1. ABSTRACT

- **Title**

Matching-adjusted indirect comparison of sotorasib versus adagrasib in previously treated advanced/metastatic non-small cell lung cancer (NSCLC) harboring *KRAS* G12C mutation (report as of June 02, 2025)

- **Keywords**

KRAS G12C mutation; matching-adjusted indirect comparison; non-small cell lung cancer; sotorasib; adagrasib.

- **Rationale and Background**

As of August 2024, sotorasib and adagrasib are the only FDA/EMA approved $KRAS^{G12C}$ inhibitors for the treatment of NSCLC harboring a *KRAS* G12C mutation. In the absence of head-to-head clinical trials between sotorasib and adagrasib, a matching-adjusted indirect treatment comparison (MAIC) [15] based on the phase 3 trial data: CodeBreaK 200 (CB200) [16] and KRYSTAL-12 (K-12) [17] was conducted to assess the relative efficacy and safety of sotorasib vs adagrasib.

- **Research Question and Objectives**

Research Question:

What is the comparative efficacy and safety of sotorasib vs adagrasib in previously treated NSCLC patients with *KRAS* G12C mutation?

Objective:

To estimate the relative efficacy and safety of sotorasib compared to adagrasib in patients with previously treated NSCLC harboring a *KRAS* G12C mutation

- **Study Design**

The indirect treatment comparison of data from two phase 3 trials using MAIC.

- **Setting**

CB200 and K-12 shared similar methodological and clinical similarities in terms of study design, eligibility criteria, primary and secondary endpoints, and baseline characteristics with the possibility of adjusting for imbalanced ones. With availability of individual patient level data from CB200, and aggregate data from K-12, an MAIC analysis was used.

- **Patients and Study Size, Including Dropouts**

Previously treated patients with *KRAS* G12C mutated advanced NSCLC (ITT or safety population for efficacy or safety outcomes, respectively) from CB200 (n=171, sotorasib; n=174, docetaxel); and K-12 (n=301, adagrasib; n=152, docetaxel); Subgroup: Patients with stable treated brain metastases at baseline. The early dropout rate in the docetaxel arm of CB200 was 65% higher compared to the early dropout rate in the docetaxel arm in K-12.

- **Data Source(s) and Methods**

Data from two eligible phase 3 randomized controlled trials (RCT) were identified using a systematic literature review. Patient-level data from CB200 (data cutoff date: August 2, 2022) were weighted for comparison with aggregate data from K-12 (data cutoff date: December 31, 2023) using MAIC. Progression-free survival (PFS), objective response rate (ORR), and treatment-related adverse events (TRAE) were assessed (only TRAEs were reported for K-12). Age, sex, region, prior chemotherapy + immunotherapy, brain

metastases, and liver metastases were adjusted in the base case per clinical guidance, using an unanchored approach. Sensitivity analyses adjusted for additional covariates, or utilized an anchored approach. For subgroup of patients with brain metastases, systemic PFS was assessed.

- **Results**

Following adjustment, the reweighted patient characteristics from CB200 and K-12 were well balanced. In the base case, the efficacy of sotorasib and adagrasib was comparable, with PFS showing a hazard ratio (HR) of 0.93 (95% confidence interval: 0.70–1.22; p=0.589) and ORR showing an odds ratio of 0.86 (0.53–1.38; p=0.524). In patients with baseline stable treated brain metastases, sotorasib was associated with a 39% reduced risk of progression compared with adagrasib (HR: 0.61; 0.38–0.98; p=0.040). Sotorasib also demonstrated a more favorable safety profile than adagrasib, with lower odds of TRAEs, TRAEs leading to dose reduction or dose interruption, and all eight individual TRAEs evaluated. Sensitivity analyses supported the robustness of base-case results. Cross-trial comparisons should be interpreted with caution given differences in study design and follow-up.

- **Discussion**

Sotorasib and adagrasib showed comparable efficacy in patients with previously treated advanced *KRAS* G12C-mutated NSCLC. Among patients with baseline stable treated brain metastases, PFS point estimates favored sotorasib. Furthermore, in this MAIC, sotorasib demonstrated a more favorable safety profile compared to adagrasib. The safety profile of sotorasib was found to be consistent with its known clinical profile,These findings can inform payer decisions and clinical practice in the treatment of *KRAS* G12C-mutated NSCLC.