US Post Marketing Commitments

Product/ Compound	Description of Commitment	NDA Number	Agreement Date	Projected Completion Date	Status
Benicar (olmesartan medoxomil) 5/20/40 MG	Pediatric assessment.	21-286	4/25/2002	Complete	Fulfilled
Benicar (olmesartan medoxomil) 5/20/40 MG	A study to evaluate olmesartan for effects on hERG and hNav1.5 currents in whole cell voltage clamp studies using ion channels expressed in a mammalian cell line.	21-286	5/26/2011	Complete	Fulfilled
Benicar (olmesartan medoxomil) 5/20/40 MG	Perform a thorough QT/QTc study for olmesartan in accordance with the FDA Guidance, "Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Anti-arrhythmic Drugs.	21-286	5/26/2011	Complete	Fulfilled

US Post Marketing Commitments

Product/ Compound	Description of Commitment	NDA Number	Agreement Date	Projected Completion Date	Status
Benicar (olmesartan medoxomil) 5/20/40 MG	Conduct an epidemiologic study using claims or electronic health records data to evaluate the comparative incidence of sudden cardiac death, in hospital fatal myocardial infarction and total mortality in olmesartan users vs. users of other angiotensin receptor blockers and in olmesartan users vs. ACE inhibitor users.	21-286	5/26/2011	Complete	Fulfilled
Benicar (olmesartan medoxomil) 5/20/40 MG	Conduct a patient-level meta-analysis evaluating the incidence of major cardiovascular events and total mortality in olmesartan treated patients compared to control patients in randomized clinical trials.	21-286	5/26/2011	Complete	Fulfilled

US Post Marketing Commitments

Product/ Compound	Description of Commitment	NDA Number	Agreement Date	Projected Completion Date	Status
Morphabond ER (morphine sulfate) 15/30/60/100 MG	2065-1: Conduct one or more studies to provide quantitative estimates of the serious risks of misuse, abuse, addiction, overdose, and death associated with long-term use of opioid analgesics for management of chronic pain, among patients prescribed ER/LA opioid products. Include an assessment of risk relative to efficacy.	206544	10/2/2015	01/2018	Released & replaced with 3033 PMR
Morphabond ER (morphine sulfate) 15/30/60/100 MG	2065-2: Develop and validate measures of the following opioid-related adverse events: misuse, abuse, addiction, overdose and death (based on DHHS definition, or any agreed-upon definition), which will be used to inform the design and analysis for PMR # 2065-1 and any future post-marketing safety studies and clinical trials to assess these risks. This can be achieved by conducting an instrument development study or a validation study of an algorithm based on secondary data sources.	206544	10/2/2015	08/2015	Released & replaced with 3033 PMR

US Post Marketing Commitments

Product/ Compound	Description of Commitment	NDA Number	Agreement Date	Projected Completion Date	Status
Morphabond ER (morphine sulfate) 15/30/60/100 MG	2065-3: Conduct a study to validate coded medical terminologies (e.g., ICD9, ICD10, SNOMED) used to identify the following opioid-related adverse events: misuse, abuse, addiction, overdose, and death in any existing post-marketing databases to be employed in the studies. Stratify misuse and overdose by intentionality wherever possible. These validated codes will be used to inform the design and analysis for PMR # 2065-1.	206544	10/2/2015	08/2015	Released & replaced with 3033 PMR
Morphabond ER (morphine sulfate) 15/30/60/100 MG	2065-4: Conduct a study to define and validate "doctor/pharmacy shopping" as outcomes suggestive of misuse, abuse and/or addiction. These validated codes will be used to inform the design and analysis for PMR # 2065-1.	206544	10/2/2015	08/2015	Released & replaced with 3033 PMR
Morphabond ER (morphine sulfate) 15/30/60/100 MG	2065-5: Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following use of ER/LA opioid analgesics for at least one year to treat chronic pain. We strongly encourage you to use the same trial to assess the development of tolerance following use of ER/LA opioid analgesics. Include an assessment of risk relative to efficacy.	206544	10/2/2015	08/2016	Released & replaced with 3033 PMR

