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RBX-2660 for the treatment of recurrent clostridium difficile infection – third line

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LAY SUMMARY

Clostridium difficile (*C. difficile*) is a type of bacterium that lives in people's guts. When this bacterium grows in number, it can cause an infection, *C. difficile* infection (CDI) that can be mild, moderate or severe. Occasionally, after initial treatment with antibiotics, the infection can re-occur, and the more times the infection re-occurs, the more likely is this to happen again. When infection happens for second and subsequent times, treatment options become more limited and less effective. Symptoms of CDI include watery diarrhoea, painful stomach cramps, dehydration, loss of appetite, weight loss.

RBX-2660 is a therapy under development for recurrent CDI. It is a non-antibiotic therapy that consists of human-derived microorganisms (microbiota suspension). It is administered directly into the patient's intestine through the rectum as an enema. RBX-2660 has the potential to treat patients re-infected by *C. difficile* that currently have limited treatment options available and are at risk of serious health consequences.

TARGET GROUP

Clostridium difficile (C. difficile) infection (CDI) - (recurrent)

TECHNOLOGY

DESCRIPTION

RBX-2660 (Microbiota Restoration Therapy™; Microbiota suspension) is a non-antibiotic therapy consisting of an intestinal preparation containing live microbes. It works by delivering human-derived microbes into a patient's intestinal tract, restoring the balance of microbes that is typically disrupted by antibiotic use. RNX-2660 is administered through rectal route which is formulated as enema.[1]

Antibiotic therapy is the standard treatment following an initial diagnosis of Clostridium difficile (C. difficle) infection (CDI). However, approximately 25% of patients initially cured will experience a recurrence. Each recurrence predisposes to further recurrence. After two or more episodes of recurrence, the risk of subsequent recurrence may reach 65%.[2] RBX-2660 is currently under development as a therapy for recurrent CDI.

In the currently ongoing phase III clinical trial (PUNCH CD3, NCT03244644), RBX-2660 is administered as an enema consisting of a microbiota suspension in a 0.9% sodium chloride irrigation USP solution and cryoprotectant.[3]

RBX-2660 does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, RBX-2660 will offer the possibility to change the therapeutic options for recurrent CDI in patients who currently have few (well-tolerated) effective therapies available. RBX-2660 presents a non-antibiotic therapy option for CDI with the potential advantage of breaking recurrence cycle resulting from the frequent use of antibiotics.[6]

DEVELOPER

Rebiotix, Inc.

AVAILABILITY, LAUNCH or MARKETING

RBX-2660 was designated orphan drug in the US for prevention of recurrent CDI by FDA in 2014.[4]

RBX-2660 received fast track designation for prevention of recurrent CDI by FDA in 2014.[5]

RBX-2660 was designated Breakthrough Therapy for prevention of recurrent CDI by FDA in 2015.[5]

The company did not provide any marketing authorisation application plans for the EU or US.

PATIENT GROUP

BACKGROUND

Clostridium difficile (*C. difficile*) is an anaerobic, gram-positive, spore-forming, toxin-producing bacillus found in the gut.[6] It can be found in healthy people, where it causes no symptoms (up to 3% of adults and 66% of babies).[7] Interest in this organism developed when it was demonstrated to be the causative agent of most cases of infectious postantibiotic colitis.[6] *C. difficile* causes disease when the normal bacteria in the gut are disadvantaged, usually by someone taking antibiotics[6] particularly the elderly and people whose immune systems are compromised.[7] This allows *C. difficile* to grow to unusually high levels. It also allows the toxin that some strains of *C. difficile* produce to reach levels where it attacks the intestines and causes mild to severe diarrhoea.[6] *C. difficile* can lead to more serious infections of the intestines with severe inflammation of the bowel (pseudomembranous colitis).[8] Other factors for infection include advanced age (greater than 65 years), antibiotic use, severe illness, and hospitalization. Secondary factors that also increase the risk include gastric acid suppression (with proton pump inhibitors or histamine-2 receptor antagonists), gastrointestinal procedures, chemotherapy, residence at a long-term care facility, inflammatory bowel disease, and immunosuppression.[8]

