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HEALTH TECHNOLOGY BRIEFING FEBRUARY 2019

Adstiladrin for high-grade, BCG unresponsive non-muscle-invasive bladder cancer

NIHRIO ID	8376	**NICE ID**	9951
Developer/Company	Ferring Pharmaceuticals Ltd Trizell Ltd	**UKPS ID**	650881

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Adstiladrin is currently in clinical development for the treatment of patients with high-grade non-muscle-invasive bladder cancer (NMIBC). It is being developed particularly for NMIBC that is not responsive to Bacillus Calmette-Guerin (BCG) therapy, the current main treatment option for early bladder cancer. Bladder cancer starts in the inner lining of the bladder and the most common symptom is passing blood in urine. NMIBC is an early bladder cancer and is the most common type. High-grade NMIBC means the cancer is more likely to grow and spread quickly and also more likely to come back after initial treatment.

Adstiladrin is given by catheter directly into the bladder. It consists of a type of virus that is able to introduce a gene into cells of the bladder. This gene then stimulates the cells of the bladder to produce high quantities of a protein that the body uses to fight cancer. This in turn enhances the body's natural defences against the cancer. If licensed, Adstiladrin will offer an advanced (gene) therapy treatment option for patients with high-grade NMIBC that are BCG unresponsive.

PROPOSED INDICATION

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

Patients with high-grade non-muscle-invasive bladder cancer (NMIBC) that are Bacillus Calmette-Guerin (BCG) unresponsive including papillary NMIBC alone (Ta or T1), carcinoma in situ (CIS) alone, or a combination of CIS and papillary disease.[a]

TECHNOLOGY

DESCRIPTION

Adstiladrin (rAd-IFN-alpha2b, nadofaragene firadenovec, previously known as Instiladrin) is a gene therapy consisting of an adenovirus containing the gene interferon (IFN)-alpha2b. Adstiladrin is given by catheter into the bladder where the virus introduces the active gene into cells of the bladder lining to do its work. The cell's internal machinery picks up the gene and translates its DNA sequence, resulting in the cells producing high quantities of interferon alpha-2b protein, a naturally occurring protein the body uses to fight cancer. This novel gene therapy approach turns the patient's own bladder wall cells into multiple interferon microfactories, enhancing the body's natural defences against the cancer.[1]

Adstiladrin is currently in phase III clinical development for the treatment of high-grade, BCG unresponsive NMIBC.[2] The proposed dose of Adstiladrin is 3x10^11viral particles (vps)/ml in 75 mL. The total dose will be given as a single, one-hour intravesical administration which may, depending on clinical response, be repeated every 3 months.[a]

INNOVATION AND/OR ADVANTAGES

Recombinant intravesical IFN alpha-2b protein demonstrated promising initial clinical results in NMIBC. Intravesical IFN alpha-2b gene delivery offers a novel approach and increases the duration of exposure to IFN alpha-2b. Recombinant adenovirus (rAd)-IFN-alpha2b is a replication-deficient adenovirus-based gene transfer vector that encodes the human IFN-alpha2b gene. Syn3, a polyamide surfactant, is incorporated into the drug formulation (rAd-IFN-alpha2b, Adstiladrin) to enhance adenoviral transduction of the bladder lining.

Improvement in rAd–IFN-alpha gene transfer and expression has been shown with Syn3 in both normal urothelium and human urothelial carcinoma that grows in mice. rAd-IFN-alpha2b gene therapy mimics the physiologic events associated with viral infection, which results in local rather than systemic IFN-alpha2b production and subsequent tumour regression.[3]

Adstiladrin is classified as an Advanced Therapy Medicinal Product (ATMP) by the European Medicines Agency.[b]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Adstiladrin does not currently have Marketing Authorisation in the EU/UK for any indication.

