US Post Marketing Commitments/Requirements

Product/ Compound	Description of Commitment	NDA/BLA Number	Agreement Date	Projected Completion Date	Status
Savaysa (edoxaban)	2852-1: Pediatric Development in VTE (AF waived) Single-dose PK/PD study	206316	01/08/2015	12/31/2021 Study Completed	Submitted on 01/28/2022 Fulfilled on 10/18/2023
Savaysa (edoxaban)	2852-2: Phase 3 multicenter, randomized, active control study of Edoxaban in pediatric patients with documented venous thromboembolism	206316	01/08/2015	6/30/2022	Submitted on 12/19/2022 Received FDA PMR not Fulfilled letter dated 10/18/2023
ENHERTU (fam-trastuzumab deruxtecan- nxki), 100mg injection	3762-5 Provide data from a media fill run to support the use of the drug product specific container closure system.	761139	12/20/2019	1/2020	Submitted 01/09/2020 Pending :FDA downgraded this to PMC final report due within 12 mos. of submission

US Post Marketing Commitments/Requirements

Product/ Compound	Description of Commitment	NDA/BLA Number	Agreement Date	Projected Completion Date	Status
TURALIO (Pexidartinib) 200 mg Capsules	3673-1: Conduct a long-term trial to further evaluate the risk of hepatoxicity in adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery, who are receiving pexidartinib. The trial will include laboratory, imaging, and pathologic assessments of patients who experience liver toxicity due to exposure to pexidartinib. The trial should enroll patients with an AST or ALT > 3 x ULN with concomitant bilirubin >2 x ULN, an isolated bilirubin > 2 x ULN (excluding those with Gilbert's syndrome), or an isolated AST or ALT > 10 x ULN. The trial should evaluate the mechanism of action of liver injury based on liver biopsy information, including a detailed assessment of changes in resident macrophage phenotype, based on marker status, as well as detailed characterization of other immune cell infiltrates. Submit cumulative, integrated safety analyses after 5 and 10 years of follow-up from an adequate number of patients to characterize the long-term risk of hepatic failure with pexidartinib. These safety evaluations should be adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modifications and monitoring recommendations.	211810	08/02/2019	06/2036	Ongoing

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Product/ Compound	Description of Commitment	NDA/ BLA Number	Agreement Date	Projected Completion Date	Status
ENHERTU (fam-trastuzumab deruxtecan-nxki), 100mg injection	3762-2 Submit the integrated immunogenicity summary report for all patients with solid tumors in clinical studies treated with DS-8201a, including the ongoing Phase 3 trials, having an immunogenicity component. The final report should include anti-drug antibody (ADA) results from screening, confirmatory, titering, domain specificity, and neutralization assays, the results of linear or non-linear correlation analyses between ADA status and titers with PK, PD, efficacy, and safety (adverse event) data. Submit the Integrated Immunogenicity Summary Report in accordance with Section VIII Documentation of the 2019 FDA Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection	761139	12/20/2019	06/2023	Submitted on 6/26/2023
ENHERTU (fam-trastuzumab deruxtecan-nxki), 100mg injection	3762-8 Perform the dye ingress method validation for container closure integrity testing of the drug product stability samples using positive controls with a ≤20 micro breach size.	761139	12/20/2019	06/2020	Submitted 06/24/2020; Pending FDA Response

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Product/ Compound	Description of Commitment	NDA/BLA Number	Agreement Date	Projected Completion Date	Status
ENHERTU (fam-trastuzumab deruxtecan-nxki), 100mg injection	3762-11 Confirm that the potency of the current DS-8201a primary reference standard 164RS03 and secondary reference standard 164WS01 is precise and accurate by conducting additional qualification of potency for primary reference standard 164RS03 using a sufficient number of independent assays and replicates. The number of independent assays and replicates will be scientifically justified. The qualification data will be reported as per 21 CFR 601.12.	761139	12/20/2019	02/2020	Submitted 2/20/2020 Pending: FDA downgraded this to PMC final report due within 12 mos. of submission
ENHERTU (fam-trastuzumab deruxtecan-nxki), 100mg injection	3762-12 Confirm that the potency of MAAL-9001 primary reference standard 159RS02 is precise and accurate by conducting additional qualification of potency of primary reference standard 159RS02 using a sufficient number of independent assays and replicates. The number of independent assays and replicates will be scientifically justified. The qualification data will be reported as per 21 CFR 601.12.		12/20/2019	02/2020	Submitted 02/20/2020 Pending: FDA downgraded this to PMC final report due within 12 mos. of submission

