POSTER # 534

A Single-Center, First-in-human, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Investigate the Safety, Tolerability and Pharmacokinetics of Escalating Single Doses of Emodepside (BAY 44-4400) in Healthy Male Subjects

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Introduction

ONCHOCERCHIASIS

- 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 37 million people suffer from onchocerciasis, with 99% cases in African countries.
- World Health Organization estimates 746,000 patients are visually impaired & 265,000 blinded.
- Programmes for the treatment and control of onchocerciasis through mass drug administration (MDA) of ivermectin have been in place for over 20 years.
- Ivermectin targets the microfilarial stage & temporarily sterilizes, but does not kill the adult worms.
- The population at risk must be given ivermectin at regular intervals for many years, which is a large economic burden with difficult implementation in endemic countries.

Thus, there is an urgent need for a macrofilaricide, targeting adult *Onchocerca* worms, as an alternative treatment for case management, to shorten MDA or tackle difficult to treat areas.

EMODEPSIDE

- Emodepside is a cyclooctadepsipeptide antihelminthic drug registered for animal health and marketed by Bayer AG in combination with praziquantel or toltrazuril.
- Emodepside interacts with SLO-1, a calcium-activated potassium channel, resulting in flaccid paralysis of parasitic nematodes. Emodepside also stimulates presynaptic receptors belonging to the secretin receptor family.
- Emodepside targets different life stages of *O. volvulus*, including the adults, and is being investigated for the oral treatment of onchocerciasis in humans.

Methods

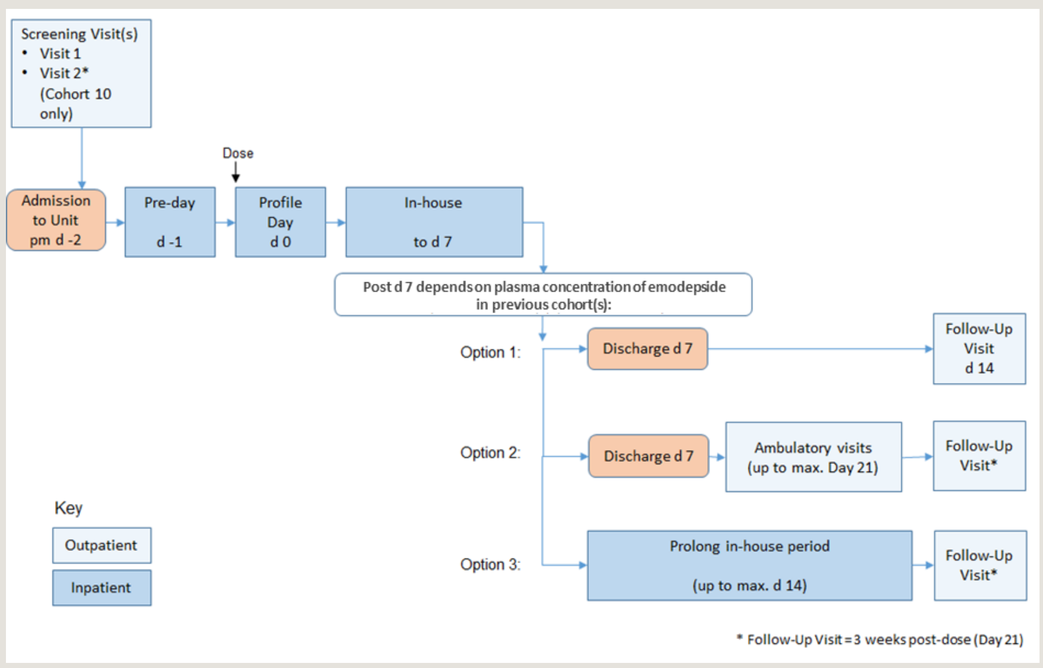
A first-in-human (FIH) study was performed in the U.K. to investigate the safety, tolerability and pharmacokinetics (PK) of single doses of emodepside (BAY 44-4400) in healthy male subjects.

- 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.
- In Part 2 - cohort 9 - the effect of food on the bioavailability of emodepside liquid service formulation (LSF) solution was determined.
- In Part 2 - cohort 10 - the relationship between emodepside administration and adverse events reported in Part 1 (in particular ophthalmological events) was investigated. Subjects received a single dose of 40 mg emodepside LSF solution or placebo in a fasted state.

Primary objectives were to investigate the safety and tolerability of emodepside after single oral doses administered as liquid service formulation (LSF) solution or immediate release (IR) tablets.

Secondary objectives were:

- to investigate the PK of emodepside, after administration as oral solution or IR tablet.
- to conduct an exploratory investigation of the relative bioavailability of the 5 mg and 20 mg IR tablet formulation using data generated in this study.
- to determine the effect of food on the bioavailability of emodepside after single oral doses administered as solution or IR tablets.



* Subjects deemed eligible at Screening visit 1 for Part 2 Cohort 10 had a second screening visit to undergo an ophthalmology assessment during the interval from 7 days before Day 0 until Day –1.