US Post Marketing Commitments

Product/ Compound	Description of Commitment	NDA Number	Agreement Date	Projected Completion Date	Status
Morphabond ER (morphine sulfate) 15/30/60/100 MG	2961-1: Conduct epidemiologic to address whether the properties intended to deter misuse and abuse of MORPHABOND (morphine sulfate extended release tablets) actually result in a significant and meaningful decrease in misuse and abuse, and their consequences, addiction, overdose, and death, in the community. The post-marketing study program must allow FDA to assess the impact, if any, that is attributable to the abuse-deterrent properties of MORPHABOND. To meet this objective, investigations should incorporate recommendations contained in the FDA draft guidance, Abuse Deterrent Opioids—Evaluation and Labeling (January 2013) and proposed comparators need to be mutually agreed upon prior to initiating epidemiologic investigations. There must be sufficient drug utilization to allow a meaningful epidemiological assessment of overall and route-specific abuse deterrence.	206544	10/2/2015	08/2020	Released & replaced with 2961-9 PMR on 5/12/17

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Product/ Compound	Description of Commitment	NDA Number	Agreement Date	Projected Completion Date	Status
Morphabond ER (morphine sulfate) 15/30/60/100 MG	2961-2: Conduct a 9-month repeat-dose oral toxicology study in the non-rodent model characterizing the toxicological potential of [REDACTED]	206544	10/2/2015	07/2018	Released on Feb 10, 2021 NDA Withdrawn
Morphabond ER (morphine sulfate) 15/30/60/100 MG	2961-3: Conduct a 6-month repeat-dose oral toxicology study in the rodent model characterizing the toxicological potential of [REDACTED]	206544	10/2/2015	05/2017	Released on Feb 10, 2021 NDA Withdrawn
Morphabond ER (morphine sulfate) 15/30/60/100 MG	2961-4: Conduct a fertility and early embryonic development study in both male and female rats with [REDACTED]	206544	10/2/2015	05/2018	Released from PMR on 01/15/2016
Morphabond ER (morphine sulfate) 15/30/60/100 MG	2961-5: Conduct an embryofetal development study for [REDACTED] in the rat model.	206544	10/2/2015	10/2017	Released from PMR on 01/15/2016
Morphabond ER (morphine sulfate) 15/30/60/100 MG	2961-6: Conduct an embryofetal development study for [REDACTED] in the rabbit model.	206544	10/2/2015	10/2017	Released from PMR on 01/15/2016

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Product/ Compound	Description of Commitment	NDA Number	Agreement Date	Projected Completion Date	Status
Morphabond ER (morphine sulfate) 15/30/60/100 MG	2961-7: Conduct an embryofetal development study for [REDACTED] in the rat model.	206544	10/2/2015	07/2018	Released from PMR on 01/15/2016
Morphabond ER (morphine sulfate) 15/30/60/100 MG	2961-8: Conduct a 2-year rodent oral carcinogenicity assessment of [REDACTED]	206544	10/2/2015	04/2020	Released on Feb 10, 2021 NDA Withdrawn

US Post Marketing Commitments

Product/ Compound	Description of Commitment	NDA Number	Agreement Date	Projected Completion Date	Status
Morphabond ER (morphine sulfate) 15/30/60/100 MG	2961-9: Conduct epidemiologic to address whether the properties intended to deter misuse and abuse of MORPHABOND (morphine sulfate extended release tablets) actually result in a significant and meaningful decrease in misuse and abuse, and their consequences, addiction, overdose, and death, in the community. The post-marketing study program must allow FDA to assess the impact, if any, that is attributable to the abuse-deterrent properties of MORPHABOND. To meet this objective, investigations should incorporate recommendations contained in the FDA draft guidance, Abuse Deterrent Opioids—Evaluation and Labeling (January 2013) and proposed comparators need to be mutually agreed upon prior to initiating epidemiologic investigations. There must be sufficient drug utilization to allow a meaningful epidemiological assessment of overall and route-specific abuse deterrence.	206544	10/2/2015	09/2020	Released on Feb 10, 2021 NDA Withdrawn

