the above question here.	recurrent urethral stricturs are a big problem, i.e. after urethrotomy. many patients wish a minimal invasive treatment.
Please provide your answer to the above question here.	Expectations for the treatment with Urethral Drug Coated Balloon: less recurrent urethral strictures less symptoms less side effects of the paclitaxel coat
For those with experience using Urethral Drug Coated Balloon what difference does/did it make to their lives?	no or less urinary retention. no or less pain during urination etc. better sleep.
In no more than ten statements, please try to summarise your submission by listing the most important points. However, please note that all information you provide in the template will be considered by the EUnetHTA (Co)-Assessors.	main patient expectations are to avoid radical surgery and recurrence of urethral strictures

Appendix B Assessment of information retrieval

The evidence base with regard to the health technology under assessment, the Optilume Urethral Drug-coated Balloon (DCB), provided by the HTD was reviewed by the assessment team. Search strategies were checked for appropriateness, and the results of information retrieval included in the HTD submission dossier were checked for completeness of studies against a search of study registries and in the Medline bibliographic database.

The documentation of searches conducted by the assessment team for the verification of the completeness of studies included in the assessment is provided below.

No concerns regarding the information retrieval in the submission dossier were raised during this completeness check.

Search strategy of the search conducted in study registries and in Medline by the assessment team for study completeness check

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: https://www.clinicaltrials.gov
- Interface: Expert Search

Search syntax
Optilume

2. Clinical Trials Information System (CTIS)

Provider: European Medicines Agency

- URL: https://euclinicaltrials.eu/search-for-clinical-trials/
- Interface: Basic Criteria (Contain any of these terms)

Search syntax
Optilume

3. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: https://trialsearch.who.int/
- Interface: Standard Search

Search syntax
Optilume

4. Medline
Provider: National Library of Medicine

- Interface: ProQuest

Search	Query
#1	Search ti,ab,if("optilume")
#2	Search tndev("Optilume")
#3	Search #1 OR #2

5. Embase

Provider: Elsevier

- Interface: ProQuest

Search	Query
#1	Search ti,ab,if("optilume")
#2	Search tndev("Optilume")
#3	Search #1 OR #2
#4	Search EMB.EXACT(conference abstract)
#5	Search #3 AND #4

Appendix C Additional safety data from the ROBUST III CSR

Table 32: Adverse Events Categorised by Common Terminology Criteria for Adverse Events (CTCAE) Severity for the Randomised Cohort (Adjudicated) - ROBUST III

	Control Arm (N=48)		Optilume Arm (N=79)	
System Organ Class/ CTCAE Term	**Grade 1-2**	**Grade 3+**	**Grade 1-2**	**Grade 3+**
Renal and urinary disorders	25/48 (52.1%)	6/48 (12.5%)	32/79 (40.5%)	8/79 (10.1%)
Urethral stricture	17/48 (35.4%)	3/48 (6.3%)	10/79 (12.7%)	3/79 (3.8%)
Urinary retention	1/48 (2.1%)	3/48 (6.3%)	5/79 (6.3%)	1/79 (1.3%)
Dysuria	1/48 (2.1%)	0/48 (0.0%)	7/79 (8.9%)	0/79 (0.0%)
Post procedural hematuria	0/48 (0.0%)	0/48 (0.0%)	6/79 (7.6%)	1/79 (1.3%)
Bladder spasm	1/48 (2.1%)	0/48 (0.0%)	4/79 (5.1%)	0/79 (0.0%)
Poor urinary stream	2/48 (4.2%)	0/48 (0.0%)	3/79 (3.8%)	0/79 (0.0%)
Hematuria	1/48 (2.1%)	0/48 (0.0%)	3/79 (3.8%)	0/79 (0.0%)
Lower urinary tract symptoms	2/48 (4.2%)	0/48 (0.0%)	0/79 (0.0%)	1/79 (1.3%)
Post micturition dribble	0/48 (0.0%)	0/48 (0.0%)	3/79 (3.8%)	0/79 (0.0%)
Voiding difficulty	0/48 (0.0%)	0/48 (0.0%)	3/79 (3.8%)	0/79 (0.0%)
Urinary incontinence	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	1/79 (1.3%)
Bladder neck contracture	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Detrusor sphincter dyssynergia	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Frequency of micturition	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Kidney stone	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Overactive bladder	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Renal calculi	0/48 (0.0%)	0/48 (0.0%)	0/79 (0.0%)	1/79 (1.3%)
Urethral bleeding	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Urethritis	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Urge incontinence	1/48 (2.1%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)
Infections and infestations	6/48 (12.5%)	2/48 (4.2%)	11/79 (13.9%)	2/79 (2.5%)
Urinary tract infection	5/48 (10.4%)	0/48 (0.0%)	9/79 (11.4%)	0/79 (0.0%)
Bacteriuria	2/48 (4.2%)	0/48 (0.0%)	5/79 (6.3%)	0/79 (0.0%)
COVID-19	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	1/79 (1.3%)
COVID-19 pneumonia	0/48 (0.0%)	1/48 (2.1%)	0/79 (0.0%)	0/79 (0.0%)

	Control Arm (N=48)		Optilume Arm (N=79)	
System Organ Class/ CTCAE Term	**Grade 1-2**	**Grade 3+**	**Grade 1-2**	**Grade 3+**
Conjunctivitis infective	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Fungal skin infection	1/48 (2.1%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)
Kidney infection	0/48 (0.0%)	0/48 (0.0%)	0/79 (0.0%)	1/79 (1.3%)
Sepsis	0/48 (0.0%)	1/48 (2.1%)	0/79 (0.0%)	0/79 (0.0%)
Staphylococcal infection	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Upper respiratory infection	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Wound infection	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Respiratory, thoracic and mediastinal disorders	7/48 (14.6%)	0/48 (0.0%)	8/79 (10.1%)	2/79 (2.5%)
Cough	2/48 (4.2%)	0/48 (0.0%)	2/79 (2.5%)	0/79 (0.0%)
Bronchitis	3/48 (6.3%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)
Cold symptoms	1/48 (2.1%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Pneumonia	0/48 (0.0%)	0/48 (0.0%)	2/79 (2.5%)	0/79 (0.0%)
Upper respiratory tract infection	0/48 (0.0%)	0/48 (0.0%)	2/79 (2.5%)	0/79 (0.0%)
Lung adenocarcinoma metastatic	0/48 (0.0%)	0/48 (0.0%)	0/79 (0.0%)	1/79 (1.3%)
Lung nodule	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Pulmonary embolism	0/48 (0.0%)	0/48 (0.0%)	0/79 (0.0%)	1/79 (1.3%)
Rhinorrhea	1/48 (2.1%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)
Rhonchi	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Gastrointestinal disorders	3/48 (6.3%)	1/48 (2.1%)	7/79 (8.9%)	4/79 (5.1%)
Abdominal pain	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	1/79 (1.3%)
Constipation	0/48 (0.0%)	0/48 (0.0%)	2/79 (2.5%)	0/79 (0.0%)
Nausea	1/48 (2.1%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Umbilical hernia	0/48 (0.0%)	0/48 (0.0%)	0/79 (0.0%)	2/79 (2.5%)
Abdominal discomfort	1/48 (2.1%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)
Acute gastroenteritis	0/48 (0.0%)	1/48 (2.1%)	0/79 (0.0%)	0/79 (0.0%)
Bowel infarction	0/48 (0.0%)	0/48 (0.0%)	0/79 (0.0%)	1/79 (1.3%)
Esophageal acid reflux	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
GI bleed	1/48 (2.1%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)

