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Pexastimogene devacirepvec (pexa-vec) for hepatocellular carcinoma – first line

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LAY SUMMARY

Liver cancer was the 17th most diagnosed cancer in the UK in 2014. This type of cancer develops from the main liver cells, called hepatocytes. Hepatocellular carcinoma is more common in people who have long-term damage to the liver tissues (cirrhosis). It is also more likely to develop in men than in women and it becomes more common as people get older.

Pexastimogene devacirepvec is under development for the first line treatment of advanced hepatocellular carcinoma. The drug is an engineered virus with a gene that promotes the body's natural response to cancerous cells in the liver. This treatment is administered by injection directly into the cancerous cells in the liver or through the veins. It is designed to selectively target and destroy cancer cells through three different ways: direct destruction of the cancer cells, reduction of the blood supply to tumours and the stimulation of the body's defense against cancer cells. If licensed, pexastimogene devacirepvec may offer an additional treatment option for patients. Currently, there are few treatment options for advanced hepatocellular carcinoma patients, with only one drug, sorafenib, approved for the first line treatment of advanced hepatocellular carcinoma.

TARGET GROUP

Advanced Hepatocellular carcinoma (HCC) – first line, not eligible for locoregional therapies.

TECHNOLOGY

DESCRIPTION

Pexastimogene devacirepvec (Pexa-vec; JX-594) is under development for the treatment of Hepatocellular carcinoma (HCC). Pexa-vec is a thymidine kinase-deleted vaccinia virus expressing human GM-CSF (hGM-CSF) with oncolytic activity. It may selectively infect and lyse tumour cells. The deletion of the thymidine kinase gene increases the tumour selectivity of vaccinia by limiting viral replication to transformed cells. hGM-CSF expression by this agent may help recruit antigen processing cells, such as dendritic cells and macrophages, to virally infected tumour cells, initiating a systemic anti-tumoural immune response. It also selectively replicates and destroys cancer cells with epidermal growth factor receptor/ ras pathway activation.[1]

Existing treatment options for HCC are liver resection and lobectomy (surgery) to remove the tumour and the surrounding tissues in the liver, liver transplantation, and locoregional therapies including radio frequencey ablation (RFA) and transarterial chemotherapy embolization (TACE) to kill cancer cells.[2] Sorafenib is the only drug that is currently approved for the first line treatment of advanced HCC in patients not eligible for, or after these locoregional therapies.[3]

In the ongoing phase III trial (PHOCUS), subjects in the experimental arm receive pexastimogene devacirepvec as 3 bi-weekly intratumoural injections of 1e9 pfu (plaque forming units) at day 1 and during weeks 2 and 4, followed by sorafenib (taken orally) starting at week 6. Subjects in the control arm receive 400 mg of sorafenib, twice daily starting on day 1.[4]

Pexastimogene devacirepvec is also under development for the following indications:[5]

- Breast cancer
- Soft tissue sarcoma
- Several solid tumours
- Renal cell carcinoma

INNOVATION and/or ADVANTAGES

If licensed, pexastimogene devacirepvec may offer an additional treatment option for patients with HCC. This treatment is advantageous in that it is designed to selectively target and destroy cancer cells. Currently, there are few first line treatment options for advanced HCC patients, with only one drug, sorafenib, approved for the treatment of HCC. With a low five-year survival rate, especially for patients diagnosed at later stages of disease, and limited available therapies, new treatments are urgently needed.[6]

DEVELOPER

Transgene SA and SillaJen Inc.

PATIENT GROUP

BACKGROUND

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, which develops from the main liver cells, called hepatocytes.[7] Most patients with HCC have liver cirrhosis, which develops following long periods of chronic liver disease. Cirrhosis is characterized by a decrease in hepatocyte proliferation, indicating an exhaustion of the regenerative capacity of the liver, and results in an increase in fibrous tissue and a destruction of liver cells, which may ultimately lead to the development of cancerous nodules.