US Post Marketing Commitments

Product/ Compound	Description of Commitment	NDA Number	Agreement Date	Projected Completion Date	Status
Morphabond ER (morphine sulfate) 15/30/60/100 MG	3033-1: Conduct a prospective, observational study designed to quantify the serious risks of misuse, abuse, and addiction associated with long-term use of opioid analgesics for management of chronic pain among patients prescribed ER/LA opioid analgesics.	206544	2/4/2016	10/2019	Released on Feb 10, 2021 NDA Withdrawn
Morphabond ER (morphine sulfate) 15/30/60/100 MG	3033-2: Conduct an observational study designed to measure the incidence and predictors of opioid overdose and death (OOD), as well as opioid abuse/addiction, using patient health records, insurance claims, and death records.	206544	2/4/2016	04/2019	Released on Feb 10, 2021 NDA Withdrawn
Morphabond ER (morphine sulfate) 15/30/60/100 MG	3033-3: Conduct a prospective observational study designed to assess the content validity and patient interpretation of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ). Patient understanding of the concepts of misuse and abuse will also be obtained.	206544	2/4/2016	10/2015	Fulfilled FDA Letter 11/26/2019

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Product/ Compound	Description of Commitment	NDA Number	Agreement Date	Projected Completion Date	Status
Morphabond ER (morphine sulfate) 15/30/60/100 MG	3033-4: Conduct an observational study to evaluate the validity and reproducibility of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ), which will be used to identify opioid abuse and misuse behaviors among participants who have chronic pain which requires long-term opioid analgesic use.	206544	2/4/2016	10/2016	Fulfilled FDA Letter 11/26/2019
Morphabond ER (morphine sulfate) 15/30/60/100 MG	3033-5: Conduct an observational study to validate measures of prescription opioid Substance Use Disorder and addiction in patients who have received or are receiving opioid analgesics for chronic pain.	206544	2/4/2016	12/2016	Fulfilled FDA Letter 11/26/2019
Morphabond ER (morphine sulfate) 15/30/60/100 MG	3033-6: Conduct an observational study to develop and validate an algorithm using coded medical terminologies and other electronic healthcare data to identify opioid-related overdose and death.	206544	2/4/2016	09/2016	Submitted* *Pending FDA confirmation as fulfilled

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Product/ Compound	Description of Commitment	NDA Number	Agreement Date	Projected Completion Date	Status
Morphabond ER (morphine sulfate) 15/30/60/100 MG	3033-7: Conduct an observational study to develop and validate an algorithm using coded medical terminologies to identify patients experiencing prescription opioid abuse or addiction, among patients receiving an ER/LA opioid analgesic.	206544	2/4/2016	10/2016	Submitted* *Pending FDA confirmation as fulfilled
Morphabond ER (morphine sulfate) 15/30/60/100 MG	3033-8: Conduct an observational study using coded medical terminologies and other electronic healthcare data to define and validate doctor and/or pharmacy shopping outcomes by examining their association with abuse and/or addiction.	206544	2/4/2016	10/2017	Submitted* *Pending FDA confirmation as fulfilled
Morphabond ER (morphine sulfate) 15/30/60/100 MG	3033-9: Conduct an observational study using a validated patient survey to evaluate the association between doctor/pharmacy shopping outcomes and self-reported misuse and abuse.	206544	2/4/2016	09/2018	Fulfilled

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Product/ Compound	Description of Commitment	NDA Number	Agreement Date	Projected Completion Date	Status
Morphabond ER (morphine sulfate) 15/30/60/100 MG	3033-10: Conduct an observational study using medical record review to evaluate the association between doctor/pharmacy shopping outcomes and patient behaviors suggestive of misuse, abuse and/or addiction.	206544	2/4/2016	03/2017	Submitted* *Pending FDA confirmation as fulfilled
Morphabond ER (morphine sulfate) 15/30/60/100 MG	3033-11: Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following the long-term use of high-dose ER/LA opioid analgesics for at least one year to treat chronic pain. Include an assessment of risk relative to efficacy.	206544	2/4/2016	02/2019	Fulfilled