	Control Arm (N=48)		Optilume Arm (N=79)	
System Organ Class/ CTCAE Term	**Grade 1-2**	**Grade 3+**	**Grade 1-2**	**Grade 3+**
Left inguinal hernia	0/48 (0.0%)	0/48 (0.0%)	0/79 (0.0%)	1/79 (1.3%)
Opioid induced constipation	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Pelvic pain	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Tooth infection	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Xerostomia	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Reproductive system and breast disorders	2/48 (4.2%)	0/48 (0.0%)	9/79 (11.4%)	0/79 (0.0%)
Prostatitis	0/48 (0.0%)	0/48 (0.0%)	3/79 (3.8%)	0/79 (0.0%)
Penile pain	0/48 (0.0%)	0/48 (0.0%)	2/79 (2.5%)	0/79 (0.0%)
Testicular pain	1/48 (2.1%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Balanitis candida	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Benign prostatic hyperplasia	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Erectile dysfunction	1/48 (2.1%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)
Perineal pain	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Peyronie's disease	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Retracted penis	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Injury, poisoning and procedural complications	2/48 (4.2%)	1/48 (2.1%)	5/79 (6.3%)	1/79 (1.3%)
Medical device site extravasation	1/48 (2.1%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Pulmonary aspiration during anaesthetic induction	0/48 (0.0%)	1/48 (2.1%)	0/79 (0.0%)	1/79 (1.3%)
Achilles tendon sprain	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Catheter site irritation	1/48 (2.1%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)
Exposure to toxic agent (non-occupational)	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Fall	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Insect bite, nonvenomous, of hip, thigh, leg, and ankle, without mention of infection	1/48 (2.1%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)
Post procedural hematuria	1/48 (2.1%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)
Postoperative hemorrhage	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)

	Control Arm (N=48)		Optilume Arm (N=79)	
System Organ Class/ CTCAE Term	**Grade 1-2**	**Grade 3+**	**Grade 1-2**	**Grade 3+**
Musculoskeletal and connective tissue disorders	3/48 (6.3%)	1/48 (2.1%)	4/79 (5.1%)	1/79 (1.3%)
Low back pain	1/48 (2.1%)	1/48 (2.1%)	2/79 (2.5%)	0/79 (0.0%)
Bone spur	0/48 (0.0%)	0/48 (0.0%)	2/79 (2.5%)	0/79 (0.0%)
Arthritis	0/48 (0.0%)	0/48 (0.0%)	0/79 (0.0%)	1/79 (1.3%)
Bursitis	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Myalgia	1/48 (2.1%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)
Osteoarthritis aggravated	1/48 (2.1%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)
Pain knee	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Shoulder pain	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
General disorders and administration site conditions	4/48 (8.3%)	0/48 (0.0%)	2/79 (2.5%)	1/79 (1.3%)
Chest pain (non-cardiac)	1/48 (2.1%)	0/48 (0.0%)	1/79 (1.3%)	1/79 (1.3%)
Fever	1/48 (2.1%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Adverse reaction to antibiotics	1/48 (2.1%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)
Alcoholic withdrawal symptoms	1/48 (2.1%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)
Edema of lower extremities	1/48 (2.1%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)
Fatigue	1/48 (2.1%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)
Pain-left side	1/48 (2.1%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)
Skin and subcutaneous tissue disorders	1/48 (2.1%)	0/48 (0.0%)	6/79 (7.6%)	0/79 (0.0%)
Actinic keratosis	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Herpes zoster	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Lower extremities ulcers of	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Penile rash	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Pruritus	1/48 (2.1%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)
Skin and subcutaneous tissue disorders - other, specify	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Smelly feet	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Vascular disorders	2/48 (4.2%)	1/48 (2.1%)	1/79 (1.3%)	2/79 (2.5%)

	Control Arm (N=48)		Optilume Arm (N=79)	
System Organ Class/ CTCAE Term	**Grade 1-2**	**Grade 3+**	**Grade 1-2**	**Grade 3+**
Hypertension	1/48 (2.1%)	0/48 (0.0%)	0/79 (0.0%)	1/79 (1.3%)
Aneurysm cerebral	0/48 (0.0%)	1/48 (2.1%)	0/79 (0.0%)	0/79 (0.0%)
Dizziness	1/48 (2.1%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)
Hematoma	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Hypertension exacerbated	0/48 (0.0%)	0/48 (0.0%)	0/79 (0.0%)	1/79 (1.3%)
Cardiac disorders	1/48 (2.1%)	0/48 (0.0%)	2/79 (2.5%)	1/79 (1.3%)
Atrial fibrillation	0/48 (0.0%)	0/48 (0.0%)	0/79 (0.0%)	1/79 (1.3%)
Coronary artery disease	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Myocardial infarction	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Sinus bradycardia	1/48 (2.1%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)
Surgical and medical procedures	1/48 (2.1%)	0/48 (0.0%)	2/79 (2.5%)	1/79 (1.3%)
Cataract operation	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Colectomy	0/48 (0.0%)	0/48 (0.0%)	0/79 (0.0%)	1/79 (1.3%)
Surgical and medical procedures - other, specify	1/48 (2.1%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)
Total knee replacement	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Immune system disorders	3/48 (6.3%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)
Allergic reaction	3/48 (6.3%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)
Psychiatric disorders	0/48 (0.0%)	0/48 (0.0%)	3/79 (3.8%)	0/79 (0.0%)
Attention deficit disorder	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Bipolar disorder	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Depression	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Blood and lymphatic system disorders	0/48 (0.0%)	0/48 (0.0%)	2/79 (2.5%)	0/79 (0.0%)
Anemia	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Swollen lymph nodes	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Endocrine disorders	1/48 (2.1%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Diabetic ulcer right foot	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Worsening of diabetes	1/48 (2.1%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)

