MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION

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OBEFAZIMOD (ABX464) FOR THE TREATMENT OF ULCERATIVE COLITIS

EXECUTIVE SUMMARY

Ulcerative colitis (UC) is a chronic immune-mediated inflammatory bowel disorder (IBD) that results in diffuse friability and superficial erosions of the colonic wall associated with bleeding.[1] It is the most common form of inflammatory bowel disease worldwide.

Obefazimod (ABX464) is a highly differentiated oral drug candidate with a novel mechanism of action based on the upregulation of a single, specific micro-ribonucleic acid (RNA) with anti-inflammatory properties known as microRNA-124 (miR-124). This new mechanism may provide an entirely new way of treating IBD. ABX464 is administered orally once daily, provides convenience, and has some advantages in compliance with the treatment of ulcerative colitis (UC).[2]

The US Food and Drug Administration (FDA) has approved Abivax's Investigational New Drug (IND) application for ABX464 to treat moderate-to-severe UC. Abivax finalised the phase 3 study design and updated its IND for ABX464 for the treatment of UC in Q1 2022.[3] A unique RNA splicing product and the ability to upregulate the production of an anti-inflammatory agent, ABX464 has shown promise in clinical trials for its ability to induce remission in patients and heal inflammatory lesions in UC.[2]

In conclusion, based on the phase II trial, ABX464 50 mg once daily was safe and well tolerated as induction therapy. ABX464 appeared to be effective in improving endoscopic and reducing Mayo Clinic score (MCS) and partial MCS (pMCS) when used as a long-term therapy. Maintenance therapy with ABX464 sustained remission and brought additional patients into remission. However, the evidence is only based on a single study with a small sample size, more evidence is required to ascertain the safety, effectiveness and cost-effectiveness of ABX464 in the treatment of patients with UC.

Keywords: obefazimod, ABX464, ulcerative colitis

INTRODUCTION

Ulcerative colitis (UC) is a chronic immune-mediated inflammatory bowel disorder (IBD) that results in diffuse friability and superficial erosions on the colonic wall associated with bleeding.[1] It is the most common form of inflammatory bowel disease worldwide. It involves inflammation restricted to the colon. Ulcerative colitis (UC) is characterised by relapsing and remitting mucosal inflammation that classically begins in the rectum and extends proximally through the colon in a continuous manner. The

inflammatory nature of UC can result in continuous bowel damage with increased risks of hospitalisations, surgeries, and colorectal cancer if inadequately treated.[1]

Worldwide, the incidence of UC is on the rise with the annual incidence of UC ranging from 8.8 to 23.1 per 100,000 person-years in North America, 0.6 to 24.3 per 100,000 person-years in Europe, and 7.3 to 17.4 in Oceania.[1] Although UC can occur at any age, the peak incidence of UC occurs in the second to fourth decade of life with a similar incidence between men and women.[1]

Based on a systematic review in 2012, the highest annual incidence of IBD was recorded in Europe (UC: 24.3 per 100,000 person-years; Crohn's disease (CD):12.7 per 100,000 person-years), followed by North America (UC: 19.2 per 100,000 person-years; CD: 20.2 per 100,000 person-years) and Asia plus the Middle East (UC: 6.3 per 100,000 person-years; CD: 5.0 per 100,000 person-years). While the IBD incidence rates in Western countries have remained relatively stable or steadily increased over time, however, there was a rapid rise in Asian countries.[4] A population-based study from South Korea showed a 10-fold increase in the incidence of IBD over two decades (UC: 0.34 to 3.08 per 100,000 person-years, CD: 0.05 to 1.34 per 100,000 person-years).[4]

In Malaysia, based on a study by Mokhtar et al., the mean crude incidence of IBD has increased steadily over the first three decades: 0.36 (from the year 1980 - 1989), 0.48 (1990 - 1999) and 0.63 per 100,000 person-years (2000 - 2009).[5] From the 2010 to 2018 period, the mean crude incidence has doubled to 1.46 per 100,000 person-years. Initially, UC was much more common than CD, however, there was a significant rise in the incidence of CD from the year 2000, as depicted by reducing UC: CD ratio: 5:1 (1980 - 1989), 5:1 (1990 - 1999), 1.9:1 (2000 - 2009) and 1.7:1 (2010 - 2018). The prevalence rate of IBD, UC and CD, were 23.0, 15.67 and 7.36 per 100,000 persons respectively. When stratified according to ethnic groups, the highest prevalence of IBD was among Indians [73.4 per 100,000 persons (UC: 45.8, CD: 27.7 per 100,000 persons)], followed by Malays [24.8 per 100,000 persons (UC: 17.1, CD: 7.8 per 100,000 persons)] and Chinese [14.6 per 100,000 persons (UC: 10.8, CD: 3.8 per 100,000 persons)].[5]