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Product/ Compound	Description of Commitment	NDA 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	Delayed Submission Pending
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	Ongoing
Welchol for Oral Suspension PMC	1729-1: 1-year, pediatric efficacy and safety study under PREA for the treatment of type 2 Diabetes in pediatric patients ages 10 to 17 years.	22362 & 21176/S-022	10/02/2009	12/31/2020	Submitted* *Pending FDA confirmation as fulfilled
Welchol Chewable Bar	3593-1: 1-year, pediatric efficacy and safety study under PREA for the treatment of type 2 Diabetes in pediatric patients ages 10 to 17 years.	210895	04/26/2019	09/2027	Released from PMR on 02/26/2021

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Product/ Compound	Description of Commitment	NDA Number	Agreement Date	Projected Completion Date	Status
Welchol (colesevelam HCl) tablets	To study Welchol as monotherapy treatment for type 2 diabetes mellitus.	21176	05/26/2000	Complete	Fulfilled
Welchol (colesevelam HCl) tablets	To study Welchol in combination with thiazolidinediones as treatment for type 2 diabetes mellitus.	21176	05/26/2000	Complete	Fulfilled
ROXYBOND (oxycodone hydrochloride) 5, 15, 30 mg	3204-1: Conduct a 9-month repeat-dose oral toxicology study in the non-rodent model characterizing the toxicological potential of [REDACTED]	209777	04/20/2017	07/01/2019	NDA Transferred to IDS on 9/26/2019 FDA Acknowledgement Letter 11/1/2019

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Product/ Compound	Description of Commitment	NDA Number	Agreement Date	Projected Completion Date	Status
ROXYBOND (oxycodone hydrochloride) 5, 15, 30 mg	3204-2: Conduct a 6-month repeat-dose oral toxicology study in the rodent model characterizing the toxicological potential of [REDACTED]	209777	04/20/2017	05/30/2018	NDA Transferred to IDS on 9/26/2019 FDA Acknowledgement Letter 11/1/2019
ROXYBOND (oxycodone hydrochloride) 5, 15, 30 mg	3204-3: Conduct a 2-year rodent oral carcinogenicity assessment of [REDACTED]	209777	04/20/2017	04/30/2021	NDA Transferred to IDS on 9/26/2019 FDA Acknowledgement Letter 11/1/2019

US Post Marketing Commitments

Product/ Compound	Description of Commitment	NDA Number	Agreement Date	Projected Completion Date	Status
ROXYBOND (oxycodone hydrochloride) 5, 15, 30 mg	3204-4: Conduct a descriptive study to collect meaningful baseline data to support subsequent studies for formal epidemiologic assessment of abuse-deterrence of ROXYBOND. The descriptive study should include data on the following: 1) Utilization of ROXYBOND and selected comparators. Reports should include nationally-projected quarterly dispensing data, overall and by age group and census region; AND 2) Abuse of ROXYBOND and related clinical outcomes. These assessments should utilize multiple data sources in different populations to establish the scope and patterns of abuse for ROXYBOND as well as mutually agreed-upon, selected comparators to provide context. Data should include route-specific abuse outcomes, be nationally representative or from multiple large geographic areas, and use meaningful measures of abuse.	209777	04/20/2017	03/30/2021	NDA Transferred to IDS on 9/26/2019 FDA Acknowledgement Letter 11/1/2019

