Lyssine specific demethylase 1 (LSD1 or KDM1A) has been shown to contribute to AML pathogenesis by inhibiting the normal pro-differentiation function. It's been clearly shown now that there is cross talk between LSD1 and HDAC and combined inhibition of LSD1 and HDAC has been shown to be more efficacious in inhibiting cancer. In this regard, we have developed a dual inhibitor JBI295 that inhibits both LSD1 and HDAC6/8. JBI295 shows good activity on a sub-set of AML and in melanoma, while being more sensitive on cell lines where LSD1 inhibitors are active. HDAC6 as well as LSD1 inhibition was confirmed by modulation of tubulin acetylation with a concomitant increase in mRNA levels of CD86 and CD11b. JBI295 shows reasonable oral exposure and showed strong efficacy in Erythroleukemia and melanoma xenograft models as compared to single agent LSD1 or HDAC6 inhibitors or SoC. Further, JBI295 shows much stronger tumor growth inhibition in combination with anti-PD-L1 and CTLA4 mAbs in syngeneic models and was tolerated well. Single dose MTD for JBI295 was >1000 mg/kg and it was tolerated well with no adverse effects in repeat dose tolerability study. Therefore, pre-clinical and advanced studies are warranted for JBI295 to be developed as a clinical candidate.

**Summary**

**Stronger Biomarker Modulation**

**Anti-proliferative Activity of JBI295**

**Modulation of Proto-oncogenes and Tumor suppressors**

**MTD and Tolerability Studies**

**Conclusions**

- **JBI295 is a novel, orally available LSD1-HDAC6/8 dual with good potency on LSD1, HDAC6 and HDAC8, while exhibiting excellent selectivity towards other HDACs.**
- **JBI295 showed a strong TGI of HEL and melanoma xenograft models as compared to single agents and SoCs. In syngeneic models it can be combined with checkpoint inhibitor safely.**
- **Shows favourable tolerability profile at efficacious doses.**
- **JBI295 can be developed as a clinical candidate for treating a subset of AML and melanoma patients.**