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Product/ Compound	Description of Commitment	NDA/BLA Number	Agreement Date	Projected Completion Date	Status
ENHERTU (fam-trastuzumab deruxtecan-nxki), 100mg injection	3762-13 Strengthen the qualification of the current MAAL-9001 primary and secondary reference standards by conducting additional characterization studies including full glycan profile analysis and FcγRIIIA binding activity of MAAL-9001 primary reference standard 159RS02 and secondary reference standard ST01-01 to support the use of these reference standards in comparability assessments. The qualification data will be reported as per 21 CFR 601.12	761139	12/20/2019	02/2020	Submitted 02/20/2020 Pending :FDA downgraded this to PMC final report due within 12 mos. of submission
ENHERTU (fam-trastuzumab deruxtecan-nxki), 100mg injection	3762-14 Strengthen the qualification of the DS-8201a primary and secondary reference standards by conducting characterization of FcγRIIIA binding activity for primary reference standard 164RS03 to support the use of these reference standards in comparability assessments. The qualification data will be reported as per 21 CFR 601.12.	761139	12/20/2019	02/2020	Submitted 02/20/2020 Pending :FDA downgraded this to PMC final report due within 12 mos. of submission

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Product/ Compound	Description of Commitment	NDA/BLA Number	Agreement Date	Projected Completion Date	Status
ENHERTU (fam-trastuzumab deruxtecan-nxki), 100mg injection	3762-15 Re-evaluate intermediate precision for the protein concentration and glycan analysis methods at Daiichi Sankyo Tatebayashi Plant, and for protein concentration, non-proteinaceous impurities (NPI) and purity of payload (PoP) methods for DS-8201a drug substance at Daiichi Sankyo Onahama Plant and report will be reported as per 21 CFR 601.12.	761139	12/20/2019	03/2020	Submitted 03/20/2020 Pending FDA Response
ENHERTU (fam-trastuzumab deruxtecan-nxki), 100mg injection	3762-16 Develop and validate a neutralizing antibody assay to test confirmed anti DS-8201a antibody positive samples from studies J101, J102, A103, A104, and U201 as well as the ongoing Phase 3 clinical studies U301, U302, and U303.	761139	12/20/2019	06/2020	Submitted 06/19/2020 Fulfilled on 07/05/2023

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Product/ Compound	Description of Commitment	NDA/BLA Number	Agreement Date	Projected Completion Date	Status
ENHERTU (fam-trastuzumab deruxtecan-nxki), 100mg injection	3762-17 Develop and validate domain specificity assays to test confirmed anti-DS 8201a antibody positive samples from studies J101, J102, A103, A104, and U201 as well as the ongoing phase 3 clinical studies U301, U302, and U303. Specifically, the assays should determine the specificity of anti-DS 8201a antibodies for the monoclonal antibody MAAL-9001, the drug MAAA-1181a, and the linker.	761139	12/20/2019	12/2020	Submitted 12/18/2020 Fulfilled on 07/05/2023
ENHERTU (fam-trastuzumab deruxtecan-nxki), 100mg injection	4269-1 Conduct the interim and final OS analysis for clinical study DESTINYBreast03 (NCT03529110) entitled “A Phase 3, multicenter, randomized, open-label, active-controlled study of T-DXd, an anti-HER2-antibody drug conjugate, versus T-DM1 for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with trastuzumab and taxane”, to further confirm the clinical benefit of T-DXd in this setting. Interim Report Submission: 04/2023 Trial Completion: 09/2026 Final Report Submission: 03/2027	761139	05/04/2022	03/2027	Submitted on 4/28/2023 OS interim analysis submitted as the final report. Pending FDA Response

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Product/ Compound	Description of Commitment	NDA/BLA Number	Agreement Date	Projected Completion Date	Status
ENHERTU (fam-trastuzumab deruxtecan-nxki), 100mg injection	4318-1 Conduct an integrated analysis containing data from clinical trials and other data sources such as post-marketing reports, real-world evidence and other sources to further characterize the safety and efficacy of T-DXd in racial and ethnic minority patients and older patients age >65 years with HER2-low metastatic breast cancer. The analyses should support comparative safety and efficacy outcome analyses between the aforementioned populations and White and younger patients. The timetable you submitted on August 1, 2022, states that you will conduct this study according to the following schedule: • Draft Protocol Submission: 05/2023 • Final Protocol Submission: 12/2023 • Trial Completion: 12/2026 • Final Report Submission: 09/2027	761139	08/05/2022	09/2027	Ongoing - Final Protocol Submitted on 12/21/2023