THE TECHNOLOGY

Obefazimod (ABX464) is a highly differentiated oral drug candidate with a novel mechanism of action based on the upregulation of a single, specific micro-ribonucleic acid (RNA) with anti-inflammatory properties known as microRNA-124 (miR-124). This new mechanism could provide an entirely new way of treating IBD. ABX464 is administered orally once daily and offers some advantages in terms of convenience and consistency in the treatment of UC.[2] It was originally developed for its antiviral potential, but in preclinical trials, it was repurposed for chronic inflammatory diseases due to its potent anti-inflammatory effects.[6]

The US Food and Drug Administration (FDA) has approved Abivax's Investigational New Drug (IND) application for ABX464 to treat moderate-to-severe UC. A two-year open-label ABX464 maintenance study was conducted in 19 patients without treatment interruption after completing a randomised, double-blind, placebo-controlled eight-week induction study and a one-year open-label maintenance study. Sixteen

patients completed the two-year open-label maintenance study of ABX464 and demonstrated long-term safety and tolerability of 50 mg given orally.[2]

To date, more than 1,000 patients have been treated with ABX464, including those who have received continuous daily dosing for more than three years. Based on observations and comparison with existing therapeutic options, ABX464 demonstrated excellent clinical safety, tolerability profile and evidence of superior long-term efficacy. Because of its unique RNA splicing product and its ability to greatly upregulate the production of miR-124, an anti-inflammatory agent, ABX464 has shown promise in clinical trials in its ability to bring patients into remission and heal inflammatory lesions in UC.[2]

The US FDA provided valuable feedback for bringing ABX464 to phase 3 clinical trials for the treatment of UC and subsequent submission and commercialisation of potential marketing authorisation. With guidance from the FDA and potential recommendations from European Medicines Agency (EMA), Abivax finalised the phase 3 study design and update its IND for ABX464 for the treatment of UC in Q1 2022.[3]

PATIENT GROUP AND INDICATION

ABX464 is used for the treatment of UC in adult patients.

CURRENT PRACTICE

Current treatments for ulcerative colitis are:[7]

- 5-Aminosalicylate (ASA): mesalazine
  - 5-ASA is considered the standard in treating mild-to-moderate UC, eventually combined oral and rectal.
- Corticosteroids: budesonide, budesonide-multimatrix (MMX), prednisone, hydrocortisone, methylprednisolone.
  - Patients with inadequate response to optimised 5-ASA therapy will escalate to budesonide-MMX or oral prednisone.
  - Corticosteroid use in UC is associated with a higher risk for relapse and colectomy.
- Immunosuppressives: azathioprine (AZA), 6-mercaptopurine (6-MP), cyclosporine, tacrolimus
  - Cyclosporin and infliximab are the mainstays of rescue therapies in acute severe UC which do not respond to IV corticosteroids
  - Thiopurine therapy increased the risk for lymphoma and non-melanoma skin cancer as well as bone marrow suppression, pancreatitis, and hepatotoxicity
- Biologics: adalimumab, golimumab, infliximab, vedolizumab
  - Several studies showed that anti-tumour necrosis factor (anti-TNF) therapy (infliximab, adalimumab, golimumab) was effective in achieving corticosteroid-free remission (in about 30%) compared with placebo in patients with moderate-to-severe UC.
  - Vedolizumab was effective to induce and maintaining corticosteroid-free remission in both anti-TNF-experienced and anti-TNF-naïve patients as well as patients with prior AZA//6-MP exposure.
- Janus kinase inhibitor: tofacitinib
  - Tofacitinib was effective to induce and maintaining remission after treatment failure with either oral corticosteroids, AZA, or anti-TNF therapy.

- Tofacitinib showed a rapid onset of action with significant improvements in symptoms (stool frequency, rectal bleeding) within 3 days.

The upcoming treatment options with different molecular pathways and different modes of action are needed for personalised medicine.[7] A better understanding of pathophysiological processes, pharmacogenomics, and predictive markers for disease activity will help to identify subpopulations of UC patients who will benefit from tailored treatment regimens to individuals.[7]

SAFETY AND EFFICACY

Based on retrieval evidence up to 28 September 2022, one randomised controlled trial was included in this review.

a. Clinical Impact

A randomised study involving an 8-week, placebo-controlled, double-blind induction phase followed by an open-label long-term extension phase enrolled adults aged ≤75 years with moderate-to-severe active UC.[2] Patients who completed the induction phase regardless of response and were willing to continue into a long-term extension phase were eligible to continue. In the induction phase, patients were randomised 2:1 to oral ABX464 50 mg and placebo once daily for 8 weeks. In the long-term extension phase, all patients received ABX464 50 mg once daily for 24 months.[6]

The primary endpoint in the induction phase was safety, assessed as the rate of treatment-emergent adverse events (AEs). The efficacy endpoints were:[6]

- the proportion of patients achieving clinical remission at week eight vs placebo
- change from baseline to week eight in Mayo Clinic score (MCS) and partial MCS (pMCS)
- rates of endoscopic remission and improvement
- change in faecal calprotectin

For the long-term extension phase, the primary endpoint was the long-term safety of ABX464. Additional efficacy endpoints included clinical and endoscopic rates of response and remission.[6]