Half of all cases of HCC are associated with hepatitis B virus infection, with a further 25% associated with hepatitis C virus. Other risk factors for developing HCC include: alcoholic liver disease, non-alcoholic steatohepatitis, intake of aflatoxin-contaminated food, diabetes and obesity.[8] Liver cancer is much more likely to develop in men than in women; one in 105 men and one in 195 women will be diagnosed with liver cancer during their lifetime. More than 44% of liver cancer cases in the UK each year are diagnosed in people aged 75 and over with the highest incidence rates in people aged 85-89 (data from 2012-2014).[9]

The symptoms of liver cancer may include: weight loss, a swollen abdomen, jaundice, loss of appetite over a period of a few weeks, being sick, feeling full or bloated after eating, even after a small meal, itching, a sudden worsening of health in somebody with known chronic hepatitis or cirrhosis, a high temperature and sweating.[10] HCC is usually diagnosed using a combination of blood tests (liver function tests, urea and electrolytes, tumour markers – particularly alpha fetoprotein), ultrasound, CT or MRI scans, biopsy (of liver tumour tissue) and laparoscopic investigation.[11]

Treatment and survival rates depend on the cancer stage at diagnosis. In relation to all stages of the disease, for adults diagnosed with liver cancer in England, almost 35 out of 100 people (almost 35%) will survive their cancer for 1 year or more after diagnosis; approximately 10 in 100 people (more than 10%) will survive their cancer for 5 years or more after they are diagnosed.[12] The symptoms of HCC in addition to the side-effects of treatment may significantly impact the quality of life of individuals with the condition, who may experience pain, fatigue, diarrhea and loss of appetite. Nine out of ten patients reported experiencing pain over their HCC treatment course in a qualitative analysis.[13]

CLINICAL NEED and BURDEN OF DISEASE

In 2014, liver cancer was the seventeenth most common cancer in the UK.[9] Incidence rates for liver cancer are projected to rise by 38% in the UK between 2014 and 2035, to 15 cases per 100,000 people by 2035.[9] There were 5,550 new cases of this type of cancer, accounting for 2% of total cancer cases in UK, during the same year.[9] In 2015-16, there were 4,502 hospital admissions, 6,981 finished consultant episodes and 22,033 bed days due to malignant neoplasm: liver cell carcinoma (C22.0) in England.[14]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology appraisal guidance in development. Regorafenib for previously treated unresectable hepatocellular carcinoma (ID991). Expected date of issue to be confirmed.
- NICE Technology appraisal guidance in development. Lenvatinib for untreated advanced unresectable hepatocellular carcinoma (ID1089). Expected date of issue to be confirmed.
- NICE Technology appraisal guidance in development. Hepatocellular carcinoma (advanced and metastatic) – sorafenib (first line) (review of TA189) (ID1012) – CDF rapid reconsideration process. Expected date of issue to be confirmed.
- NICE Technology appraisal guidance in development. Nivolumab for untreated advanced hepatocellular carcinoma (ID1248). Expected date of issue to be confirmed.
- NICE Technology appraisal. Sorafenib for the treatment of advanced hepatocellular carcinoma (TA189). May 2010.
- NICE MedTech innovation briefing. SIR-Spheres for treating inoperable hepatocellular carcinoma (MIB63). March 2016.
- NICE MedTech innovation briefing. TheraSphere for treating operable and inoperable hepatocellular carcinoma (MIB62). March 2016.
- NICE Interventional procedures guidance. Chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation for primary and metastatic liver cancer (IPG488). May 2014.
- NICE Interventional procedures guidance. Selective internal radiation therapy for primary hepatocellular carcinoma (IPG460). July 2013
- NICE Interventional procedures guidance. Irreversible electroporation for treating primary liver cancer (IPG444). February 2013.
- NICE Interventional procedures guidance. Ex-vivo hepatic resection and reimplantation for liver cancer (IPG298). April 2009.
- NICE Interventional procedures guidance. Microwave ablation of hepatocellular carcinoma (IPG214). March 2007.
- NICE Interventional procedures guidance. Laparoscopic liver resection (IPG135). July 2005.
- NICE Interventional procedures guidance. Radiofrequency ablation of hepatocellular carcinoma (IPG2). July 2003.
- NICE quality standard. Liver disease (QS152). June 2017.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. Clinical commissioning policy: the use of sterotactic ablative radiotherapy (SABR) as a treatment option for patients with hepatocellular carcinoma or cholangiocarcinoma. 16022/P. July 2016.
- NHS England. 2013/14 NHS standard contract for specialist liver disease service (children). E03/S (HSS)/d.
- NHS England. Intrim clinical commissioning policy statement: selective internal radiotherapy (SIRT). B01/PS/a. June 2013.

