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HEALTH TECHNOLOGY BRIEFING SEPTEMBER 2020

ABBV-951 for motor fluctuations in Parkinson's disease

NIHRIO ID	27135	**NICE ID**	10372
Developer/Company	AbbVie Ltd	**UKPS ID**	655489

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

ABBV-951 is currently in clinical development for the treatment of motor fluctuations in Parkinson's Disease (PD). PD is a progressive neurological disease which is caused by a loss of nerve cells in a particular part of the brain and a reduction in the levels of the chemical messenger dopamine. Loss of these nerve cells and a reduction in dopamine levels results in motor symptoms such as tremor, slow movement and muscle stiffness, which impact quality of life. As PD progresses, symptoms may re-emerge between doses with current treatment options, this is known as "wearing off".

ABBV-951 is administered under the skin (subcutaneous infusion) to deliver therapeutic quantities of the drugs levodopa and carbidopa. Levodopa can be converted by the body into dopamine in order to supplement the low levels of dopamine in PD patients and improve motor symptoms. Carbidopa makes more levodopa available for transport into the brain. ABBV-951 eliminates the 'wearing off' effect by providing a continuous infusion of levodopa into the bloodstream so there is less fluctuation in dopamine levels and improved motor control. If licenced, ABBV-951 would provide an additional treatment option for PD patients who are levodopa responsive and who have inadequately controlled motor fluctuations.

PROPOSED INDICATION

Adults aged 30 years and older with idiopathic Parkinson's Disease (PD) that is levodopa-responsive who have inadequately controlled motor fluctuations.[1]

TECHNOLOGY

DESCRIPTION

ABBV-951 (a combination of foslevodopa + foscarbidopa) is a novel levodopa/carbidopa prodrug which can be administered through a minimally invasive subcutaneous infusion and provide therapeutic levels of levodopa.[2] Levodopa is a prodrug of dopamine that is administered to patients with PD due to its ability to cross the blood-brain barrier (BBB).[3] Once it has passed through the BBB, and into the brain, levodopa is metabolised to dopamine and supplements the low endogenous levels of dopamine to improve nerve conduction and assist the movement disorder symptoms in PD. Levodopa can be metabolised to dopamine on either side of the BBB[3,4] and so it is generally administered with a dopa decarboxylase inhibitor, like carbidopa, to prevent metabolism until after it has crossed the BBB.[3] The addition of carbidopa allows lower doses of levodopa to be used which reduces the risk of side effects from levodopa.[4]

ABBV-951 is currently in clinical development for the treatment of motor fluctuations in PD. In the phase III clinical trial (NCT03781167, EudraCT 2018-002144-85) patients are given ABBV-951 which consists foslevodopa and foscarbidopa via continuous subcutaneous infusion for 52 weeks.[1,5]

INNOVATION AND/OR ADVANTAGES

Early stage PD symptoms are well managed with oral treatment. However, as PD progresses, symptoms are no longer well controlled by oral medication due to the short half-life of levodopa and a narrowing therapeutic window, resulting in "wearing off".[2] In 40%-50% of patients, motor fluctuations will develop within five years of chronic levodopa treatment and in 70%-80% of patients after 10 years of treatment.[6]

Duodopa (carbidopa and levodopa) is currently approved in Europe and works by continually delivering a combination of carbidopa and levodopa in a suspension form (gel) directly into the duodenum/jejunum of the intestines by a pump for up to 16 hours.[7,8] Duodopa provides a continuous infusion of carbidopa-levodopa therapy which reduces the fluctuations of carbidopa-levodopa levels in the bloodstream compared to oral medications, which improves the daily "on" and "off" times compared to oral carbidopa-levodopa therapy. However, this delivery requires percutaneous endoscopic gastrostomy tube (PEG-J) placement which comes with potential complications including infection at the insertion point, pancreatitis, bleeding, dislocation of the tube or blockage of the tube.[7] ABBV-951 is delivered through a minimally invasive subcutaneous infusion and provides therapeutic levels of levodopa without the associated complications of Duodopa.[9]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

ABBV-951 does not currently have Marketing Authorisation in the EU/UK for any indication.