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Product/ Compound	Description of Commitment	NDA/BLA Number	Agreement Date	Projected Completion Date	Status
ENHERTU (fam-trastuzumab deruxtecan-nxki), 100mg injection	4321-1 Complete a clinical trial to obtain data on the clinical efficacy of fam-trastuzumab deruxtecan nxki for the treatment of patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have an activating HER2 (ERBB2) mutation and have previously received systemic therapy, to provide a more precise estimation of the blinded independent central review-assessed overall response rate and duration of response. This report will contain data from patients with NSCLC harboring HER2 mutations and data from at least 102 patients who have received prior systemic therapy, after all responders have been followed for at least 6 months from the date of initial response (or until disease progression, whichever comes first). • Draft Protocol Submission: 11/2022 • Final Protocol Submission: 02/2023 • Trial Completion: 09/2023 • Final Report Submission: 03/2024	761139	08/05/2022	03/2024	Submitted 03/29/2024 Pending FDA response.

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Product/ Compound	Description of Commitment	NDA/BLA Number	Agreement Date	Projected Completion Date	Status
ENHERTU (fam-trastuzumab deruxtecan-nxki), 100mg injection	4321-2 Conduct a multicenter, randomized clinical trial of fam-trastuzumab deruxtecan-nxki in patients with treatment-naïve, unresectable or metastatic non-small cell lung cancer whose tumors have an activating HER2 (ERBB2) mutation. The final analysis should include the final progression-free survival and overall survival results. • Final Protocol Submission: 07/2021 (completed; DL-04) • Trial Completion: 03/2028 • Final Report Submission: 09/2028	761139	08/11/2022	09/2028	Ongoing
VANFLYTA (quizartinib) tablets	4467-1 Conduct a clinical study to confirm the appropriate dose of quizartinib, and to assess safety, tolerability, pharmacokinetics, and pharmacodynamics of quizartinib in combination with fludarabine and cytarabine, in pediatric patients ages ≥1 month to < 12 years old. • Interim Report Submission: 12/2025 • Study Completion: 08/2030 • Final Report Submission: 02/2031	216993	7/20/2023	02/2031	Ongoing

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Product/ Compound	Description of Commitment	NDA/BLA Number	Agreement Date	Projected Completion Date	Status
VANFLYTA (quizartinib) tablets	4467-2 Conduct an observational study using electronic health records (EHR) to further assess the risk of severe (Grades 3-4) and fatal ventricular arrhythmia events in adult patients treated with quizartinib for the indication of acute myeloid leukemia (AML) that is FLT3-ITD positive as detected by an FDA-approved test. The selected EHR data source should contain access to clinical data elements including ECG results, laboratory results, concomitant medications, and clinical data to allow for outcome validation (i.e., via chart review). Evaluate the incidence of severe and fatal arrhythmia events and collect detailed clinical features of the adverse reactions, to investigate associations and temporal relationships between the incidence and severity of arrhythmia events and other potential associated risk factors. Specify case definitions, measurement, validation methods, and procedures for all study outcomes. • Draft Protocol Submission: 05/2024 • Final Protocol Submission: 11/2024 • Interim Report Submission 1: 11/2025 • Interim Report Submission 2: 11/2026 • Interim Report Submission 3 11/2027 • Interim Report Submission 4: 11/2028 • Study Completion: 11/2029 • Final Report Submission: 05/2030	216993	7/20/2023	05/2030	Ongoing

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Product/ Compound	Description of Commitment	NDA/BLA Number	Agreement Date	Projected Completion Date	Status
VANFLYTA (quizartinib) tablets	4467-3 Conduct an exercise test study in healthy subjects to further evaluate the serious risk of QTc prolongation with quizartinib. Evaluate the impact of rapid acceleration in heart rate on the cardiac safety of quizartinib using a standardized test protocol such as Bruce protocol, modified Bruce protocol, or graded-intensity bicycle exercise test. Identify QT/QTc and RR intervals at rest, peak exercise, and recovery, and capture the incidence of arrhythmias and other adverse reactions. • Draft Protocol Submission: 03/2024 • Final Protocol Submission: 09/2024 • Study Completion: 10/2025 • Final Report Submission: 04/2026	216993	7/20/2023	04/2026	Ongoing Draft protocol submitted on 03/25/2024