	Control Arm (N=48)		Optilume Arm (N=79)	
System Organ Class/ CTCAE Term	**Grade 1-2**	**Grade 3+**	**Grade 1-2**	**Grade 3+**
Nervous system disorders	0/48 (0.0%)	1/48 (2.1%)	1/79 (1.3%)	0/79 (0.0%)
Headache	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Thalamus hemorrhage	0/48 (0.0%)	1/48 (2.1%)	0/79 (0.0%)	0/79 (0.0%)
Ear and labyrinth disorders	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Vertigo	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Eye disorders	1/48 (2.1%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)
Double vision	1/48 (2.1%)	0/48 (0.0%)	0/79 (0.0%)	0/79 (0.0%)
Hepatobiliary disorders	0/48 (0.0%)	0/48 (0.0%)	0/79 (0.0%)	1/79 (1.3%)
Gallstones	0/48 (0.0%)	0/48 (0.0%)	0/79 (0.0%)	1/79 (1.3%)
Investigations	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Alanine aminotransferase increased	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Aspartate aminotransferase increased	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Metabolism and nutrition disorders	0/48 (0.0%)	0/48 (0.0%)	0/79 (0.0%)	1/79 (1.3%)
Hyperkalemia	0/48 (0.0%)	0/48 (0.0%)	0/79 (0.0%)	1/79 (1.3%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0/48 (0.0%)	0/48 (0.0%)	0/79 (0.0%)	1/79 (1.3%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps) - other, specify	0/48 (0.0%)	0/48 (0.0%)	0/79 (0.0%)	1/79 (1.3%)
Penile and scrotal disorders (excl. infections and inflammations)	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Hydrocele	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Respiratory, thoracic and mediastinal disorders	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Dyspnea	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Respiratory disorders NEC	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)
Cough	0/48 (0.0%)	0/48 (0.0%)	1/79 (1.3%)	0/79 (0.0%)

Only the AE terms before crossover were included.
Each subject is counted once within each System Organ Class and CTCAE Term according to the maximum intensity for all AEs within that System Organ Class or CTCAE Term.
Effect measures and p values were not provided by the HTD.

AE: adverse events; CTCAE: Common Terminology Criteria for Adverse Events; GI: gastrointestinal; HTD: Health Technology Developper; NEC: not elsewhere classifiable

Table 33: Reasons for Study Exit ROBUST III

Measure	Control % (n/N)	Optilume % (n/N)	Crossover[a] % (n/N)	Total % (n/N)
Total Study Exit	25.0% (12/48)	38.0% (30/79)	37.5% (12/32)	38.3% (54/141)
All required follow-up completed	4.2% (2/48)	0.0% (0/79)	0.0% (0/32)	1.4% (2/141)
Investigator discretion	4.2% (2/48)	2.5% (2/79)	0.0% (0/32)	2.8% (4/141)
Subject withdrew consent	6.3% (3/48)	6.3% (5/79)	0.0% (0/32)	5.7% (8/141)
Lost to follow-up	4.2% (2/48)	2.5% (2/79)	9.4% (3/32)	5.0% (7/141)
Adverse Event	0.0% (0/48)	1.3% (1/79)	0.0% (0/32)	0.7% (1/141)
Treatment Failure – Subject Received Alternative Therapy	6.3% (3/48)	21.5% (17/79)	28.1% (9/32)	20.6% (29/141)
Death	0.0% (0/48)	2.5% (2/79)	0.0% (0/32)	1.4% (2/141)
Other	0.0% (0/48)	1.3% (1/79)	0.0% (0/32)	0.7% (1/141)
a: crossover subjects were enrolled in the Control arm and are not included in denominator for 'Total'.				

Appendix D RoB 2.0 tables

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)
TEMPLATE FOR COMPLETION

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne
on behalf of the RoB2 Development Group

Version of 22 August 2019

The development of the RoB 2 tool was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- N61), with the support of the host MRC ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures - MR/K025643/1), by MRC research grant MR/M025209/1, and by a grant from The Cochrane Collaboration.

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Study details

Reference	Elliott SP, Coutinho K, Robertson KJ, D'Anna R, Chevli K, Carrier S, Aube-Peterkin M, Cantrill CH, Ehlert MJ, Te AE, Dann J, DeLong JM, Brandes SB, Hagedorn JC, Levin R, Schlaifer A, DeSouza E, DiMarco D, Erickson BA, Natale R, Husmann DA, Morey A, Olsson C, Virasoro R. One-Year Results for the ROBUST III Randomized Controlled Trial Evaluating the Optilume Drug-Coated Balloon for Anterior Urethral Strictures. J Urol. 2022 Apr;207(4):866-875. doi: 10.1097/JU.0000000000002346. Epub 2021 Dec 2. PMID: 34854748.

Study design

X Individually-randomized parallel-group trial

☐ Cluster-randomized parallel-group trial

☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental:	OPTILUME DCB	Comparator:	Standard of care endoscopic management as determined by the treating physician, including rigid rod dilation, DVIU, uncoated balloon dilation or a combination

Specify which outcome is being assessed for risk of bias	Primary efficacy end point: % Stricture-free **at 6 months**
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Difference (OPTILUME vs control) = 44.4% (95% CI 27.6 to 61.1) In Table 2

Is the review team's aim for this result…?

x to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

x Journal article(s) with results of the trial
x Trial protocol
☐ Statistical analysis plan (SAP)
x Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
x Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

(1) Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	From the protocol: "Subjects will be randomized in a 2:1 allocation of treatment vs control. Randomization will be stratified by investigational center and by prior radiation treatment (yes or no) and number of prior dilation treatments (i.e. less than 5 prior dilations versus ≥ 5prior dilations). Each treatment group will have its own randomization schedule within each participating center. For each randomization schedule, randomization will be performed using randomly permuted blocks." There is no specific information on the concealment of the allocation sequence.	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		PY
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias arising from the randomization process?		NA

