P2724

Safety profile of oral zoliflodacin for uncomplicated gonorrhoea in a Phase 3 trial

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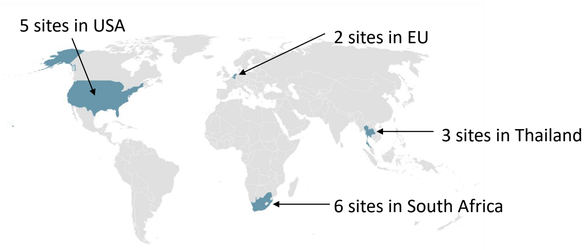
BACKGROUND & METHODS

BACKGROUND: Zoliflodacin is a first-in-class oral spiropyrimidinetrione antibiotic being developed for patients with uncomplicated gonorrhea, including those infected with multidrug-resistant strains. Zoliflodacin has been well tolerated in previous Phase 1 and Phase 2 trials and no major safety concerns have been identified. This GARDP-sponsored and fully publicly-funded Phase 3 clinical trial assessed efficacy and safety of zoliflodacin compared to standard of care (SOC) for the treatment of uncomplicated gonorrhoea.

!!! **Other zoliflodacin abstracts at ECCMID 2024** !!!

- **Topline Phase 3 efficacy and safety results [1]:** Oral presentation (Abstract 01099) on 30/04/2024, 08:30, Hall H
- **Poster P2527**: Antimicrobial susceptibility of baseline *Neisseria gonorrhoeae* isolates from the zoliflodacin Phase 3 trial
- **Poster P2424**: PK of zoliflodacin in healthy participants in the presence of itraconazole suggest no clinically meaningful drug-drug interactions (Phase 1)

For all posters: Poster session: 28/04/2024 , 12:00 in Poster Area



METHODS: A Phase 3, multicentre, randomised, open-label, non-inferiority trial was conducted at 16 sites in South Africa, Thailand, U.S.A, Netherlands and Belgium.

The safety population (all randomised participants who received trial treatment) consisted of 927 participants aged ≥ 12 years, of which 619 were treated with zoliflodacin and 308 with a combination of ceftriaxone and azithromycin (2:1 ratio).

Mean age of the randomised population included in the analysis was 29.7 years (range 15 – 73 years), 87.6% male at birth, 55.3% Black or African American, 30.6% Asian and 12.2% White.

Zoliflodacin was administered as a single 3 g oral dose (granules for suspension) and comparator treatment (SOC) as a single dose each of intramuscular 500 mg ceftriaxone and oral 1 g azithromycin at Day 1.

At Day 6, participants were scheduled for a test of cure visit. Safety follow-up was conducted at each visit up to 30 days after treatment and included evaluation of adverse events, safety laboratory assessments (full blood count and differentials, liver and renal function) and targeted physical examination.

RESULTS

Table 1: Treatment Emergent Adverse Events reported in > 1% participants overall by Treatment Group

MedDRA Preferred Term(s)	Zoliflodacin (N=619) n (%) E	Ceftriaxone + azithromycin (N=308) n (%) E	Overall (N=927) n (%) E
Neutropenia / Neutrophil count decreased (combined)	63 (10.2) 63	39 (12.7) 39	102 (11.0) 102
Headache	61 (9.9) 65	14 (4.5) 15	75 (8.1) 80
Injection site pain	5 (0.8) 6	38 (12.3) 38	43 (4.6) 44
Leukopenia / White blood cell count decreased (combined)	30 (4.9) 30	9 (2.9) 9	39 (4.2) 39
Diarrhea	15 (2.4) 15	22 (7.1) 22	37 (4.0) 37
Nausea	16 (2.6) 16	12 (3.9) 13	28 (3.0) 29
Dizziness	21 (3.4) 21	5 (1.6) 5	26 (2.8) 26
Alanine aminotransferase increased	12 (1.9) 12	5 (1.6) 5	17 (1.8) 17

Abbreviations: MedDRA: medical dictionary for regulatory activities, N: number of participants in the safety population, n: number of participants with AEs, E: number of AEs

- The most frequently reported TEAEs (>1% of participants, see Table 1) were neutropenia and neutrophil count decreased, headache, injection site pain, leukopenia and white blood cell count decreased, diarrhoea, nausea, dizziness and alanine transaminase (ALT) increased.

- Within the TEAE ≤1%, 4 TEAEs of vomiting were reported: 3 in the zoliflodacin arm and 1 in ceftriaxone-azithromycin arm. None of these patients vomited within 30 min of IMP administration.

- No deaths or serious AEs (SAEs) were observed during the trial. No participant withdrew from the trial due to a TEAE. No new safety signals were identified from analysis of laboratory or physical examination data.