ABBV-951 is not currently in phase II or III clinical development for any other indications.[10]

PATIENT GROUP

DISEASE BACKGROUND

Parkinson's disease (PD) is a progressive neurodegenerative disease, characterised by progressive degeneration of the dopaminergic system due to a loss of nerve cells in part of the brain called the substantia nigra. Dopamine plays a vital role in regulating the movement of the body as it is the chemical messenger (neurotransmitter) that transmits messages between nerves that control muscle movements.[11,12] A reduction in dopamine is responsible for the motor symptoms of Parkinson's disease which are bradykinesia (slow movement), rigidity, tremor and postural instability.[2,12]

It is not known exactly what causes the loss of nerve cells associated with PD but it is believed to be a combination of genetic changes and environmental factors such as pesticides and herbicides used in farming and traffic or industrial pollution.[13] The biggest risk factor for developing PD is advancing age, with the average age of onset being 60 years old. Men are also more likely to develop PD than women.[11]

Early stage symptoms of PD are managed with oral levodopa treatment. However, as the disease progresses, symptoms are no longer well controlled by oral medication and the symptoms re-emerge or worsen usually around 3-4 hours after a dose of levodopa.[2,14] This phenomenon is called "wearing off" and is when the control of motor and non-motor symptoms fluctuates. Wearing off can occur at any time after starting to take levodopa, after the so-called 'honeymoon period', although it more commonly develops five or more years after the onset of motor symptoms and happens more frequently as PD progresses.[14] Living with PD can complicate the basic activities of daily living such as bathing, dressing, eating, sleeping and walking.[15]

CLINICAL NEED AND BURDEN OF DISEASE

PD is the second most common neurodegenerative disorder after Alzheimer's disease.[9] The prevalence of PD amongst all adults in the UK in 2015 was 266.5 per 100,000 of the population and PD diagnoses are set to rise by nearly a fifth by 2025.[16,17] The incidence of PD rises with age and the greatest prevalence of PD is amongst 80-84 year olds, affecting 1,696 per 100,000 of the population.[16,18] PD affects men more commonly than women. In the UK in 2015, the prevalence amongst adult males was 315.6 per 100,000 and amongst adult females was 219.8 per 100,000.[16]

In England, in 2018-19 there were 184,020 diagnoses of PD (ICD-10 code G20), of which 114,381 were male and 69,629 were female. There were 13,315 finished consultant episodes (FCE) for PD, resulting in 6,878 admissions and 97,804 FCE bed days.[19]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There is currently no cure for PD, but treatments are available to help relieve the symptoms and maintain the quality of life of the patient.[20] Every person with PD has a different experience of the condition, so PD patients work with a specialist, PD nurse or pharmacist to

adapt the type of drug, dosing and timing to find the best treatment regime for the patient. Which medication patients take will depend on the type and severity of their symptoms as well as other factors such as age and lifestyle.[21]

Most patients initially respond well to levodopa therapy.[6] Once a patient develops insufficient symptom control or fluctuations in motor control, the treatment regime may be adapted through measures such as optimising the dose and timing of levodopa used or the addition of drugs to the treatment regime.[22] If patients do not respond well to oral levodopa therapy then deep brain stimulation may be considered.[18]

CURRENT TREATMENT OPTIONS

Currently NICE recommends offering levodopa as a first-line treatment option for people in the early stages of PD whose motor symptoms impact on their quality of life.[23]

If a person with PD has developed dyskinesia and/or motor fluctuations despite optimal levodopa therapy then the following treatment options are considered as an adjuvant therapy to levodopa:[24]

- dopamine agonists
- monoamine oxidase-B (MAOB) inhibitors
  - safinamide[25]
  - rasagiline
  - selegiline
- catechol-O-methyltransferase (COMT) inhibitors:[26]
  - opicapone[26]
  - entacapone
  - tolcapone

If patients do not respond to oral medication they may be considered for advanced therapies such as:[18]

- apomorphine subcutaneous infusions
- duodopa

PLACE OF TECHNOLOGY

If licensed, ABBV-951 will offer an additional treatment option for PD patients whose motor fluctuations are inadequately controlled on current therapy.[1]