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Some participants were unblinded before 6 months if they experienced recurrent stricture requiring intervention. Surgeons and investigators were not blinded to the intervention over the entire study period.	PN
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		PN
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Intention-to-treat analysis with multiple imputation of missing data was prespecified and conducted.	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		**Low**
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	67 out 79 for OPTILUME group and 41 out of 48 for the control group: 15% patients in both groups were not evaluable=> missing data for them.	N
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	A sensitivity analysis was conducted with 5 different analyses (Observed, Worst Case Imputation, Late Cystoscopy as Observed, IPSS Responder Status at 6m, IPSS Responder Status at Last Visit) that were all in the same directionality as the primary analysis.	PY
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	This outcome is measured by the ability to pass a 16Fr flexible cystoscope or 14Fr rubber catheter through the treated area by the surgeon. It's measured as prespecified in the protocol.	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	The same measurement method was probably used in both groups.	PN
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Surgeons were unblinded to the treatment over the entire study period.	Y
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	One limitation of the study stated by the authors "surgeons were not blinded to the type of treatment; this might bias their interpretation of cystoscopic findings or the decision to proceed with repeat treatment."	PY
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		PY
Risk-of-bias judgement		High risk
Optional: What is the predicted direction of bias in measurement of the outcome?		Favours experimental

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	There are several revisions of the protocol and it's not clear if the analysis plan was finalised before the outcome data were unblinded for analysis.	PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	There was only one defined outcome measurement for the "stricture free" outcome.	N
5.3 ... multiple eligible analyses of the data?	There is only one way in which the outcome measurement can be analysed. Analysis reported in the CSR is consistent with what was planned in the protocol.	N
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		**High risk**
Optional: What is the overall predicted direction of bias for this outcome?		Favours experimental

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Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)
TEMPLATE FOR COMPLETION

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne
on behalf of the RoB2 Development Group

Version of 22 August 2019

The development of the RoB 2 tool was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- N61), with the support of the host MRC ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures - MR/K025643/1), by MRC research grant MR/M025209/1, and by a grant from The Cochrane Collaboration.

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Study details

Reference	Elliott SP, Coutinho K, Robertson KJ, D'Anna R, Chevli K, Carrier S, Aube-Peterkin M, Cantrill CH, Ehlert MJ, Te AE, Dann J, DeLong JM, Brandes SB, Hagedorn JC, Levin R, Schlaifer A, DeSouza E, DiMarco D, Erickson BA, Natale R, Husmann DA, Morey A, Olsson C, Virasoro R. One-Year Results for the ROBUST III Randomized Controlled Trial Evaluating the Optilume® Drug-Coated Balloon for Anterior Urethral Strictures. J Urol. 2022 Apr;207(4):866-875. doi: 10.1097/JU.0000000000002346. Epub 2021 Dec 2. PMID: 34854748

Study design

X Individually-randomized parallel-group trial

☐ Cluster-randomized parallel-group trial

☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental:	OPTILUME	Comparator:	Standard of care endoscopic management as determined by the treating physician, including rigid rod dilation, DVIU, uncoated balloon dilation or a combination

Specify which outcome is being assessed for risk of bias	Freedom from repeat intervention rate (also referred to as Time to treatment failure rate) at 12 months
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	83.2% vs 21.7% (logrank test p<0.0001) from figure 3 in Elliott publication

Is the review team's aim for this result…?

x to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

x Journal article(s) with results of the trial
x Trial protocol
☐ Statistical analysis plan (SAP)
x Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
x Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

(2) Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	From the protocol: "Subjects will be randomized in a 2:1 allocation of treatment vs control. Randomization will be stratified by investigational center and by prior radiation treatment (yes or no) and number of prior dilation treatments (i.e. less than 5 prior dilations versus ≥ 5prior dilations). Each treatment group will have its own randomization schedule within each participating center. For each randomization schedule, randomization will be performed using randomly permuted blocks." There is no specific information on the concealment of the allocation sequence.	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		PY
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias arising from the randomization process?		NA

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Some participants were unblinded before 6 months 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.	PN
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		PN
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	If a Kaplan-Meier curve is available as well as the p-value of a log rank test, no difference in medians (point estimate and confidence interval), nor a hazard ratio (point estimate and confidence interval), are available, while they could have been estimated.	PY
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	According to the Kaplan-Meier curve available in the publication, for most of the follow-up, there is a low rate of lost-to follow up in both groups. However, between 340 and 360 days (the last 20 days of follow-up), more patients are censored in the Optilume group than in the control group.	PY
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	The measurement of the "freedom from repeat intervention" outcome is detailed in the protocol for treatment failure as: "Any subjects who have a second dilation procedure, pursue surgical intervention, or otherwise seek alternative treatment for the target stricture after the index procedure are considered treatment failures for the primary analysis. Subjects who cross-over to receive treatment with the Optilume device will be considered a treatment failure for the primary therapy. At the 6 months follow up, if a 16F flexible cystoscope or a 14F rubber catheter cannot cross the treated stricture, the subject will be considered a treatment failure. This 6 month follow-up urethral lumen test will be analyzed as occurring at 180 days for time-to-event analyses." This outcome is assessed by the surgeon (clinically-reported outcome). However, it can be assumed that the measuring method of the treatment failure was not changed for measuring this outcome at 12 months.	PN
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	The same measurement method was probably used in both groups.	PN
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Surgeons were unblinded to the treatment over the entire study period.	Y
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	One limitation of the study stated by the authors "surgeons were not blinded to the type of treatment; this might bias their interpretation of cystoscopic findings or the decision to proceed with repeat treatment."	PY
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		PY

Risk-of-bias judgement		**High risk**
Optional: What is the predicted direction of bias in measurement of the outcome?		Favours experimental

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	This analysis of this outcome was prespecified in the hierarchical testing procedure at 6 months but not at 12 months. However, group Kaplan-Meier estimates are only reported at 12 months in the publication. Additionally, there are several revisions of the protocol and it's not clear if the analysis plan was finalised before the outcome data were unblinded for analysis.	N
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	See above.	PY
5.3 ... multiple eligible analyses of the data?	Several analyses are reported in the CSR (2 for 6 months) and in the publication (1 at 12 months).	PY
Risk-of-bias judgement		**High risk**
Optional: What is the predicted direction of bias due to selection of the reported result?		Favours experimental

Overall risk of bias

Risk-of-bias judgement		**High risk**
Optional: What is the overall predicted direction of bias for this outcome?		Favours experimental

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Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)
TEMPLATE FOR COMPLETION

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne
on behalf of the RoB2 Development Group