- The incidence of adverse events (AEs) was similar in the two treatment arms with 46.2% of participants treated with zoliflodacin reporting an AE versus 46.4% of participants treated with ceftriaxone-azithromycin. The majority of treatment emergent AEs (TEAEs) (668/709; 94%) were mild or moderate (Grade 1 or 2 per CTCAE classification) in severity. There were few Grade 3 TEAEs (3.2% vs 5.8% for the zoliflodacin and ceftriaxone-azithromycin arms, respectively) and one Grade 4 TEAE of an asymptomatic clinically significant laboratory abnormality (neutrophil count decreased) that occurred in the zoliflodacin treatment arm. Overall, the frequency of TEAEs considered by the investigator to be related to treatment was generally balanced between treatment arms, with 18.9% of participants in the zoliflodacin arm compared with 24.7% in the ceftriaxone-azithromycin arm.

- Mean values for white cell count and absolute neutrophil count were noted to be lower at every time point, including baseline, for Black or African American participants compared with other races, with no notable difference between the treatment arms. Post hoc logistic regression analysis shows a statistically significant association between combined neutropenia/low neutrophil count events and Black or African American race (Black or African American: 101/411 [19.7%]; All Other: 1/414 [0.2%]; p<0.0001), with no statistical association with treatment. The observed frequency of combined TEAEs of neutropenia/low neutrophil count is consistent with the application of standard normal ranges to a population that predominantly consisted of Black or African American participants. It is well-known that haemoglobin, WBC and ANC differ considerably between African Americans and European Americans with African Americans having lower haemoglobin, WBC and ANC than European Americans (Lim et al, 2010).

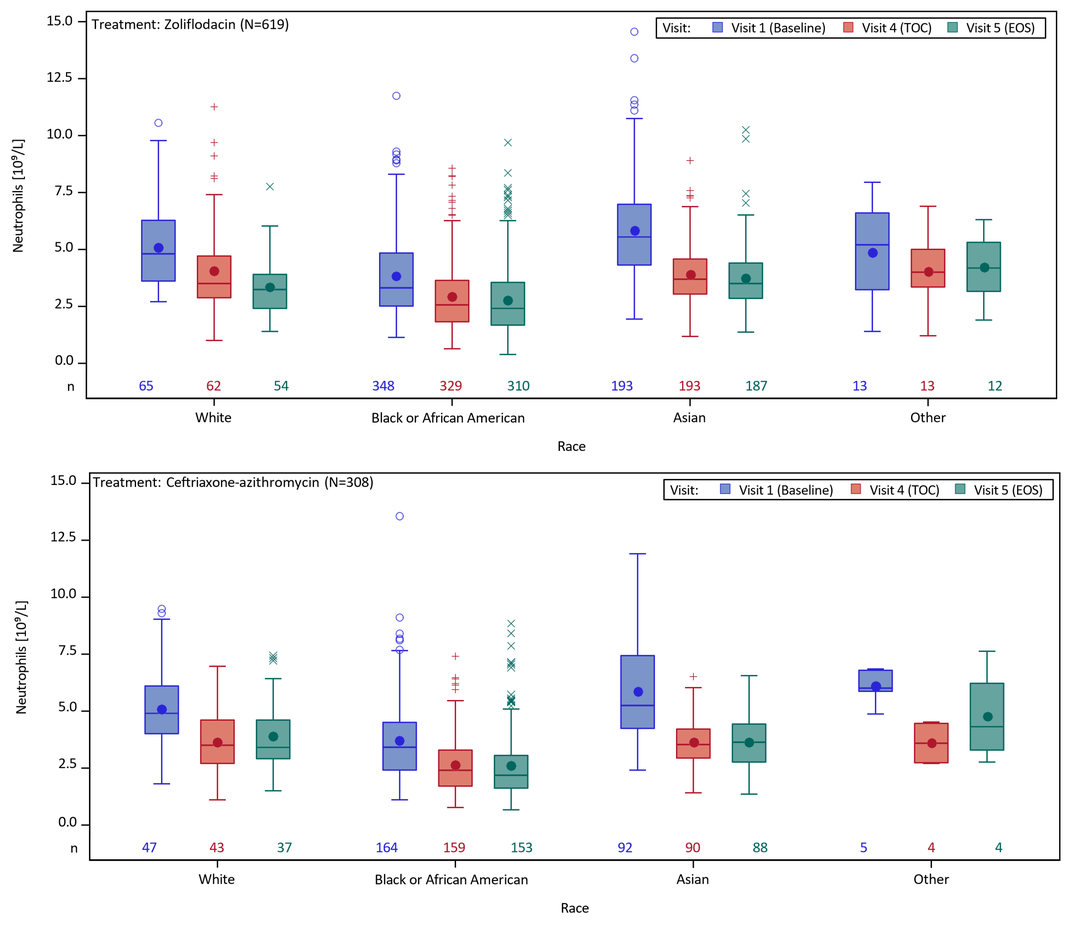


Figure 1: Boxplot of Absolute Neutrophil count at each visit by race for zoliflodacin-arm.

Abbreviations: TOC: Test of cure. EOS: End of study

CONCLUSION

Zoliflodacin was generally well-tolerated when administered as a single 3 g oral dose in participants with uncomplicated gonorrhoea. The observed safety data is consistent with the previously known safety profile of zoliflodacin.

References:
Lim EM, Cembrowski G, Cembrowski M, Clarke G. Race-specific WBC and neutrophil count reference intervals. Int J Lab Hematol. 2010;32(6 Pt 2):590-597.

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