TBAJ-587 and ERA4TB: a productive clinical development partnership

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Background

TBAJ-587 is a drug candidate from TB Alliance's pipeline to develop a safer, more effective diarylquinoline for novel TB regimens. ERA4TB is a public-private consortium devoted to accelerating development of new TB regimens. ERA4TB integrates 31 organizations – seven academic institutions, four non-profits, nine public research organizations, five small-medium enterprises, three EFPIA members, and three Associated Partners. TB Alliance, an Associated Partner of ERA4TB, is developing TBAJ-587 through the ERA4TB platform. TBAJ-587 is the first compound to have completed a first-in-human (FIH) study as part of ERA4TB.

Methods

ERA4TB organizes preclinical through phase-1 development of new compounds into 20 Modules distributed among 9 Work Packages. To date, TBAJ-587 has activated 9 Modules among 4 Work Packages. A validation tool was developed to assess the readiness of clinical sites. The FIH trial, comprising Single Ascending Dose (SAD), Food Effect (FE) and Multiple Ascending Dose (MAD) parts, was executed in collaboration with the Work Package coordination team at SERMAS and used QPS NL., an ERA4TB-approved Clinical Trial Unit in the Netherlands and their associated vendors. Project Management was provided by TB Alliance. Population PK models were developed for TBAJ-587 and its metabolites M2 and M3 based on the FIH data. To further support clinical translation, TBAJ-587, M2, and M3 were evaluated in time kill assays through the in vitro work package platform, and the potential for synergism between parent and metabolites was assessed in checkerboard assays. In vitro PK and PK/PD data were further integrated with FIH pharmacokinetic data through modeling to assess the clinical relevance of circulating metabolites.

Results

Nonclinical:

- Checkerboard assays suggested synergistic interactions between TBAJ-587 and M2 and M3 under selected culture conditions.
- Integrated modeling identified the M3 metabolite as a potentially clinically relevant metabolite.

Clinical:

- The FIH study enrolled 92 healthy participants in 6 fasting SAD cohorts + 1 FE cohort and 3 fed MAD cohorts.
- No severe or serious AEs; most were mild; all resolved.
- Fed exposure with FDA high-fat, high-calorie breakfast ~ 2x – 3x fasted exposure.
- Less-than-dose-proportional increase in exposure observed under fasting conditions in the SAD, but dose-proportional behavior under fed conditions in the

MAD:

- Long terminal half-life of ~ 16 weeks, similar to that of bedaquiline (~ 24 weeks).
- Modeling results are being integrated to guide dose selection in future studies.

Lessons Learned:

- TBAJ-587 was generally safe and well tolerated in healthy participants and no safety signals were identified.
- ERA4TB collaboration provided access to scientific expertise and novel technologies.
- Clinical sites within ERA4TB have been validated for future phase 1 trials.

Conclusion

TBAJ-587 remains a viable, second-generation diarylquinoline candidate. ERA4TB allows diverse organizations to collaborate, integrating data gathered from in vitro and in vivo studies with modeling tools to assess new compounds rapidly and comprehensively and streamline development. The standardized and unified platform of drug evaluation in the in vitro and in vivo work streams imparts a high level of confidence in the understanding of molecules and supports regulatory submissions.

Acknowledgments

This work has received support from the Innovative Medicines Initiatives 2 Joint Undertaking (grant No 853989).