Version of 22 August 2019

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Study details

Reference	Elliott SP, Coutinho K, Robertson KJ, D'Anna R, Chevli K, Carrier S, Aube-Peterkin M, Cantrill CH, Ehlert MJ, Te AE, Dann J, DeLong JM, Brandes SB, Hagedorn JC, Levin R, Schlaifer A, DeSouza E, DiMarco D, Erickson BA, Natale R, Husmann DA, Morey A, Olsson C, Virasoro R. One-Year Results for the ROBUST III Randomized Controlled Trial Evaluating the Optilume® Drug-Coated Balloon for Anterior Urethral Strictures. J Urol. 2022 Apr;207(4):866-875. doi: 10.1097/JU.0000000000002346. Epub 2021 Dec 2. PMID: 34854748

Study design

X Individually-randomized parallel-group trial

☐ Cluster-randomized parallel-group trial

☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental:	OPTILUME DCB	Comparator:	Standard of care endoscopic management as determined by the treating physician, including rigid rod dilation, DVIU, uncoated balloon dilation or a combination

Specify which outcome is being assessed for risk of bias	Change in Qmax at 6 months + 4.78 ml/s 90% CI 1.94 to 7.61
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Change in Qmax at 6 months = + 4.78 ml/s 90% CI 1.94 to 7.61 (from the CSR)

Is the review team's aim for this result…?

x to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

x Journal article(s) with results of the trial
x Trial protocol
☐ Statistical analysis plan (SAP)
x Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
x Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

(3) Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	From the protocol: "Subjects will be randomized in a 2:1 allocation of treatment vs control. Randomization will be stratified by investigational center and by prior radiation treatment (yes or no) and number of prior dilation treatments (i.e. less than 5 prior dilations versus ≥ 5prior dilations). Each treatment group will have its own randomization schedule within each participating center. For each randomization schedule, randomization will be performed using randomly permuted blocks." There is no specific information on the concealment of the allocation sequence.	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		PY
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias arising from the randomization process?		NA

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Some participants were unblinded before 6 months 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.	PN
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		PN
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Change in Qmax at 6 months was assessed as the secondary endpoint #2, according to a prespecified hierarchical testing procedure. It was analysed in an ITT analysis with multiple imputation for missing data.	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	67 out of 79 for OPTILUME group and 44 out of 48 for the control group for Qmax at 6 months => missing data for 15% patients in OPTILUME group and 8% in control group	N
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	No sensitivity analysis was conducted for this outcome.	N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	This outcome is a Performance outcome (PerfO) and patients could be unblinded before 6 months if they experienced recurrence symptoms and were unblinded after 6 months. Therefore the missingness of this outcome data may depend on its true value.	Y
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		PY
Risk-of-bias judgement		**High risk**
Optional: What is the predicted direction of bias due to missing outcome data?		Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	This outcome is a performance outcome (clinician-reported outcome which requires active patient involvement to complete a standardised task) used in routine care for assessing urological symptoms. However, the measurement tool for this outcome is not detailed in the study.	PN
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	The same measurement method was probably used in both groups.	PN
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Surgeons were unblinded to the treatment over the entire study period.	Y
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Even though the measurement tool for this outcome is not detailed in the study, it can be assumed that, like in most routine care situations, uroflowmetry is carried out in a fully automatic way without any need for medical staff to read out the results.	PN
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias in measurement of the outcome?		Favours experimental

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	There are several revisions of the protocol and it's not clear if the analysis plan was finalised before the outcome data were unblinded for analysis.	PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Change in Qmax was defined for this outcome measurement in the protocol.	PN
5.3 ... multiple eligible analyses of the data?	There is only one way in which this outcome measurement can be analysed. Analysis reported in the CSR is consistent with what was planned in the protocol.	N
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		**High risk**
Optional: What is the overall predicted direction of bias for this outcome?		Favours experimental

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Version of 22 August 2019

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Study details

Reference	Elliott SP, Coutinho K, Robertson KJ, D'Anna R, Chevli K, Carrier S, Aube-Peterkin M, Cantrill CH, Ehlert MJ, Te AE, Dann J, DeLong JM, Brandes SB, Hagedorn JC, Levin R, Schlaifer A, DeSouza E, DiMarco D, Erickson BA, Natale R, Husmann DA, Morey A, Olsson C, Virasoro R. One-Year Results for the ROBUST III Randomized Controlled Trial Evaluating the Optilume® Drug-Coated Balloon for Anterior Urethral Strictures. J Urol. 2022 Apr;207(4):866-875. doi: 10.1097/JU.0000000000002346. Epub 2021 Dec 2. PMID: 34854748

Study design

X Individually-randomized parallel-group trial

☐ Cluster-randomized parallel-group trial

☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental:	OPTILUME DCB	Comparator:	Standard of care endoscopic management as determined by the treating physician, including rigid rod dilation, DVIU, uncoated balloon dilation or a combination

Specify which outcome is being assessed for risk of bias	Qmax at 30 days, 3 months, 6 months and 12 months
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Table 3 in Elliott at al. Results at 30 days, 3 months, 6 months and 12 months

Is the review team's aim for this result…?

x to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

x Journal article(s) with results of the trial
x Trial protocol
☐ Statistical analysis plan (SAP)
x Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
x Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

(4) Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	From the protocol: "Subjects will be randomized in a 2:1 allocation of treatment vs control. Randomization will be stratified by investigational center and by prior radiation treatment (yes or no) and number of prior dilation treatments (i.e. less than 5 prior dilations versus ≥ 5prior dilations). Each treatment group will have its own randomization schedule within each participating center. For each randomization schedule, randomization will be performed using randomly permuted blocks." There is no specific information on the concealment of the allocation sequence.	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		PY
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias arising from the randomization process?		NA

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Some participants were unblinded before 6 months 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.	PN
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		PN
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	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
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		**High risk**
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	67 out of 79 for OPTILUME group and 44 out of 48 for the control group for Qmax at 6 months => missing data for 15% patients in OPTILUME group and 8% in control group	N
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	Only descriptive results provided for this outcome.	N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	There is no explanation for the missing data. This outcome is a Performance outcome (PerfO) and patients could be unblinded before 6 months if they experienced recurrence symptoms and were unblinded after 6 months. Therefore, the missingness of this outcome data may depend on its true value.	Y
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		PY
Risk-of-bias judgement		**High risk**
Optional: What is the predicted direction of bias due to missing outcome data?		Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	This outcome is a performance outcome (clinician-reported outcome which requires active patient involvement to complete a standardised task) used in routine care for assessing urological symptoms. However, the measurement tool for this outcome is not detailed in the study.	PN
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	The same measurement method was probably used in both groups.	PN
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Surgeons were unblinded to the treatment over the entire study period.	Y
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Even though the measurement tool for this outcome is not detailed in the study, it can be assumed that, like in most routine care situations, uroflowmetry is carried out in a fully automatic way without any need for medical staff to read out the results.	PN
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias in measurement of the outcome?		Favours experimental