OTHER GUIDANCE

No other guidance is currently available.

CURRENT TREATMENT OPTIONS

The treatment of HCC depends on the stage of cancer at diagnosis. The NHS uses the Barcelona clinic liver cancer staging system to define liver cancer stages, as follows:[15]

- Stage 0: single tumour <2cm, patient feels well and liver is functioning normally
- Stage A: single tumour <5cm or up to 3 tumours all <3cm, patient feels well and liver is functioning well
- Stage B: multiple tumours, patient feels well and liver is functioning well.
- Stage C: cancer spread to the blood vessels, lymph nodes or other organs, patient does not feel well, and liver is functioning
- Stage D: severe liver damage or patient does not feel well and liver is functioning poorly

Curative treatment is possible for HCC if it is at Stage A when diagnosed. Treatments available for Stage A HCC are:[16,17]

- Surgical liver resection – removal of a section of the liver recommended for those with minimal liver damage and localised cancer
- Liver transplant – recommended for those with a single tumour <5cm or less than 3 tumours each <3cm or a good response to other treatments with no tumour growth in the last 6 months
- Microwave/radiofrequency ablation – targeting tumours with microwaves or radio waves (via small electrodes introduced percutaneously, laparoscopically or surgically) with the aim of shrinking the tumour. This is recommended for treatment of early cancer in tumours <5cm

Treatments available for Stage B and C HCC aims to slow the progression of the cancer, relieve symptoms and prolong life but cannot sure the cancer. These treatments include: [16,17]

- Chemotherapy – specifically the TACE procedure where chemotherapy medication and small plastic beads are injected into the hepatic artery via a catheter inserted into the femoral artery (in the groin), with the aim of slowing cancer growth
- Alcohol injections – recommended for small tumours as alcohol dehydrates the cells
- Sorafenib – oral medication which disrupts blood supply to liver tumours and slows their growth (not available in the NHS)

EFFICACY and SAFETY

Trial	Hepatocellular carcinoma study comparing vaccinia virus based immunotherapy plus sorafenib vs sorafenib alone; NCT02562755, GDC40000633, NCI-2016-00198, EudraCT-2014-001985-86, 200385, GDCT0188227; phase III

Sponsor	Sillajen Biotherapeutics and Lee's Pharmaceutical Holdings Ltd
Status	Ongoing
Source of Information	Trial registry[18]
Location	EU (incl UK), USA, Canada Asia, NZ and Australia
Design	Randomised, active-controlled, parallel groups trial
Participants	n=600 (planned); aged ≥ 18 years; histological/cytological diagnosis of primary HCC; advanced stage HCC (Barcelona clinic liver cancer stage c or b per American association for the study of liver disease guidelines); Child-Pugh class A Note: this is not an exhaustive list of the inclusion criteria
Schedule	Subjects were randomized in a 1:1 ratio into two arms: Arm I –subjects receive pexastimogene devacirepvec as 3 bi-weekly intratumoural injections of 1e9 pfu (plaque forming units) at day 1 and during weeks 2 and 4, followed by sorafenib (taken orally) at week 6 Arm II - subjects receive 400 mg of sorafenib, twice daily starting on day 1
Follow-up	Not reported
Primary Outcomes	Overall survival from the date of randomisation to the date of death due to any cause up to study completion (approximately 53 months)
Secondary Outcomes	Time to progression from date of randomisation to the date of first documented radiographic tumour progression up to 53 months. Progression free survival from date of randomisation to the date of first documented radiographic tumour progression or death, whichever occurs first, assessed up to 53 months. Overall response rate from the date of randomisation until disease progression, up to 53 months. Disease control rate from date of randomisation to end of participation in the study up to 53 months. Proportion of patients whose best overall response during their participation in the study is either CR, PR, or stable disease. Incidence of adverse events (AEs) and serious adverse events (SAEs) from date of randomisation to end of participation in the study, up to 53 months. Assessed by the NCI CTCAE (version 4.03). Incidence of AEs and SAEs will be reported. Time to symptomatic progression from randomisation until the first documented event of symptomatic progression, up to 53 months
Key Results	-
Adverse effects (AEs)	-

