Aim 2: MLi-2 LRRK2 Kinase Inhibitor Has No Effect on Pulmonary Function

LRRK2 Kinase Inhibitors Reduce pS935 and Total LRRK2 Protein

Conclusions
- Three distinct LRRK2 kinase inhibitors produced the previously reported lung histopathology (mild to moderate lung changes) in NHPs - confirming an on-target lung effect.
- No morphologic effects were seen with any LRRK2 inhibitor in brain or kidney.
- Di-22:6-BMP was lower in urine and kidney and increased in lung in all groups given LRRK2 inhibitors.
- GNE7915 effects on lung and BMP were reversed after 14d washout.
- PFE360 and MLi-2 induced lung histologic effects only at high doses, despite both low and high dose groups at Cmax reducing pS935 in lung by ~90%. Notably, the lower dose of MLi-2 left reduced LRRK2 pS935 at ~Cmax by ~90%.
- MLi-2 effects on lung histology were not associated with functionally significant alterations in any pulmonary functional endpoint examined.
- Overall, these data suggest that the on target morphological changes observed in the lungs of LRRK2 kinase inhibitor treated NHPs may not prevent the clinical evaluation of the therapeutic potential of LRRK2 kinase inhibitors in PD.