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	The analysis of this outcome was not prespecified in the protocol, only change in Qmax was prespecified.	N
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	See above.	PN
5.3 ... multiple eligible analyses of the data?	Change from baseline in Qmax was prespecified at 12, 24, 36, 48 and 60 months as an ancillary endpoint, however not reported in the CSR nor in the publication, only average Qmax over time was reported. Therefore, it could have been selected from other eligible outcome measurements.	Y
Risk-of-bias judgement		**High risk**
Optional: What is the predicted direction of bias due to selection of the reported result?		Favours experimental

Overall risk of bias

Risk-of-bias judgement		**High risk**
Optional: What is the overall predicted direction of bias for this outcome?		Favours experimental

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Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)
TEMPLATE FOR COMPLETION

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne
on behalf of the RoB2 Development Group

Version of 22 August 2019

The development of the RoB 2 tool was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- N61), with the support of the host MRC ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures - MR/K025643/1), by MRC research grant MR/M025209/1, and by a grant from The Cochrane Collaboration.

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Study details

Reference	Elliott SP, Coutinho K, Robertson KJ, D'Anna R, Chevli K, Carrier S, Aube-Peterkin M, Cantrill CH, Ehlert MJ, Te AE, Dann J, DeLong JM, Brandes SB, Hagedorn JC, Levin R, Schlaifer A, DeSouza E, DiMarco D, Erickson BA, Natale R, Husmann DA, Morey A, Olsson C, Virasoro R. One-Year Results for the ROBUST III Randomized Controlled Trial Evaluating the Optilume® Drug-Coated Balloon for Anterior Urethral Strictures. J Urol. 2022 Apr;207(4):866-875. doi: 10.1097/JU.0000000000002346. Epub 2021 Dec 2. PMID: 34854748

Study design

X Individually-randomized parallel-group trial

☐ Cluster-randomized parallel-group trial

☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental:	OPTILUME DCB	Comparator:	Standard of care endoscopic management as determined by the treating physician, including rigid rod dilation, DVIU, uncoated balloon dilation or a combination

Specify which outcome is being assessed for risk of bias	PVR at 30 days, 3 months, 6 months and 12 months
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Table 3 in Elliott at al. Results at 30 days, 3 months, 6 months and 12 months

Is the review team's aim for this result…?

x to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

x Journal article(s) with results of the trial
x Trial protocol
☐ Statistical analysis plan (SAP)
x Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
x Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

(5) Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	From the protocol: "Subjects will be randomized in a 2:1 allocation of treatment vs control. Randomization will be stratified by investigational center and by prior radiation treatment (yes or no) and number of prior dilation treatments (i.e. less than 5 prior dilations versus ≥ 5prior dilations). Each treatment group will have its own randomization schedule within each participating center. For each randomization schedule, randomization will be performed using randomly permuted blocks." There is no specific information on the concealment of the allocation sequence.	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		PY
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias arising from the randomization process?		NA

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Some participants were unblinded before 6 months 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.	PN
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		PN
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	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
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		**High risk**
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	67 out of 79 for OPTILUME group and 44 out of 48 for the control group for PVR urine at 6 months => missing data for 15% patients in OPTILUME group and 8% in control group	N
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	Only descriptive results provided for this outcome.	N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	There is no explanation for the missing data.	Y
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		PY
Risk-of-bias judgement		**High risk**
Optional: What is the predicted direction of bias due to missing outcome data?		Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	The method for measuring PVR urine is not detailed in the CSR. Therefore, it might have differed between centres in the study. There is no information on the type of healthcare professional who measured this outcome.	PN
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Surgeons and investigators were not blinded to the intervention over the entire study period.	PY
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	There is no information on the methods used to assess PVR urine. The ultrasound method could imply some subjectivity from the assessor.	Y
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		PN
Risk-of-bias judgement		**Some concerns**
Optional: What is the predicted direction of bias in measurement of the outcome?		Favours experimental

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	This outcome was not prespecified in the protocol.	N
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	This outcome was not prespecified in the protocol. However, it was reported in the CSR and in the publication. Therefore, it could have been selected from other eligible outcome measurements.	Y
5.3 ... multiple eligible analyses of the data?	This outcome was not prespecified in the protocol. However, it was reported in the CSR and in the publication. Therefore, it could have been selected from other eligible analyses.	Y
Risk-of-bias judgement		**High risk**
Optional: What is the predicted direction of bias due to selection of the reported result?		Favours experimental

Overall risk of bias

Risk-of-bias judgement		**High risk**
Optional: What is the overall predicted direction of bias for this outcome?		Favours experimental

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Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)
TEMPLATE FOR COMPLETION

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne
on behalf of the RoB2 Development Group

Version of 22 August 2019

The development of the RoB 2 tool was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- N61), with the support of the host MRC ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures - MR/K025643/1), by MRC research grant MR/M025209/1, and by a grant from The Cochrane Collaboration.

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Study details

Reference	Elliott SP, Coutinho K, Robertson KJ, D'Anna R, Chevli K, Carrier S, Aube-Peterkin M, Cantrill CH, Ehlert MJ, Te AE, Dann J, DeLong JM, Brandes SB, Hagedorn JC, Levin R, Schlaifer A, DeSouza E, DiMarco D, Erickson BA, Natale R, Husmann DA, Morey A, Olsson C, Virasoro R. One-Year Results for the ROBUST III Randomized Controlled Trial Evaluating the Optilume® Drug-Coated Balloon for Anterior Urethral Strictures. J Urol. 2022 Apr;207(4):866-875. doi: 10.1097/JU.0000000000002346. Epub 2021 Dec 2. PMID: 34854748.

Study design

X Individually-randomized parallel-group trial

☐ Cluster-randomized parallel-group trial

☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental:	OPTILUME DCB	Comparator:	Standard of care endoscopic management as determined by the treating physician, including rigid rod dilation, DVIU, uncoated balloon dilation or a combination

Specify which outcome is being assessed for risk of bias

Patients reported outcomes at 30 days, 3 months and 6 months*:
- International Prostatic Symptom Score (IPSS)
- IPSS - QoL
- International Index of Erectile Function (IIEF)
- Periprocedural pain

*Patients were blinded to the treatment until 6 months. After this 6 months timepoint we assume that the risk of bias of these outcomes will be higher.