Clostridium difficile infection (CDI) is the most frequent cause of nosocomial diarrhoea. It has become a significant dilemma in the treatment of patients and causes increasing morbidity that, in extreme cases, may result in death. Persistent and recurrent disease hamper attempts at eradication of this infection. Infection can occur by ingestion of the bacteria (through contact with a contaminated environment or person).[7] Patients may also pass the infection to each other, making it necessary to identify and isolate infected patients. Lending to the difficulty of controlling this often indolent infection, colonization of *C. difficile* is seen in 20 to 50% of the adults in hospitals and long-term care facilities. Furthermore, there has been an increase in community-acquired CDI that may not be associated with antibiotic use or recent hospitalization.[8]

Recurrent CDI occurs in 20 to 30% of patients treated initially with either metronidazole or vancomycin,[7] after a first recurrence, the risk of another infection increases to 45–60%.[16] A variable proportion of recurrences are reinfections (20-50%) as opposed to relapses due to the same strain; relapses tend to occur in the first two weeks after treatment cessation.[16] In clinical settings, it is impossible to distinguish a recurrence that develops as a relapse of CDI with the same strain of *C. difficile* versus a reinfection that is the result of a new strain.[8]

CLINICAL NEED and BURDEN OF DISEASE

Since the early 2000s, an increased incidence and severity associated with CDI that has coincided with the emergence and rapid spread of a previously rare strain, ribotype 027. However in more recent years, data from the U.S. and Europe suggest the incidence of CDI may have reached a crescendo and is perhaps beginning to plateau.[9] Studies in North America and Europe have implicated the ribotype 027 strain in CDI outbreaks characterized by an increased incidence and severity, refractory to traditional therapy, and a greater risk of relapse.[9]

In England, between September 2016 and September 2017, there were a total of 5,115 cases of CDI in patients aged two years and over in NHS acute trusts.[10] There are limited national epidemiological

data for community-associated (CA) or community onset-CDIs.[11] A 2010 study estimated the prevalence of community-onset CDI as 1.29 per 10,000 people in a community in the south of England.[12]

Hospital Episode Statistics of admitted patients for England for 2016/2017 recorded a total of 10,683 finished consultant episodes (FCE), 4,193 admissions, 86 day cases and 88,360 FCE bed days (ICD-10 code: A04.7) from enterocolitis due to Clostridium difficile.[13]

The number of death certificates in England and Wales mentioning *C. difficile* fell for the fifth consecutive year in 2012, from 2,053 (19.6 deaths per million population) in 2011 to 1,646 (15.3 per million) in 2012. This represents a reduction of 20% in one year.[14]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Bezlotoxumab for preventing recurrent *Clostridium difficile* infection (GID-TA10178). Expected publication date: 23 May 2018
- NICE clinical guideline. Healthcare-associated infections: prevention and control in primary and community care (CG139). Published March 2012, updated February 2017.
- NICE guideline. Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (NG15). August 2015
- NICE quality standard. Healthcare-associated infections (QS113) February 2016
- NICE quality standard. Infection prevention and control (QS61). April 2014
- NICE interventional procedures guidance. Faecal microbiota transplant for recurrent *Clostridium difficile* infection (IPG485). March 2014
- NICE public health guideline. Healthcare-associated infections: prevention and control (PH36). November 2011

NHS ENGLAND and POLICY GUIDANCE

- NHS England. *Clostridium difficile* infection objectives for NHS organisation sin 2017/2018 and guidance on sanction implementation. 2017.
- NHS England. 2013/14 NHS Standard contract for specialised services for infectious diseases (Adult). B07/S/a
- NHS England. 2013/14 NHS Standard contract for high security infectious disease unit (All ages). B07/S/b

OTHER GUIDANCE

- Department of Health*. Updated guidance on the diagnosis and reporting of clostridium difficile.* March 2012.
- Public Health England. Updated guidance on the management and treatment of *Clostridium difficile* infection. London: Public Health England, 2013. Debast SB, Bauer MP, Kuijper EJ. European Society of Clinical Microbiology and Infectious Diseases: Update of the Treatment

Guidance Document for Clostridium difficile Infection. *Clin. Microbiol. Infect*. 2014(20),sup 2:1-26.

