**LBP17**

# BMS-986263 (novel targeted lipid nanoparticle delivering HSP47 siRNA) safety and target engagement in patients with advanced hepatic fibrosis: week 36 results from a phase 2 randomized, double-blind, placebo-controlled trial

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**Background and Aims:** BMS-986263 is a lipid nanoparticle (LNP) containing a small interfering ribonucleic acid (siRNA) that degrades heat shock protein 47 (*HSP47)* mRNA, which encodes HSP47, a collagen chaperone. In the Phase 2 IM025-006 (NCT03420768) study, BMS-986263 weekly (QW) x12 weeks (wks) was generally well tolerated and demonstrated METAVIR and Ishak improvements in patients (pts) with advanced liver fibrosis from chronic hepatitis C who had achieved sustained virologic response (HCV-SVR). Here, we present HSP47 target engagement (TE) data (liver *HSP47* mRNA and protein), quantitative fibrosis measurement using dual-photon microscopy (qFIB), and safety through wk 36.

**Method:** This was a Phase 2, randomised, double-blind, placebo-(PBO) controlled study in pts with METAVIR F3-F4 fibrosis (local liver biopsy) at screening. BMS-986263 (45 or 90mg) or PBO were IV infused QW x12 wks; follow-up was until wk 36. Objectives included METAVIR (≥1 stage) and Ishak (≥2 stages) improvements (central-, pair-read liver biopsies); liver *HSP47* mRNA (EDGEseq) changes; HSP47 protein (IHC) and qFIB at wk12; safety and tolerability.

**Results:** Reduced liver *HSP47* mRNA levels were observed at wk 12 compared with baseline in 13% (2/15; PBO), 44% (8/18; 45mg), and 71% (20/28; 90mg) of pts. BMS-986263 45 and 90mg groups showed a trend for decreased median liver HSP47 protein at wk 12. In IM025-006, 13% (2/15; PBO), 17% (3/18; 45mg), and 21% (6/28; 90mg) had METAVIR improvements; 0% (0/15; PBO), 0% (0/18), and 19% (5/27) of 90mg pts had Ishak improvements. Of pts with METAVIR improvements at wk 12, 50% (1/2; PBO), 67% (2/3; 45mg), and 100% (6/6; 90mg) also showed qFIB improvement. All pts with Ishak improvement (5/5, all in the 90mg group) had improved qFIB. qFIB improvements were observed for some METAVIR and Ishak non-responders. At wk 36, safety findings were consistent with wk 12. Most AEs were mild to moderate infusion-related reactions (IRRs); of all BMS-986263 infusions, IRRs occurred in 7% (15/216; 45mg) and 11% (37/336; 90mg) of pts. No meaningful bone biomarker changes occurred.

**Conclusion:** In this study of a limited number of pts with HCV-SVR and fibrosis, BMS-986263 IV QW x12 wks demonstrated TE by reducing liver *HSP47* mRNA. The majority of METAVIR and Ishak responders had improved qFIB. BMS-986263 was generally well tolerated through wk 36. These data support further evaluation of BMS-986263 in pts with advanced liver fibrosis.

**Figure:**