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Table 3 Results at 30 days, 3 months and 6 months

Is the review team's aim for this result…?

x to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

x Journal article(s) with results of the trial
x Trial protocol
☐ Statistical analysis plan (SAP)
x Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
x Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	From the protocol: "Subjects will be randomized in a 2:1 allocation of treatment vs control. Randomization will be stratified by investigational center and by prior radiation treatment (yes or no) and number of prior dilation treatments (i.e. less than 5 prior dilations versus ≥ 5prior dilations). Each treatment group will have its own randomization schedule within each participating center. For each randomization schedule, randomization will be performed using randomly permuted blocks." There is no specific information on the concealment of the allocation sequence.	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		PY
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias arising from the randomization process?		NA

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Some participants were unblinded before 6 months 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.	PN
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		PN
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Unclear how the analyses were conducted: ITT, per protocol, or other analysis? There is no clear explanation for the handling of missing data, which vary along time and are not the same for IPSS than for IIEF (slightly less patients at each timepoint). It was only stated in the CSR that failure carried forward analysis was performed for the IPSS outcomes.	N
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		PY
Risk-of-bias judgement		High risk
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	71 out of 79 for OPTILUME group and 43 out of 48 for the control group for IPSS and IPSS-QoL at 6 months => missing data for 10% patients in both groups 68 out of 79 for OPTILUME group and 30 out of 48 for the control group for IIEF at 6 months => missing data for 14% patients in OPTILUME group and for 38% patients in the control group	N
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	No sensitivity analysis was carried out for these outcomes.	N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	These outcomes are PROMS and patients could be unblinded before 6 months if they experienced recurrence symptoms and were unblinded after 6 months. Therefore the missingness of these outcome data may depend on its true value.	Y
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		Y
Risk-of-bias judgement		**High risk**
Optional: What is the predicted direction of bias due to missing outcome data?		Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	These outcomes are PROMs measured with structured self-administered questionnaires used in routine care for assessing urological symptoms (IPSS, IIEF) and for assessing pain (VAS).	PN
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	The same measurement methods were probably used in both groups.	PN
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Some participants (12/48, 25%) from the control group were unblinded before 6 months if they experienced recurrent stricture requiring intervention.	Y
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Even if patients were blinded to the intervention until 6 months, some patients were unblinded in case of medical necessity (stricture recurrence).	Y
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	The answer to 4.5 is "probably yes", because it can be assumed that the patients from control group who crossed over are likely to have been influenced by the knowledge of their treatment assignment when answering these questionnaires.	PY
Risk-of-bias judgement		**High risk**
Optional: What is the predicted direction of bias in measurement of the outcome?		Favours experimental

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	IPSS: is stated as an additionnal outcome to the primary efficacy and safety endpoints in the publication, but it was not mentioned as such in the protocol where only "percent responder at 6 months (IPSS)" was indicated as the 3rd secondary endpoint but also as one the ancillary endpoints, at 12, 24, 36, 48 and 60 months. The analyses at 30 days, 3 months and 6 months are not mentioned in the protocol. IPSS-QoL: is stated as an additionnal outcome to the primary efficacy and safety endpoints in the publication, but it was not mentioned in the protocol where only "QoL" was indicated as one the ancillary endpoints IIEF is mentioned as an additionnal outcome to the primary efficacy and safety endpoints in the publication, but it was not planned in the protocol	N
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	See above.	PY
5.3 ... multiple eligible analyses of the data?		NI
Risk-of-bias judgement		**High risk**
Optional: What is the predicted direction of bias due to selection of the reported result?		Favours experimental

Overall risk of bias

Risk-of-bias judgement		**High risk**
Optional: What is the overall predicted direction of bias for this outcome?		Favours experimental

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Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)
TEMPLATE FOR COMPLETION

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on behalf of the RoB2 Development Group

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Study details

Reference	Elliott SP, Coutinho K, Robertson KJ, D'Anna R, Chevli K, Carrier S, Aube-Peterkin M, Cantrill CH, Ehlert MJ, Te AE, Dann J, DeLong JM, Brandes SB, Hagedorn JC, Levin R, Schlaifer A, DeSouza E, DiMarco D, Erickson BA, Natale R, Husmann DA, Morey A, Olsson C, Virasoro R. One-Year Results for the ROBUST III Randomized Controlled Trial Evaluating the Optilume® Drug-Coated Balloon for Anterior Urethral Strictures. J Urol. 2022 Apr;207(4):866-875. doi: 10.1097/JU.0000000000002346. Epub 2021 Dec 2. PMID: 34854748.

Study design

X Individually-randomized parallel-group trial

☐ Cluster-randomized parallel-group trial

☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental:	OPTILUME DCB	Comparator:	Standard of care endoscopic management as determined by the treating physician, including rigid rod dilation, DVIU, uncoated balloon dilation or a combination

Specify which outcome is being assessed for risk of bias	Primary safety end point: freedom from a composite of serious device- or procedure related events including urethral fistula, unresolved *de novo* stress urinary incontinence or urethral rupture through 3 months.
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI	No subject experienced a primary safety end point event through 3 months (from the Elliott *et al.* publication).

0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Table: Primary Safety Endpoint – Freedom from Composite Serious Complications (from the CSR)

Endpoint	Control Arm	Optilume Arm
Serious device / procedure related complications at 3 months post-treatment	0/48 (0%)	0/79 (0%)
Formation of Fistula	*0/48 (0%)*	*0/79 (0%)*
Unresolved De Novo Stress Urinary Incontinence	*0/48 (0%)*	*0/79 (0%)*
Urethra Rupture or Burst	*0/48 (0%)*	*0/79 (0%)*

Is the review team's aim for this result…?