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Product/ Compound	Description of Commitment	NDA/BLA Number	Agreement Date	Projected Completion Date	Status
VANFLYTA (quizartinib) tablets	4467-4 Conduct a sub-maximal exercise test study in patients with AML to further evaluate the serious risk of QTc prolongation with quizartinib. Evaluate the impact of rapid acceleration in heart rate on the cardiac safety of quizartinib using a 24-Hour Holter study with sub-maximal exercise (e.g., postural provocation – i.e., supine to standing). Identify QT/QTc and RR intervals at rest and sub-maximal exercise and capture the incidence of arrhythmias and other adverse reactions. Include patients on betablockers in order to observe for mitigating effects on the incidence of quizartinib-related adverse reactions. • Draft Protocol Submission: 03/2024 • Final Protocol Submission: 09/2024 • Study Completion: 04/2027 • Final Report Submission: 10/2027	216993	7/20/2023	10/2027	Ongoing Draft protocol submitted on 03/25/2024

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Product/ Compound	Description of Commitment	NDA/BLA Number	Agreement Date	Projected Completion Date	Status
VANFLYTA (quizartinib) tablets	4467-5 Conduct a randomized trial of quizartinib maintenance therapy that compares the recommended dosage of 53 mg daily to a lower dosage (e.g., 26.5 mg daily) to further characterize serious adverse reactions including but not limited to the rates of Grade ≥3 adverse reactions, Grade ≥ 3 neutropenia, QTc interval prolongation, and dose reductions, interruptions, and discontinuations due to adverse reactions and provide an analysis of dose- and exposure-response relationships for safety. Incorporate systematically assessed patient-reported outcome assessments to further characterize safety and tolerability, including patient-reported symptoms, function, and overall side effect impact. Eligible patients will include newly diagnosed, FLT3-ITD positive AML patients in complete remission following consolidation and exclude patients who underwent allogeneic hematopoietic stem cell transplantation. The study should also provide an analysis of dose- and exposure-response relationships for efficacy, including overall survival and relapse-free survival. • Draft Protocol Submission: 03/2024 • Final Protocol Submission: 09/2024 • Interim Report Submission: 04/2029 • Trial Completion: 09/2032 • Final Report Submission: 03/2033	216993	7/20/2023	03/2033	Ongoing Draft protocol submitted on 03/25/2024

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Product/ Compound	Description of Commitment	NDA/BLA Number	Agreement Date	Projected Completion Date	Status
VANFLYTA (quizartinib) tablets	4467-6 Conduct a clinical pharmacokinetic trial to assess the magnitude of change in exposure of quizartinib and its metabolite AC886 and to determine appropriate dosing recommendations of quizartinib in patients with severe hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling. • Draft Protocol Submission: 03/2024 • Final Protocol Submission: 09/2024 • Trial Completion: 09/2025 • Final Report Submission: 03/2026	216993	7/20/2023	03/2026	Ongoing Draft protocol submitted on 03/25/2024
VANFLYTA (quizartinib) tablets	4467-7 Conduct exploratory analyses aimed at identifying potential mechanisms of primary and acquired resistance to quizartinib using longitudinal samples for cytogenetic and mutational analyses collected at baseline and at the end of treatment or time of relapse from patients treated with quizartinib in QuANTUM-First. Include a discussion of the results in the context of the available published literature. • Draft Protocol Submission (Analysis Plan): 01/2024 • Final Protocol Submission (Analysis Plan): 05/2024 Study Completion: 09/2024 • Final Report Submission: 12/2024	216993	7/20/2023	12/2024	Ongoing Draft Protocol Submitted 01/24/2024

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Product/ Compound	Description of Commitment	NDA/BLA Number	Agreement Date	Projected Completion Date	Status
VANFLYTA (quizartinib) tablets	4467-8 Conduct a clinical pharmacokinetic trial to assess the magnitude of decreased exposure of quizartinib and its metabolite AC886, and to determine appropriate dosing recommendations for quizartinib, with coadministration of a weak CYP3A inducer. Design and conduct the trial in accordance with the FDA Guidance for Industry: Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions. • Draft Protocol Submission: 03/2024 • Final Protocol Submission: 09/2024 • Trial Completion: 01/2025 • Final Report Submission: 07/2025	216993	7/20/2023	07/2025	Ongoing Draft protocol submitted on 03/25/2024