Introduction

ONCHOCERCIASIS

- Onchocerciasis (river blindness) is caused by the parasitic nematode Onchocerca volvulus.
- This is the world’s 2nd leading infectious cause of blindness.
- Visual impairment and blindness are the most severe complications of the disease.
- An estimated 22 million people suffer from onchocerciasis, with 99% cases in African countries.
- World Health Organization estimates 746,000 patients are visually impaired & 265,000 blinded.

Methods

A first-in-human (FIH) study was performed in the U.K. to investigate the safety, tolerability and pharmacokinetics (PK) of single doses of emodepside (BAY 44-4460) in healthy male subjects.

- Part 1 was a FIH investigation of single ascending doses in 8 cohorts of 8 subjects each, 6 subjects being randomized to emodepside and 2 to placebo.

Results

- Emodepsides displayed dose-proportional increases in exposure up to the 40 mg dose level (LSF), with moderate between-subject variability in PK parameters.
- Emodepsides was rapidly absorbed, with median Tmax 1-5 h. Most of the administered emodepside was cleared from plasma in the first 24 h after dosing (apparent T1/2 = 11 h), but thereafter the rate of elimination was very slow. Plasma concentrations after doses of 20 and 40 mg suggested an estimated clearance from plasma by 24 h after dosing of approximately 90%.
- When administered after a high-fat, high-calorie meal, there was a 1.5-fold decrease in the oral exposure (AUC0-24 h) and a 2.4-fold decrease in Cmax compared to emodepside and a median Tmax values of 4 h, suggesting absorption of emodepside is slower in the fed state.
- All treatment-emergent adverse events (TEAEs) were mild or moderate in severity and resolved spontaneously. Across both most treatment groups (including placebo), whereas blurred vision was reported in only the highest emodepside LSF treatment group.
- Eye disorders (15.9% in Part 1 and 31.3% in Part 2), and nervous system disorders (19% in Part 1 and 37.5% in Part 2), were reported as the most commonly reported TEAEs across the whole study.
- Headache and blurred vision were the most frequently reported TEAEs across the whole study. Headache was reported in most treatment groups (including placebo), whereas blurred vision was reported in only the highest emodepside LSF treatment group.

Conclusions

Overall, emodepside was found to be safe up to 20 mg and well tolerated up to 20 mg, with rapid absorption, dose-proportional increase in exposure (AUC and Cmax) and a long terminal half-life of approximately 500 h. Emodepside is a promising compound for the treatment of onchocerciasis.