Expected reporting date	Primary completion date reported as Oct 2017

Trial	A clinical study to evaluate the biological effects of pre-operative Intravenous administration of JX-594 (thymidine kinase-deactivated vaccinia virus plus GM-CSF) prior to planned surgical resection of locally advanced/poor prognosis or metastatic cancers; GDCT0243540, UKCRN-19097, ISRCTN13913966, EudraCT-2012-000704-15; phase II
Sponsor	University of Leeds
Status	Ongoing
Source of Information	ISRCNT registry, Global data[19,20]
Location	UK
Design	Non-randomised study
Participants	n=40 (planned); aged ≥ 18 years; histologically proven or radiological findings consistent with locally advanced/poor prognosis or metastatic cancer; planned for surgical resection (curative or palliative) of primary or metastatic disease as part of standard clinical care. Note: this is not an exhaustive list of the inclusion criteria
Schedule	Subjects receive pre-operative intravenous administration of JX-594
Follow-up	Not reported
Primary Outcomes	Tissue and blood presence of JX-594
Secondary Outcomes	Not reported
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Not reported

Trial	A phase IIa study of modified vaccinia virus to treat sorafenib-naïve advanced liver cancer (FLASH); NCT01636284, JX594-IV-HEP021, 2012-000591-42, EudraCT-2012-000591-42, CDR736830;
Sponsor	Jennerex Biotherapeutics
Status	Completed but unpublished
Source of Information	Trial registry[21]
Location	EU (not UK), Korea, Republic of Spain, United States
Design	Non-randomised, uncontrolled
Participants	n=16; aged ≥ 18 years; histologic or cytologic confirmation of advanced primary hepatocellular carcinoma (HCC); measurable tumour (at least one tumour with ≥1 cm longest diameter of contrast-enhancement during the arterial phase on CT scanning). Note: this is not an exhaustive list of the inclusion criteria

Schedule	Subjects received five weekly intravenous (IV) infusions on days 1, 8, 15, 22 and 29. After day 43, if their disease has improved or remained stable and they have not started other cancer therapy, they may have been able to continue to receive JX-594 via IV infusion every three weeks. This treatment extension may have continued until radiologic progressive disease, initiation of other cancer therapy, or subject withdrawal
Follow-up	Not reported
Primary Outcomes	Tumour response [time frame: CT scans evaluated at Weeks 6, 12, 18, 24, 30, 36, 42, 48] CT scans every six weeks until documented progression or date of death, whichever comes first, assessed up to 104 weeks
Secondary Outcomes	Safety profile of JX-594 [time frame: safety assessments related to JX-594 up to 28 days after last IV infusion] Safety assessed by the number of adverse events and serious adverse events up to 28 days after last JX-594 administration for an expected average of 52 weeks Time to progression [time frame: From the earliest date of either documented progression or death of any cause, assessed up to 104 weeks] Overall survival [time frame: from date of final clinic visit until date of death, assessed up to 104 weeks] After radiographic progression, beginning other cancer therapy, or early withdrawal, patients and/or their specified contacts continued to be contacted approximately every 4 weeks for survival and information on subsequent anti-cancer therapy including dose, duration, significant associated toxicities and efficacy
Key Results	Not reported
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as June 2013

Trial	A phase IIb study of modified vaccinia virus to treat patients advanced liver cancer who failed sorafenib (TRAVERSE); NCT01387555, JX594-HEP018, CDR703389, EudraCT-2011-000051-16, 2011-000051-16, KCT0000519, HEP018;
Sponsor	Jennerex Biotherapeutics
Status	Completed
Source of Information	Trial registry[22]
Location	EU (not UK), Canada, Hong Kong, Korea, Republic of, Taiwan, United States
Design	Randomised, controlled, open label
Participants	n=129; aged ≥ 18 years; diagnosis of primary hepatocellular carcinoma (HCC) by tissue biopsy (histological/cytological diagnosis), or clinical diagnosis; previously treated with sorafenib