Overall, 32 patients were enrolled in the induction phase (23 in the ABX464 group and 9 in the placebo group). All patients in the placebo group completed the induction phase while only 20 patients in ABX464 completed the induction phase. One patient in the induction phase received ABX464 prematurely with-drew because of an elevated transaminase three times the upper level of normal. Two patients who had missing endoscopies were considered failures in the intention-to-treat population. However, only 22 patients continued the long-term extension phase.[6]

At week eight, 35% and 70% of patients in the ABX464 group achieved clinical remission and response respectively, compared with 11.1% and 33.3% in the placebo group. Endoscopic improvement and remission were observed in 50% and 10% of patients receiving ABX464, respectively, compared with 11.1% each for placebo. The MCS and pMCS mean change from baseline ± standard deviation was -4.6 ± 2.8 vs -2.1 ± 2.5 (p=0.0292) for the ABX464 group and -3.9 ± 2.2 vs -1.8 ± 2.0 (p=0.0209) for the placebo group, respectively. For the modified pMCS at week eight, there was a statistically significant difference between ABX464 vs placebo (p=0.0212).[6]

At 12 months of ABX464 treatment, 12 of 16 patients (75%) with an assessable endoscopy were in clinical remission i.e. 33.3% sustained remission and 66.7% acquired clinical remission during the long-term extension phase. For the 22 patients who moved into the long-term extension phase, 55% were in clinical remission, with 18% and 36% sustaining remission and acquiring remission, respectively. The mean change from baseline ± standard deviation in the MCS was -2.6 ± 2.9 overall. Median faecal calprotectin decreased from 153.1 mg/g (baseline) to 27.9 mg/g at week 52.[6]

At 24 months, 66.7% of the 12 patients in clinical remission at 12 months remained in clinical remission. Two patients lost clinical remission but remained in clinical response. Additionally, one patient withdrew at month 23 because of worsening UC and one withdrew at month 14 because of non-compliance. Endoscopic improvement was observed in 68.8% of patients at 24-month which 43.8% showed endoscopic remission.[6]

b. Safety
Overall, 78.3% of patients receiving ABX464 experienced AEs vs 55.6% receiving placebo. The most common AEs in the ABX464 group were abdominal pain and headache (17.4% each). One patient in the induction phase receiving ABX464 prematurely withdrew because of an elevated transaminase three times the upper level of normal. The most common AEs through month 24 were nasopharyngitis and abdominal pain (31.3% each). There were no deaths.[6]

ESTIMATED COST

The raw cost of ABX464 for research purposes is around USD357 (MYR1,590) for 5 mg and USD1117 (MYR4,976; conversion rate = 4.456) for 25 mg.[8]

OTHER ISSUES

There was no organisational/ethical issue identified.

POTENTIAL IMPACT

In conclusion, based on the phase II trial, ABX464 50 mg once daily was safe and well tolerated as induction therapy. ABX464 appeared to be effective in improving endoscopic and reducing Mayo Clinic score (MCS) and partial MCS (pMCS) when used as a long-term therapy. Maintenance therapy with ABX464 sustained remission and brought additional patients into remission. However, the evidence is only based on a single study with a small sample size, more evidence is required to ascertain the safety, effectiveness and cost-effectiveness of ABX464 in the treatment of patients with UC.

REFERENCES

1. Du L, Ha C. Epidemiology and Pathogenesis of Ulcerative Colitis. Gastroenterol Clin North Am. 2020 Dec;49(4):643-654.
2. Abivax. Obefazimod for Ulcerative Colitis. Available at: https://www.abivax.com/pipeline/abx464-ibd-uc/ [Accessed on 13 July 2022]
3. Biospace. Abivax Receives FDA Feedback with Guidance on Advancing ABX464 into Phase 3 Clinical Testing in Ulcerative Colitis. Available at: https://www.biospace.com/article/releases/abivax-receives-fda-feedback-with-guidance-on-advancing-abx464-into-phase-3-clinical-testing-in-ulcerative-colitis/ [Accessed on 21 July 2022]
4. Molodecky NA, Soon IS, Rabi DM et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012 Jan;142(1):46-54.e42; quiz e30.
5. Mokhtar NM, Nawawi KNM, Verasingam J et al. A four-decade analysis of the incidence trends, sociodemographic and clinical characteristics of inflammatory bowel disease patients at single tertiary centre, Kuala Lumpur, Malaysia. BMC Public Health. 2019 Jun 13;19(Suppl 4):550.
6. Vermeire S, Hébuterne X, Tilg H et al. Induction and Long-term Follow-up With ABX464 for Moderate-to-severe Ulcerative Colitis: Results of Phase IIa Trial. Gastroenterology. 2021 Jun;160(7):2595-2598.e3.
7. Burri E, Maillard MH, Schoepfer AM et al. Treatment Algorithm for Mild and Moderate-to-Severe Ulcerative Colitis: An Update. Digestion. 2020;101 Suppl 1:2-15.
8. Selleckchem.com. ABX464. Available at: https://www.selleckchem.com/products/abx464.html [Accessed on 4 August 2022]

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