CURRENT TREATMENT OPTIONS

The decision to treat CDI and the type of therapy administered depends on the severity of infection, as well as the local epidemiology and type of *C. difficile* strains present. A number of different treatment algorithms have been described in detail in the updated guidance on the management and treatment of CDI published by Public Health England (PHE) recently.[16]

In 2013, the European Society of Clinical Microbiology and Infection released updated guidelines for the treatment of CDI, which include antibiotic treatment for all but very mild cases. Recommendations include the following:[15]

- For patients with non-epidemic, non-severe CDI clearly induced by antibiotic use, with no signs of severe colitis, it may be acceptable to stop antibiotic treatment and observe the clinical response for 48 hours
- Antibiotic treatment is recommended for all except very mild cases actually triggered by antibiotic use; suitable treatments include metronidazole, vancomycin, and fidaxomicin
- For mild/moderate disease, oral metronidazole (500 mg 3 times daily for 10 days) is recommended as initial treatment
- In patients for whom oral treatment is inappropriate, fidaxomicin may be used; specific indications include first-line treatment in patients with recurrence or at risk for recurrence
- For patients with severe CDI, suitable antibiotic regimens include vancomycin (125 mg 4 times daily for 10 days; may be increased to 500 mg 4 times daily) or fidaxomicin (200 mg twice daily for 10 days)
- Use of fidaxomicin is not supported in life-threatening CDI
- Use of oral metronidazole in severe or life-threatening CDI is discouraged
- Fecal transplantation is recommended for multiple recurrent CDI
- For patients with colonic perforation and/or systemic inflammation and deteriorating clinical condition despite antibiotic treatment, total abdominal colectomy or diverting loop ileostomy combined with colonic lavage is recommended
- Additional management measures include discontinuing unnecessary antimicrobial therapy, adequate replacement of fluids and electrolytes, avoiding antimotility medications, and reviewing the use of proton pump inhibitors

For England, NICE recommendations for first-line treatment of CDI involve rehydration and antibiotic therapy.[17] Public Health England (PHE) recommends the interruption of the antibiotics that caused the CDI and recommends for a different antibiotic to be prescribed if the underlying infection still requires treatment.[16]

For refractory or recurrent CDIs, further courses of antibiotics are used.[17] The same antibiotic that had been used initially can be used to treat the first recurrence.[16] In this setting, PHE recommends the use of oral fidaxomicin 200 mg every 12 hours with oral vancomycin 125 mg every 6 hours as an alternative.[16]

With regards faecal microbiota transplant for patients with recurrent CDIs, NICE has issued an interventional procedure guidance to the NHS in England, Wales, Scotland and Northern Ireland,[17] however full clinical guidelines have not been issued yet.

EFFICACY and SAFETY

Trial	PUNCHCD3, NCT03244644, phase III
Sponsor	Rebiotix Inc
Status	ongoing
Source of Information	Trial registry[3]
Location	United States
Design	Randomised, placebo-controlled
Participants	N=270 (planned); aged 18 or over; at least two recurrences after a primary episode and has completed at least two rounds of standard-of-care oral antibiotic therapy or had at least two episodes of severe CDI resulting in hospitalization within the last year; positive stool test for the presence of toxigenic *C. difficile* within 30 days prior to or on the date of enrolment; currently taking or was just prescribed antibiotics to control CDI related diarrhoea at the time of enrolment.
Schedule	Randomised to enema of a microbiota suspension in a 0.9% sodium chloride irrigation USP solution and cryoprotectant or placebo (doses not specified).
Follow-up	Follow up for up to 6 months after completing study treatment.
Primary Outcomes	Efficacy (defined as the absence of C. difficile diarrhoea without the need for retreatment)
Secondary Outcomes	Number of adverse events; Health Related Quality of Life (HRQoL)
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study estimated completion date reported as September 2018

ESTIMATED COST and IMPACT

COST

The cost of RBX-2660 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: *uncertain unit cost compared to existing treatments*

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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