Title of Research
A Five-Year Follow-Up Study of Subjects Who Completed the REALM-China Study (AI463-520/REALM-SON STUDY)

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Summary of Research
The REALM Study (AI463080) was a randomized, open-label, observational study in which patients with chronic hepatitis B virus (HBV) infection were randomized 1:1 to entecavir vs. other standard of care HBV nucleoside or nucleotide analogues, chosen at the investigator’s discretion. Long-term clinical outcomes were then followed prospectively. Some 5,332 REALM study participants were randomized to treatment with entecavir (n=2,667) or other standard of care (n=2,665) across 50 sites in China. The REALM study – which has been completed – represents the largest chronic hepatitis B (CHB) patient cohort to be treated with nucleoside or nucleotide analogues in China. The majority of participants remained on the study and on their originally randomized and assigned study therapy, and had received treatment for eight-to-10 years when the study was completed.

The new, investigator-initiated, prospective, observational study (Study AI463520/REALM-SON study) will follow the REALM study participants for another five years. The primary objective will be to evaluate treatment patterns and HBV-related clinical outcomes in the REALM-SON study, and in REALM and REALM-SON combined. Secondary objectives will be to assess long-term efficacy and safety endpoints in REALM; explore the potential relationship between pre-treatment biomarkers and antiviral efficacy endpoints on anti-HBV treatment in REALM; and evaluate the relationship between baseline liver stiffness measurement (LSM) and HBV-related clinical outcomes in REALM-SON.

Study Design
No randomization will be carried out, and no protocol-driven treatment will be provided. Instead, clinically appropriate decisions not to treat or to change medications will be made by treating physicians. In order to maintain continuity and integrity of this cohort since their entry into REALM, select legacy data from that study will be shared and integrated with data obtained from subjects during their participation in the new study. An external event adjudication committee will be established to validate reported HBV-related clinical outcomes and mortality.

At the first, baseline visit in REALM-SON, certain clinical and laboratory data collected during REALM will be compiled retrospectively from each study participant’s REALM study file and, where available, from their medical record from the site where routine HBV-related care is given. In addition, stored blood samples obtained from the subject pre-treatment and during years one through five of REALM will be retrospectively assayed to obtain additional HBV-related data, which will enrich the data on this subject population. During the five-year follow-up phase of REALM-SON, all eligible subjects will be followed every six months.

Study Population
The study population will include participants who completed the REALM study in China and who are willing to give consent to continue anti-viral treatment or post-treatment follow up, and agree that legacy data and

1 https://clinicaltrials.gov/ct2/show/NCT00388674
blood/liver histology samples collected in REALM may be used for the analyses planned for the new study. REALM participants will be excluded if they have subsequently enrolled in an investigational drug clinical trial.

**Funding Source of Research**
BMS and the Chinese Government.

**Requested Study**
AI463-080 (NCT02974829): Randomized, Observational Study of Entecavir to Assess Long-term Outcomes Associated With Nucleoside/Nucleotide Monotherapy for Patients with Chronic HBV Infection: The REALM Study