Discovery of MK-6158 an oral, once daily, Soluble Guanylate Cyclase (sGC) Stimulator for the treatment of Pulmonary Arterial Hypertension

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Soluble Guanylate Cyclase (sGC) is a heme containing enzyme that upon activation by nitric oxide (NO) catalyzes the conversion of guanosine-5'-triphosphate (GTP) into cyclic guanosine-3',5'-monophosphate (cGMP). Activation of the NO-sGC-cGMP pathway not only results in vasorelaxation and blood pressure lowering, but also leads to anti-remodeling, anti-proliferative and anti-fibrotic effects in pulmonary hypertension, heart failure and fibrosis in animal models.

sGC can be activated by small molecule "stimulators" that activate the enzyme independently of the NO tone and have the ability to synergize with NO. Two approved sGC stimulators include Riociguat (for treatment of chronic thromboembolic pulmonary hypertension (CTEPH)) and Vericiguat for treatment of chronic heart failure (HF). Here we will present the discovery of MK-6158, a novel sGC stimulator that demonstrates high potency both *in-vitro* and *in-vivo*. We will discuss the SAR progression leading to the discovery of the clinical candidate with an optimized balanced clearance profile, a clean off-target profile needed to reduce the risk of drug-drug interaction, and a half-life in preclinical species compatible with once daily- oral dosing.