	for ≥ 14 days and has discontinued sorafenib treatment at least 14 days prior to randomisation due to either intolerance or radiographic progression (note: sorafenib is not required to be the most recent treatment received for HCC). Note: this is not an exhaustive list of the inclusion criteria
Schedule	Arm I: subjects received JX-594 recombinant vaccinia GM-CSF, at a dose of 1 e^9 pfu (plaque forming units) total dose on each of six treatments, on days 1, 8, 22, week 6, week 12, and week 18 plus best supportive care as needed. Arm II: subjects received best supportive care as needed
Follow-up	Not reported
Primary Outcomes	Survival (CT scan every six weeks until progression or death, assessed up to 21 months) Determine overall survival for patients receiving JX-594 plus best supportive care (arm I) compared with those patients receiving best supportive care (arm II) in patients with advanced HCC who have failed sorafenib treatment, CT scan every six weeks until progression or death, assessed up to 21 months
Secondary Outcomes	Time to tumour progression [time frame: CT scan every six weeks until progression or death, assessed up to 21 months] Determine time-to-tumour-progression for arm I compared with arm II based on mRECIST for HCC. Quality of life [time frame: assessed up to 21 months (average)] Determine the quality of life of patients treated in arm I compared with arm II Tumour response [time frame: CT scan every 6 weeks until progression or death, assessed up to 21 months (average)] Determine tumour response based on mRECIST for HCC of arm I versus arm II Safety profile of JX594 [time frame: assessed up to 21 months (average)] Safety will be assessed by the number of adverse events and serious adverse events Time-to-symptomatic-progression [time frame: assessed up to 21 months (average)] Determine time to progression of arm I compared to arm II
Key Results	Pexa-Vec in combination with best supportive care (BSC) was found to be ineffective.
Adverse effects (AEs)	The most frequent adverse events were mild to moderate fever, chills, headache, gastro-intestinal symptoms like anorexia,

	vomiting. Transient hypotension and grade 1 Pexa-Vec-containing pustules were observed during the study. Procedure related haemorrhage and sepsis along with injection site pain were observed. Procedure related deaths were not observed during the study.
Expected reporting date	Study completion date reported as December 2011

Trial	A study of recombinant vaccinia virus prior to sorafenib to treat unresectable primary hepatocellular carcinoma; NCT01171651, JX594-HEP016, CDR682736, phase II
Sponsor	Sillajen Biotherapeutics
Status	Completed
Source of Information	Trial registry[23]
Location	Korea, Republic of
Design	Non-randomised, open label
Participants	n=25; ≥ aged 18 years; histological confirmation or clinical/laboratory diagnosis of primary hepatocellular carcinoma (HCC); cancer is not surgically resectable for cure. Note: this is not an exhaustive list of the inclusion criteria
Schedule	Subjects received JX-594 intravenously and intratumourally prior to standard sorafenib therapy. Subjects received a total dose of 1e9 per treatment starting with one IV dose on day 1 and injected intratumourally in 1-5 intrahepatic tumours on day 8 and 22. Starting on day 25 (3 days after the final JX-594 dose) subjects initiated oral sorafenib therapy twice daily according to standard approved guidelines. An optional maintenance JX-594 dose may have be given intratumourally at week 12 (sorafenib briefly interrupted)
Follow-up	-
Primary Outcomes	Determine safety and tolerability of intravenous infusion of JX-594 followed by intratumoural injections with JX-594 prior to standard sorafenib therapy [time frame: safety evaluations through 28 days after last dose of JX-594] Adverse events collected and assessed to assess safety and tolerability through 28 days after last dose of JX-594 (or until all events considered probably or possibly related to JX-594 were resolved, stabilized, or returned to baseline status)
Secondary Outcomes	Determine disease control rate (DCR) at 12 weeks [time frame: disease control and response assessment at 12 weeks from first JX-594 dose]

	DCR: confirmed complete response, partial response or stable disease based on modified RECIST and/or Choi response criteria Determine radiographic response rate [time frame: periodically throughout study participation (average of up to 1 year)] Response rate evaluation based on modified RECIST and/or Choi response criteria Determine overall survival time [time frame: ongoing (average of 1 year)]
Key Results	JX-594 administered intravenously and intratumorally prior to standard sorafenib therapy has been found to be effective in subjects with unresectable primary HCC.
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as December 2015.

