Poster 13

Novel small molecule shows increased confidence in drug product performance in human

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Purpose

AZ'331 is a weak base with a pKa of 4.64. It is likely a BCSII molecule with poor solubility but high permeability. At the predicted human dose of 350mg, less than 50% absorption is estimated from an oral solid dosage form. The work presented here discusses efforts made to identify a novel solid form with improved oral absorption as well as increased confidence in drug product performance in human.

Methods

Salt screening, solid form characterization, solubility determination, and single crystal structure analysis were carried out for AZ'331. A suitable mesylate salt was identified and virtual polymorph landscape screening was performed on this salt. AZ'331 mesylate was scaled up and further characterized in vitro using u-DISS apparatus and TIM-1. Moreover, preclinical pharmacokinetic (PK) studies were conducted on the mesylate salt in comparison with the free form.

Results

The AZ'331 mesylate solid form A provides good solid state characteristics and a significant solubility enhancement in biorelevant media. However, predicting the virtual polymorph landscape was challenging. The complexity of this prediction increases substantially because there is more than one independent molecule (Z' > 1) in the salt crystal lattice and this causes a significant increase in degrees of freedom. With Z'=2, the crystal structure of AZ'331-MSA salt was successfully predicted, which confirmed that Form A is likely to be the most stable form. More importantly, in vitro dissolution data and in vivo PK profiles confirmed that mesylate salt can overcome not only solubility/dissolution limited absorption but also the negative impact on exposure in the fasted state when co-dosed with acid reducing agents (ARA) (ie, where stomach pH elevates to 4-6).

Conclusion

AZ'331 mesylate salt form A shows good solid state properties and significant solubility enhancement, and is likely to be the most stable solid form. Both in vitro dissolution and in vivo PK in preclinical species increases our confidence in the drug product performance of AZ'331 mesylate in human.

Keywords: poorly soluble, crystal structure informatics, oral absorption