Adstiladrin is in phase III clinical development for malignant pleural mesothelioma.[4]

[a] information provided by company
[b] Information provided by Ferring Pharmaceuticals Ltd on UK PharmaScan

PATIENT GROUP

DISEASE BACKGROUND

Bladder cancer is cancer that starts in the inner lining of the bladder.[5] Bladder cancer can be classified by how far it has spread. If the cancerous cells are contained inside the inner lining of the bladder, it is described as non-muscle-invasive, early or superficial, i.e. NMIBC. This is the most common type of bladder cancer.[6,7] Early bladder cancer usually appears as small growths, shaped like mushrooms, which grow out of the bladder lining. This is called papillary bladder cancer. These growths can be surgically removed and they may never come back. However, some types of NMIBC are more likely to come back, including carcinoma in situ (CIS) and high-grade T1 tumours, both of which can grow quickly. CIS are flat cancers that do not grow out of the bladder wall, but the cancer cells look very abnormal; this is known as high-grade cancer. High-grade T1 tumours are superficial cancers that have grown from the bladder lining into a layer underneath, called the lamina propria.[7,8].High grade means the cancer is more likely to grow spread and come back after treatment.[9]

Bladder cancer is caused by changes to the cells of the bladder. It is often linked with exposure to certain chemicals, but the cause is not always known.[10] There are certain factors that can increase the risk for bladder cancer. These include smoking, exposure to chemicals such as arylamines and polycyclic aromatic hydrocarbons, exposure to water disinfection chemicals such as chlorine and trihalomethanes, treatment for some other cancers, other medical conditions such as diabetes and spinal cord injury, bladder infections and chronic bladder irritation, diet and alcohol intake, previous bladder cancer, and family history.[11]

The most common symptom of bladder cancer is blood in urine that is usually painless. Less common symptoms of bladder cancer include a need to urinate on a more frequent basis, sudden urges to urinate, and a burning sensation when passing urine.[12]

A diagnosis of bladder cancer, and some treatments for the condition, can have a significant impact on a patient's life. The emotional impact of living with bladder cancer can be huge which can sometimes trigger depression. If the bladder is removed, an alternative way of passing urine out of the body will be created during the operation. This is called urinary diversion. There are various types of urinary diversion such as urostomy, bladder reconstruction, and continent urinary diversion. Patients with bladder cancer may also have sexual problems.[13]

CLINICAL NEED AND BURDEN OF DISEASE

Bladder cancer accounted for 3% of all new cancer cases in 2015. In England in 2016, newly diagnosed registered cases of malignant neoplasms of bladder (ICD 10 code: C67) were 8,437, and directly age-standardised incidence rate in males was 27.3 per 100,000 and in females was 8.2 per 100,000.[14] Bladder cancer incidence rates are projected to fall by 34% in the UK between 2014 and 2035, from 20.44 cases per 100,000 (10,057 observed cases) to 13.43 cases per 100,000 population by 2035 (10,386 projected cases).[15,16]

At diagnosis, 70–80 % of bladder cancers are NMIBC.[17] This would be equivalent to between 5,906 and 6,750 of the newly diagnosed cases in England in 2016. Up to 50% of patients fail BCG, significantly increasing the risk of progression and death.[18] Approximately 10–20 % of complete responders eventually progress to muscle-invasive disease, compared with 66 % of non-responders. Patients with high-risk [high-grade T1 and/or CIS] represent a challenging group, with an increased 5-year risk of recurrence (up to 80%) and progression (up to 50%).[17] In 2017-18 there were 69,854 hospital admissions and 40,796 day cases in England for malignant neoplasm of bladder.[19]

Registered deaths in England due to bladder cancer in 2017 were 5,014.[20] Bladder cancer mortality rates are projected to fall by 14% in the UK between 2014 and 2035, from 11 deaths per 100,000 to 9 deaths per 100,000 people by 2035.[21]

Age-standardised one-year and five-year survival rates for patients aged 15 to 99 years diagnosed with bladder cancer in England between 2011 and 2015 were 75.0% and 56.4% respectively.[22] Bladder cancer survival is higher in men than women.[23]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Bladder cancer is treated by a multidisciplinary team that may include a urologist, a clinical oncologist, a pathologist, and a radiologist. The recommended treatment plan for NMIBC depends on the risk of the cancer returning or spreading beyond the lining of the bladder. This risk is calculated using a series of factors, including the number of tumours present in the bladder, whether the tumours are larger than 3cm (1 inch) in diameter, whether the patient has had bladder cancer before, and the grade of the cancer cells.[24] People with high-risk NMIBC have transurethral resection of a bladder tumour (TURBT) operation to remove the cancer from the bladder lining (TURBT procedure may be performed during the first cystoscopy, when tissue samples are taken for testing). Patients should be offered a second TURBT, within 6 weeks of the initial investigation. A CT scan or an MRI scan may also be required.[24,25]