CLINICAL TRIAL INFORMATION

Trial	NCT04380142, **EudraCT 2019-003930-18;** A Randomised, Double-Blind, Double-Dummy, Active-Controlled Study Comparing the Efficacy, Safety and Tolerability of ABBV-951 to Oral Carbidopa/Levodopa in Advanced Parkinson's Disease Patients **Phase III –** recruiting **Locations:** Australia and United States **Estimated Primary Completion Date:** January 2021
Trial design	Randomised, double-blind, double-dummy, active-controlled study
Population	N=130; adults aged 30 years and older; diagnosis of idiopathic PD that is levodopa-responsive; symptoms inadequately controlled by

	current therapy; have recognizable/identifiable "Off" and "On" states (motor fluctuations)
Intervention(s)	ABBV-951 solution (continuous subcutaneous infusion) and placebo for levodopa/carbidopa (oral capsule)
Comparator(s)	Levodopa/Carbidopa (oral tablet) a placebo for ABBV-951 solution (continuous subcutaneous infusion)
Outcome(s)	Primary outcome measure: • Change in "On" time (hours) without troublesome dyskinesia [Time frame: baseline (week 0) up to week 12] See trial record for full list of outcome measures.
Results (efficacy)	-
Results (safety)	-

Trial	NCT03781167, EudraCT 2018-002144-85; A 52-Week, Open-label, Single-arm, Study to evaluate the Safety and Tolerability of 24-hour Daily Exposure of Continuous Subcutaneous Infusion of ABBV-951 in Subjects With Parkinson's Disease **Phase III –** recruiting **Locations:** 7 EU countries (incl UK), USA, Canada and other counties **Estimated primary completion date:** October 2021	NCT04379050, **EudraCT 2019-004235-23, An Open-label Extension of Study M15-741 to Evaluate the Safety and Tolerability of 24-hour Daily Exposure of Continuous Subcutaneous Infusion of ABBV-951 in Subjects With Parkinson's Disease** **Phase III –** enrolling by invitation **Locations:** 4 EU countries (incl UK), USA, Canada and other counties **Estimated primary completion date:** June 2023
Trial design	Open-label, single-arm, single-group assignment	Single group assignment, open label
Population	N=130 (planned); adults aged 30 years and older; patients with idiopathic PD that is levodopa responsive; judged by the investigator to be inadequately controlled by current therapy with recognizable/identifiable 'Off' and 'On' motor states and have a minimum of 2.5 hours of 'Off' time per day	N=121 (planned), adults aged 30 years and older; patients who have PD and who have successfully completed the parent study (NCT03781167
Intervention(s)	foslevodopa (subcutaneous infusion) foscarbidopa (subcutaneous infusion)	Participants will receive ABBV-951 solution by continuous subcutaneous infusion (CSCI), at the discretion of the investigator, for 96 weeks.
Comparator(s)	No comparator	No comparator
Outcome(s)	Adverse Events [Time frame: from initiation of CSCI through 30 days after last infusion device is removed (up to 56 weeks)] See trial record for full list of other outcomes	Percentage of Participants With Adverse Events (AE) [Time frame: up to week 96] See trial record for full list of other outcomes
Results (efficacy)	-	-

Results (safety)	-	-

ESTIMATED COST

The estimated cost of ABBV-951 is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Parkinson's disease in adults (NG71). July 2017.
- NICE quality standard. Parkinson's disease (QS164). February 2018.
- NICE interventional procedures guidance. Unilateral MRI-guided focused ultrasound thalamotomy for moderate to severe tremor in Parkinson's disease (IPG606). February 2018.
- NICE interventional procedures guidance. Subthalomotomy for Parkinson's disease (IPG65). June 2004.
- NICE interventional procedures guidance. Deep brain stimulation for Parkinson's disease (IPG19). November 2003.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Neurosciences: Specialised Neurology (Adult). D04/S/a.
- NHS England. Clinical Commissioning Policy: Levodopa-Carbidopa Intestinal Gel (LCIG). Publication date: to be confirmed.
- NHS England. Clinical Commissioning Policy: Stereotactic Radiosurgery (SRS) for adults with Parkinson's tremor and Familial Essential Tremor. 16007/P. July 2016.

OTHER GUIDANCE

- UK Parkinson's Excellence Network. Non-oral treatment integrated pathway in Parkinson's. 2016.[27]
- Journal of the American Medical Association (JAMA). Pharmacological Treatment of Parkinson Disease. 2014.[28]
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ADDITIONAL INFORMATION

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