Trial	A study of recombinant vaccinia virus to treat unresectable primary hepatocellular carcinoma; NCT00554372, JX594-IT-HEP007, CDR577189, phase IIa
Sponsor	Sillajen Biotherapeutics
Status	Completed
Source of Information	Trial registry[24]
Location	Canada, Korea, Republic of, United States
Design	Randomised study, open label
Participants	n=30; ≥ aged 18 years; histological confirmation or clinical/laboratory diagnosis of primary hepatocellular carcinoma (HCC); cancer is not surgically resectable for cure Note: this is not an exhaustive list of the inclusion criteria.
Schedule	Arm I (low dose): subjects received $1x10^8$ pfu (plaque forming units) of JX-594 (recombinant vaccinia virus) intratumourally in 1-5 intrahepatic tumours on 1, 15, and 29 days. Arm II (high dose): subjects received $1x10^9$ pfu of JX-594 (recombinant vaccinia virus) intratumourally in 1-5 intrahepatic tumours on 1, 15, and 29 days.
Follow-up	-
Primary Outcomes	Proportion of subjects achieving disease control (non-progressive Disease) at 8 weeks after initiation of treatment - Initial progression status and response assessment at 8 weeks from first dose Proportion of subjects achieving disease control at 8 weeks based on a modified response evaluation criteria in solid tumours v1.0 (mRECIST). Per mRECIST for target lesions as assessed by dynamic

	contrast enhanced dynamic MRI: complete response (CR), disappearance of all tumour(s); partial response (PR), >=30% decrease in the sum of longest diameter (LD) of tumour(s) taking as reference the baseline sum; stable disease (SD), any cases that do not qualify for PR or progressive disease (PD); PD, any increase of >= 20% in the sum of LD of tumour(s) taking as reference the baseline sum. Disease control (DC) = CR or PR or SD. For mRECIST criteria, new tumour(s) that developed within the liver were measured (a new tumour was defined as a malignant tumour not present at baseline, was ≥ 1 cm in LD had typical hypervascular features of HCC). Their maximum diameter(s) were included in the sum of the maximum diameter; new tumours were not considered evidence for progression
Secondary Outcomes	Safety and tolerability of JX-594 administered at two dose levels [time frame: safety and tolerability were evaluated throughout the 8 week period of study participation] Treatment-related serious adverse events in patients treated at two dose levels Number of subjects achieving disease control as determined using intrahepatic modified RECIST Criteria [Time Frame: At week 8] Number of subjects achieving disease control (non-progressive disease) at 8 weeks after treatment was initiated based on modified response evaluation criteria in solid tumours for HCC (mRECIST for HCC). mRECIST for HCC adopted the concept of viable tumour as tumour tissue showing uptake in arterial phase of contrast enhanced radiologic imaging techniques. Per mRECIST for HCC, for target lesions as assessed by contrast enhanced dynamic MRI: CR, disappearance of any intratumoural arterial enhancement in all target (viable) lesions; PR, >=30% decrease in the sum of diameters of viable target lesions; SD, any cases that do not qualify for PR or progressive disease PD; PD, any increase of >= 20% in viable target lesions Median overall survival [time frame: to 760 days post treatment] Overall survival after treatment in days
Key Results	The median overall survival (OS) of patients receiving the high dose was significantly improved (14.1 m) compared to the OS of patients receiving the low dose (6.7 m) with a hazard ratio of 0.39[25]
Adverse effects (AEs)	The most common serious adverse event, reported in 12.5% of arm II (high dose) subjects, was occurrence or risk of bile duct obstruction. The most common serious adverse events (reported in > 10% of JX-594 (recombinant vaccinia virus) treated subjects) included:

	nausea, vomiting, pyrexia, chills and headache. Note, this is not an exhaustive list [5/55].
Expected reporting date	Study completion date reported as December 2011.

ESTIMATED COST and IMPACT

COST

The cost of pexastimogene devacirepvec is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☐ Other:

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other:

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs:

☐ Other reduction in costs:

☐ Other:

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified:

☒ None identified

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