The treatment option for patients with high-risk NMIBC includes either a course of BCG treatment (using a variant of the BCG vaccine), or an operation to remove the bladder (cystectomy). If BCG treatment does not work, or the side effects are too strong, the patient will be referred back to a specialist urology team. The patient should be offered regular follow-ups.[24]

The patient can have the growths removed with cystoscopy again if stage Ta or T1 bladder cancer comes back (relapses) after treatment. Biopsies are usually taken to check that the cancer is still at an early stage. If it is, the patient usually has chemotherapy or BCG treatment into the bladder. Then they go back to having regular cystoscopies to check the bladder. The patient may need more intensive treatment if the cancer is grade 3, at a more advanced stage than before, or CIS that has come back after treatment into the bladder.[25]

CURRENT TREATMENT OPTIONS

- For patients with high-grade NMIBC after one or two TURBT operations, NICE recommend to:[26]Offer the choice of intravesical BCG or radical cystectomy
- Offer induction and maintenance intravesical BCG to people having treatment with intravesical BCG. If induction BCG fails (because it is not tolerated, or bladder cancer persists or recurs after treatment with BCG), NICE recommend to refer the person's care to a specialist urology multidisciplinary team. For people in whom induction BCG has failed, the specialist urology multidisciplinary team should assess the suitability of radical cystectomy, or further intravesical therapy if radical cystectomy is unsuitable or declined by the person, or if the bladder cancer that recurs is intermediate- or low-risk.

PLACE OF TECHNOLOGY

If licensed, Adstiladrin will offer an advanced therapy treatment option for patients with high-grade NMIBC that are BCG unresponsive including papillary NMIBC alone (Ta or T1), CIS alone, or a combination of CIS and papillary disease.

CLINICAL TRIAL INFORMATION

Trial	NCT02773849, rAd-IFN-CS-003; Adstiladrin; phase III
Sponsor	FKD Therapies Oy
Status	Ongoing
Source of Information	Trial registry[2]
Location	USA
Design	Non-randomised (Open label), single group assignment
Participants	n=150 (planned); aged 18 years and older; NMIBC; high-grade; BCG unresponsive; received at least 2 previous courses of BCG within a 12 month period; have, at entry, confirmed by a pathology report Carcinoma in situ (CIS) only, Ta/T1 high-grade disease with concomitant CIS, or Ta/T1 high-grade disease without concomitant CIS life expectancy >2 years; Eastern Cooperative Oncology Group (ECOG) status 2 or less; absence of concomitant upper tract urothelial carcinoma or urothelial carcinoma within the prostatic urethra.
Schedule	Participants received intravesical administration of Adstiladrin into the bladder. No further details about the treatment schedule are specified.
Follow-up	Active treatment duration: The active treatment duration will be depending on the clinical response, be repeated every 3 months up to a maximum of four instillations in the first 12 months. After Month 12, patients will be assessed on a 3 monthly basis for further treatment at the discretion of the treating physician (per last protocol version V6).[c] Follow up duration: Per last protocol version V6 (Oct 2018) long term follow-up safety and survival data will be collected for all patients dosed, including information regarding progression to invasive disease and cystectomy for up to 4 years from first dose.[c]
Primary Outcomes	To evaluate the complete response rate in patients with CIS, with or without concomitant high-grade Ta or T1 papillary disease. [Time frame: 12 months]
Secondary Outcomes	Time frame: 12 months - To determine the incidence of cystectomy in the study - To determine the overall survival in all patients - To determine the anti-adenoviral antibody levels for correlation to response rate

[c] Information provided by company

	Time Frame: up to 12 months - To evaluate the rate of event-free survival, where event-free survival is defined as high-grade recurrence free survival in patients with high-grade Ta or T1 disease (without concomitant CIS) Time frame: 24 months - To evaluate the safety of Adstiladrin Time frame: up to 24 months - To evaluate the durability of complete response in patients with CIS (with or without concomitant Ta or T1 papillary disease) who achieve a complete response. - To evaluate the durability of event-free survival in patients with high-grade Ta or T1 papillary disease (without concomitant CIS), who have no recurrence of high-grade Ta or T1 papillary disease. Time frame: 36 months - To determine the durability of response during the long term follow up period.
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as June 2019.