Study flow chart

Demographic characteristics of subjects in Part 1 (Cohorts 1–8) and in Part 2 (Cohorts 9 & 10)

		Placebo		Emodepside								Placebo		Emodepside	
				Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 5	Cohort 7	Cohort 8	Cohort 9	Cohort 10	Cohort 9	Cohort 10
		LSF (N=12)	IR (N=4)	1 mg LSF (N=5)	2.5 mg LSF (N=6)	5 mg LSF (N=6)	5 mg IR (N=5)	10 mg LSF (N=6)	20 mg LSF (N=6)	20 mg IR (N=6)	40 mg LSF (N=6)	LSF fed (N=2)	LSF fasted (N=2)	10 mg LSF fed (N=6)	40 mg LSF fasted (N=6)
Age (years)	Mean (SD)	30.7 (7.46)	28.0 (3.56)	38.6 (10.06)	34.8 (9.20)	29.3 (8.12)	36.8 (10.69)	34.2 (10.55)	32.8 (9.75)	31.3 (8.91)	30.8 (10.83)	–	–	27.7 (7.34)	38.5 (10.67)
	Range	21–42	23–31	29–50	25–52	20–43	27–53	26–54	22–47	22–42	19–47	22–51	32–48	21–38	25–52
Height (cm)	Mean (SD)	180.0 (7.98)	183.3 (2.99)	176.8 (4.87)	179.8 (6.24)	175.5 (5.82)	177.2 (10.87)	177.2 (3.54)	179.0 (7.51)	179.5 (7.45)	183.3 (7.63)	–	–	183.2 (6.37)	176.0 (5.22)
	Range	167–193	179–186	172–183	169–185	169–184	161–191	173–182	169–190	169–190	175–192	172–184	178–184	174–190	171–185
Weight (kg)	Mean (SD)	79.52 (10.130)	85.15 (7.217)	70.64 (6.815)	75.47 (11.331)	75.83 (3.506)	76.56 (13.197)	74.80 (11.383)	81.93 (10.397)	81.73 (9.075)	83.27 (11.267)	–	–	82.20 (7.979)	82.65 (13.598)
	Range	63.4–97.2	79.0–94	62.6–80.2	65.0–97.6	71.0–80.0	57.2–94.2	59.0–88.4	63.6–94.0	70.4–94.6	67.6–96.8	71.4–74.2	66.2–101.2	72.0–93.4	60.0–100.0
BMI (kg/m^2)	Mean (SD)	24.49 (2.131)	25.38 (2.291)	22.60 (2.117)	23.30 (2.683)	24.65 (1.162)	24.20 (1.707)	23.75 (2.868)	25.55 (2.651)	25.43 (3.169)	24.72 (2.613)	–	–	24.5 (2.137)	26.55 (3.213)
	Range	21.6–28.4	23.3–28	19.3–24.9	20.9–28.5	23.6–26.8	22.1–26.0	19.0–26.8	22.3–28.9	22.1–29.7	22.1–29.2	21.1–25.1	20.9–29.9	22.5–28.5	20.5–29.2

BMI=body mass index; IR=immediate release, LSF=liquid service formulation, values in parentheses: SD=standard deviation

Plasma pharmacokinetic parameters of emodepside after single doses in healthy subjects

				Emodepside							
Parameter		1 mg LSF (fasted) N=5	2.5 mg LSF (fasted) N=6	5 mg LSF (fasted) N=6	5 mg IR (fasted) N=5	10 mg LSF (fasted) N=6	20 mg LSF (fasted) N=6	20 mg IR (fasted) N=6	40 mg LSF (fasted) N=6	10 mg LSF (fed) N=6	40 mg LSF (fasted) N=6
C_{max} (ng/Ml)	Geometric mean (%CVb)	18.6 (20.8)	37.6 (15.5)	92.1 (16.2)	25.7 (23.9)	172 (32.3)	306 (28.7)	30.2 (62.5)	595 (27.9)	71.9 (29.6)	434 (32.7)
t_{max} (h)	Median (range)	1.00 (1.00–1.05)	1.00 (1.00–2.50)	1.00 (1.00–1.50)	2.00 (1.02–2.55)	1.00 (1.00–1.00)	1.50 (1.00–2.53)	2.00 (1.50–2.02)	1.05 (1.00-8.00)	2.50 (2.00–2.52)	0.967 (0.950–3.00)
$t_{½,0\text{-}24}$ (h)	Geometric mean (%CVb)	8.45 (84.7)	10.6 (24.9)	11.6 (21.7)	10.8 (9.2)	10.9 (26.8)	10.5 (28.7)	11.3 (23.8)	11.1 (24.7)	11.1 (33.9)	11.3 (29.5)
$t_{½}$ (h)	Geometric mean (%CVb)	42.7 (531)	449 (74.0)	415 (117)	267 (392)	365 (286)	590 (68.1)	348 (171)	392 (31.7)	531 (99.3)	440 (49.9)
AUC_{24} (h.ng/mL)	Geometric mean (%CVb)	100 (50.4)	250 (6.50)	522 (25.8)	183 (24.3)	996 (21.2)	1910 (16.3)	223 (58.0)	4110 (33.6)	673 (26.4)	3320 (26.0)
V_Z/F (L)	Geometric mean (%CVb)	239 (88.0)	885 (27.4)	802 (49.1)	1850 (56.1)	748 (68.7)	1140 (47.1)	6700 (40.1)	888 (21.3)	1090 (36.2)	1070 (41.8)
CL/F (L/h)	Geometric mean (%CVb)	3.88 (151)	1.37 (44.1)	1.34 (57.8)	4.79 (179)	1.42 (115)	1.34 (24.8)	13.3 (150)	1.57 (32.6)	1.42 (57.3)	1.69 (22.1)