☐ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

x to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
x non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

x Journal article(s) with results of the trial
x Trial protocol
☐ Statistical analysis plan (SAP)
☐ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)

☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
x Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐ Personal communication with trialist
☐ Personal communication with the sponsor

(6) Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	From the protocol: "Subjects will be randomized in a 2:1 allocation of treatment vs control. Randomization will be stratified by investigational center and by prior radiation treatment (yes or no) and number of prior dilation treatments (i.e. less than 5 prior dilations versus ≥ 5prior dilations). Each treatment group will have its own randomization schedule within each participating center. For each randomization schedule, randomization will be performed using randomly permuted blocks." There is no specific information on the concealment of the allocation sequence.	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		PY
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias arising from the randomization process?		NA

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Some participants were unblinded before 6 months if they experienced recurrent stricture requiring intervention. Surgeons and investigators were not blinded to the intervention over the entire study period.	PN
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	We consider crossovers as non-adherences.	PY
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NI
Risk-of-bias judgement		**High risk**
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	For this outcome, the protocol states "Unless there is evidence of occurrence of a primary safety endpoint, subjects with missing data for the primary safety endpoint are presumed to not have experienced a primary safety endpoint." Therefore, we cannot be sure that this outcome is available for all, or nearly all, participants.	PY
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Surgeons and investigators were not blinded to the intervention over the entire study period.	Y
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Surgeons were not blinded to the type of treatment; this might have biased their assessment of the clinical status of the patient regarding formation of urethral fistula, unresolved *de novo* stress urinary incontinence or urethral rupture through 3 months after intervention (the 3 components of this composite safety outcome).	PY
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NI
Risk-of-bias judgement		**High risk**
Optional: What is the predicted direction of bias in measurement of the outcome?		Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	The protocol planned a descriptive analysis of this primary safety outcome.	PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		PN
5.3 ... multiple eligible analyses of the data?		PN
Risk-of-bias judgement		**Low risk**
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		**High risk**
Optional: What is the overall predicted direction of bias for this outcome?		Unpredictable

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Appendix E Partial use of GRADE

Table 34: Uncertainties of the evidence categorised according to the partial use of GRADE

Outcome	Design	Factors that may affect certainty of evidence					Number of patients		Effect estimate
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other	Optilume DCB	Dilation or DVIU	p-value[a]
Stricture-free rate at 6 months	1 RCT	High[b,c,d,e]	Indirectness issues are flagged[f]	1 study	No issues are flagged.	None	79	48	Risk difference Optilume vs dilation or DVIU: 44.4%, 95% CI 27.6 to 61.1 p-value: <0.0001[*, #,$]
Freedom from repeat intervention rate at 12 months	1 RCT	High[b,e,g]	Indirectness issues are flagged[f]	1 study	Imprecision issues are flagged[h]	None	79	48	p-value: <0.0001
Change in Qmax at 6 months (ml/s)	1 RCT	High[b,c,i,j,k]	Indirectness issues are flagged[f]	1 study	No issues are flagged.	None	79	48	Mean difference Optilume vs dilation or DVIU:+ 4.78 ml/s 90% CI 1.94 to 7.61 p-value: 0.0031[*, #,$]
Qmax at 30 days, 3 months, 6 months and 12 months	1 RCT	High[b,i,k,l]	Indirectness issues are flagged[f]	1 study	Imprecision issues are flagged[m]	None	79	48	NA
PVR at 30 days, 3 months, 6 months and 12 months	1 RCT	High[b,i,k,l,n]	Indirectness issues are flagged[f]	1 study	Imprecision issues are flagged[m]	None	79	48	NA

IPSS at 30 days, 3 months and 6 months	1 RCT	High[b,j,l,o,q]	Indirectness issues are flagged[f]	1 study	Imprecision issues are flagged[m]	None	79	48	NA
IPSS-QoL at 30 days, 3 months and 6 months	1 RCT	High[b,j,l,o,q]	Indirectness issues are flagged[f]	1 study	Imprecision issues are flagged[m]	None	79	48	NA
IIEF (overall satisfaction) at 30 days, 3 months and 6 months	1 RCT	High[b,j,l,p,q]	Indirectness issues are flagged[f]	1 study	Imprecision issues are flagged[m]	None	79	48	NA
Periprocedural pain at 30 days, 3 months and 6 months	1 RCT	High[b,j,l,q]	Indirectness issues are flagged[f]	1 study	Imprecision issues are flagged[m]	None	79	48	NA
Freedom from a composite of serious device- or procedure related events including: - urethral fistula, - unresolved de novo stress urinary incontinence or - urethral rupture through 3 months	1 RCT	High[b,e]	Indirectness issues are flagged[f]	1 study	Imprecision issues are flagged[m]	None	79	48	NA
All-cause mortality	1 RCT, 2 single-arm studies	NA	Indirectness issues are flagged[f,r]	NA[s]	Imprecision issues are flagged[m]	None	NA	NA	NA

Other adverse events	1 RCT, 2 single-arm studies	NA	Indirectness issues are flagged[f,r,t]	NA[s]	Imprecision issues are flagged[m]	None	NA	NA	NA

a: Use of an * indicates statistical significance versus a pre-specified alpha level, use of a # indicates a pre-specified analysis according to the SAP (for individual studies) or evidence synthesis protocol, use of a $ indicates control for multiplicity.
b: According to the protocol, randomisation was planned in a 2:1 allocation of treatment vs 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. Some participants were unblinded before 6 months 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.
c: Intention-to-treat analysis with multiple imputation of missing data was pre-specified and conducted.
d: 12 patients in the Optilume group and 7 patients in the control group (15% in each group) with missing data for this outcome. Sensitivity analysis was conducted with 5 different analyses that were all in the same directionality as the primary analysis.
e: As the surgeons and investigators were not blinded to the intervention over the entire study period, it 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.
f: The RCT was conducted in North America, not in Europe. 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 second-line treatment after stricture recurrence, but the majority of patients included in ROBUST III 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. It included different procedures (rigid rod dilation, DVIU, balloon dilation or a combination) which was a mix of PICO 1 and PICO 2 comparators (urethrotomy and dilation respectively). Additionally, there is no internationally agreed on single outcome measure, which defines stricture recurrence.
g: 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).
h: 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.
i: Missing data for 12/79 (15%) patients in intervention 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).
j: No sensitivity analysis was conducted for this outcome.
k: Even though the measurement tool for this performance outcome is not detailed in the study, it can be assumed that, like in most routine care situations, uroflowmetry is carried out in a fully automatic way without any need for medical staff to read out the results.
l: The analysis of the outcome was not pre-specified in the protocol.
m: Only descriptive statistics used to report the outcome. No confidence interval was provided.
n: 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.
o: 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.
p: Missing data for 11/79 (14%) patients in intervention group and 18/48 (38%) in control group for IIEF at 6 months. No explanation provided for the handling of missing data.
q: 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.

r: The single-arm prospective, interventional studies included for safety outcomes only were conducted in Latin American and North America, not in Europe. Inclusion criteria in these two studies are narrower than in the RCT, possibly resulting in more severe patients.
s: Variation in treatment effects between studies was not assessed, as only descriptive statistics were used to assess the outcome.
t: There was no data reported for the drug-related adverse events which were requested in the PICO question.

Source: Clinical study reports.
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.