Trial	NCT01687244, rAd-IFN-CS-002; Adstiladrin; phase II
Sponsor	FKD Therapies Oy
Status	Published
Source of Information	Publication,[27] trial registry[4]
Location	USA
Design	Randomised, parallel assignment, open label
Participants	n=40; aged 18years and older; NMIBC; high grade; BCG-refractory or relapsed.
Schedule	Participants were randomised to Adstiladrin 1x10^11vps/ml or Adstiladrin 3x10^11 vps/ml. The total dose will be given as a single, one-hour intravesical administration which may, depending on clinical response, be repeated every 3 months up to a maximum of 4 instillations.
Follow-up	Active treatment duration: not specified. Follow-up duration up to 360 days
Primary Outcomes	Incidence of high grade-recurrence free survival at 360 days [Time frame: 360 days]
Secondary Outcomes	Time frame: 360 days - Safety of Adstiladrin - Incidence of cystectomy in all patients - Overall survival in all patients. - Number of patients with elevated IFN alpha2b protein levels in serum - Number of patients with elevated levels of anti-IFN alpha2b antibodies in serum

	- Number of patients with elevated levels of anti-adenovirus type 5 antibodies in serum Time frame: 90 days - Incidence of high grade recurrence-free survival at 3 months (90 days). Time frame: 103 days - Number of patients with elevated levels of viral vector in blood - Number of patients with elevated levels of viral vector in urine - Number of patients with elevated IFN alpha2b protein levels in urine Time frame: 180 days - Incidence of high grade-recurrence-free survival at 6 months (180 days). Time frame: 270 days - Incidence of high grade-recurrence-free survival at 9 months (270 days).
Key Results	Forty patients received Adstiladrin (1 × 10^11 vp/mL, n = 21; 3 × 10^11 vp/mL, n = 19) between November 5, 2012, and April 8, 2015. Fourteen patients (35.0%; 90% CI, 22.6% to 49.2%) remained free of HG recurrence 12 months after initial treatment. Comparable 12-month HG RFS was noted for both doses. Of these 14 patients, two experienced recurrence at 21 and 28 months, respectively, after treatment initiation, and one died as a result of an upper tract tumour at 17 months without a recurrence.
Adverse effects (AEs)	Adstiladrin was well tolerated; no grade four or five adverse events (AEs) occurred, and no patient discontinued treatment because of an adverse event. The most frequently reported drug-related AEs were micturition urgency (n = 16; 40%), dysuria (n = 16; 40%), fatigue (n = 13; 32.5%), pollakiuria (n = 11; 28%), and haematuria and nocturia (n = 10 each; 25%).
Expected reporting date	-

ESTIMATED COST

The cost of Adstiladrin is not yet known.

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Bladder cancer: diagnosis and management (NG2). February 2015.
- NICE quality standard. Bladder cancer (QS106). December 2015.
- NICE interventional procedure guidance in development. Transurethral laser ablation for non-muscle invasive bladder cancer (GID-IPG10100). Expected date of issue to be confirmed.

- NICE interventional procedure guidance in development. Electrically-stimulated intravesical chemotherapy for non-muscle invasive bladder cancer (IPG638). January 2019.
- NICE interventional procedure guidance. Intravesical microwave hyperthermia and chemotherapy for non-muscle-invasive bladder cancer (IPG628). September 2018.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. Clinical Commissioning Policy: Robotic Assisted Surgery for Bladder Cancer. July 2016. 16033/P

OTHER GUIDANCE

- NHS England. Guidelines for the Management of Bladder Cancer. 2016.[28]
- European Society for Medical Oncology (ESMO). Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. 2014.[29]

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