AUC_{24}: AUC from zero to 24 h; C_{max}: maximum concentration; CL/F: total clearance from plasma after administration; IR=immediate release tablet, LSF=liquid service formulation, $t_{½}$: terminal half-life; $t_{½,0–24}$: half-life calculated from the 0–24 h PK timepoints; t_{max}: time to reach C_{max}; VZ/F: volume of distribution during terminal phase.

Summary of adverse events (Part 1, Cohorts 1–8)

	Placebo		Emodepside							
	LSF N=12 n (%)	IR N=4 n (%)	1 mg LSF N=5 n (%)	2.5 mg LSF N=6 n (%)	5 mg LSF N=6 n (%)	5 mg IR N=5 n (%)	10 mg LSF N=6 n (%)	20 mg LSF N=6 n (%)	20 mg IR N=6 n (%)	40 mg LSF N=6 n (%)
Number (%) of deaths	0	0	0	0	0	0	0	0	0	0
Number (%) of subjects with any SAE	0	0	0	0	0	0	0	0	0	0
Number (%) of subjects with any TEAE	5 (41.7)	1 (25.0)	3 (60.0)	0	3 (50.0)	3 (60.0)	5 (83.3)	3 (50.0)	2 (33.3)	5 (83.3)
Number (%) of subjects with any drug-related TEAE	3 (25.0)	0	2 (40.0)	0	2 (33.3)	0	3 (50.0)	2 (33.3)	0	5 (83.3)
Number (%) of subjects who discontinued study medication due to a TEAE	0	0	0	0	0	0	0	0	0	0
Total (%) of subjects with a TEAE by severity										
Mild	3 (25.0)	0	2 (40.0)	0	2 (33.3)	2 (40.0)	5 (83.3)	2 (33.3)	1 (16.7)	5 (83.3)
Moderate	2 (16.7)	1 (25.0)	1 (20.0)	0	1 (16.7)	1 (20.0)	0	1 (16.7)	1 (16.7)	0
Severe	0	0	0	0	0	0	0	0	0	0

Summary of adverse events (Part 2, Cohorts 9–10)

	Placebo	Emodepside		
	LSF (fed) N=2 n (%)	LSF (fasted) N=2 n (%)	10 mg LSF (fed) N=6 n (%)	40 mg LSF (fasted) N=6 n (%)
Number (%) of deaths	0	0	0	0
Number (%) of subjects with any SAE	0	0	0	0
Number (%) of subjects with any TEAE	0	0	3 (50.0)	5 (83.3)
Number (%) of subjects with any drug-related TEAE	0	0	2 (33.3)	5 (83.3)
Number (%) of subjects who discontinued study medication due to a TEAE	0	0	0	0
Total (%) of subjects with a TEAE by severity				
Mild	0	0	2 (33.3)	3 (50.0)
Moderate	0	0	1 (16.7)	2 (33.3)
Severe	0	0	0	0

TEAE = Treatment-emergent adverse event

Results

- Emodepside displayed dose-proportional increases in exposure up to the 40 mg dose level (LSF), with moderate between-subject variability in PK parameters.
- Emodepside was rapidly absorbed, with median tmax 1–1.5 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 to emodepside, with 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 study parts, the most frequently affected primary system organ classes (SOCs) were:
  - Nervous system disorders (19% in Part 1 and 37.5% in Part 2), and
  - Eye disorders (15.9% in Part 1 and 31.3% in Part 2).
- In the 40 mg LSF treatment group in Part 2, gastrointestinal disorders, general disorders, and administration site conditions were also frequent (each at a frequency of 50.0%) for TEAEs.
- 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 groups. The occurrence of eye disorder TEAEs (that were judged to be drug related) increased with emodepside dose.
- There were no clinically significant changes, or differences between treatment groups, in laboratory variables (clinical chemistry, hematology, urinalysis), vital signs (systolic and diastolic BP, HR), or 12-lead ECG variables. There were no abnormal physical or neurological examination findings during the study.

Conclusions

Overall, emodepside was found to be safe up to 40 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.

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