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Product/ Compound	Description of Commitment	NDA Number	Agreement Date	Projected Completion Date	Status
ROXYBOND (oxycodone hydrochloride) 5, 15, 30 mg	3204-5: As part of the ongoing stability studies, commit to repeating the small volume extraction studies, using water and solvents at pH 2 and 3.5, using tablets that are pre-treated with heat and no heat, crushed and intact. Further use the same study conditions in the completed in vitro studies submitted to the NDA, to demonstrate that there is no change in syringeability of the product and in the extraction recovery of the drug product stored over time. Commit to repeating these studies yearly.	209777	04/20/2017	04/01/2022	NDA Transferred to IDS on 9/26/2019 FDA Acknowledgement Letter 11/1/2019
ROXYBOND (oxycodone hydrochloride) 5, 15, 30 mg	3204-6: Commit to the submission of an updated in-process sampling plan and associated acceptance criteria for the stratified content uniformity for the cured diffusion coated tablets to ensure that batches of drug products meet appropriate statistical quality criteria. The proposed statistical plan and acceptance criteria shall be adequate to ensure that appropriate quality conclusions can be made about this in process material based on final critical quality attributes and shall be justified with supporting statistical analyses or rationale.	209777	04/20/2017	N/A	NDA Transferred to IDS on 9/26/2019 FDA Acknowledgement Letter 11/1/2019

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Product/ Compound	Description of Commitment	NDA 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	On-Going

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Product/ Compound	Description of Commitment	NDA Number	Agreement Date	Projected Completion Date	Status
TURALIO (Pexidartinib) 200 mg Capsules	3673-2: Complete a pharmacokinetic trial to determine an appropriate dose of pexidartinib to minimize toxicity in patients with moderate hepatic impairment in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling” found at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072123.pdf	211810	08/02/2019	09/2020	**Study Completed#** #: Delayed due to COVID-19. Updated projected Final report submission date (Mar 2021) was acknowledged by FDA (FDA letter dated Nov 23)
TURALIO (Pexidartinib) 200 mg Capsules	3673-3: Complete a pharmacokinetic trial to determine the effect of a low-fat meal on the bioavailability of pexidartinib in accordance with the FDA Guidance for Industry entitled “Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations” found at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM631941.pdf	211810	08/02/2019	08/2019	Fulfilled ** ** FDA letter dated 04/28/2020

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Product/ Compound	Description of Commitment	NDA Number	Agreement Date	Projected Completion Date	Status
TURALIO (Pexidartinib) 200 mg Capsules	3673-4: Complete a pharmacokinetic trial to determine the effect of a moderate CYP3A4 inhibitor on the exposure to pexidartinib in accordance with the FDA Guidance for Industry entitled “Clinical Drug Interaction Studies- Study Design, Data Analysis, and Clinical Implications” found at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf.	211810	08/02/2019	08/2019	Fulfilled** ** FDA letter dated 04/17/2020
TURALIO (Pexidartinib) 200 mg Capsules	3673-5: Submit the final trial report and results from the ongoing DDI Study PL3397-AU126 evaluating the effect of pexidartinib on the exposure of midazolam (a CYP3A4 substrate) and tolbutamide (a CYP2C9 substrate).	211810	08/02/2019	09/2019	Fulfilled** ** FDA letter dated 04/17/2020

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Product/ Compound	Description of Commitment	NDA Number	Agreement Date	Projected Completion Date	Status
TURALIO (Pexidartinib) 200 mg Capsules	3673-6: Complete a pharmacokinetic trial or PBPK modeling to determine the effect of a moderate CYP3A4 inducer on the exposure to pexidartinib following single and multiple doses of pexidartinib in accordance with the FDA Guidance for Industry entitled “Clinical Drug Interaction Studies - Study design, Data Analysis, and Clinical Implications” found at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf.	211810	08/02/2019	08/2019	Fulfilled** ** FDA letter dated 04/17/2020
TURALIO (Pexidartinib) 200 mg Capsules	3673-7: Given the abundance of the ZAAD-1006a metabolite in human plasma following exposure to pexidartinib, assess the potential for off-target effects of ZAAD-1006a using in vitro screening assays (panels of kinases and receptors).	211810	08/02/2019	09/2020	Fulfilled ** FDA letter dated 09/29/2020

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Product/ Compound	Description of Commitment	BLA Number	Agreement Date	Projected Completion Date	Status
ENHERTU (fam-trastuzumab deruxtecan-nxki), 100mg injection	3762-1 Submit the final progression free survival analysis and datasets with the final report from a confirmatory Phase 3, multicenter, randomized, open- label, active-controlled study of DS-8201a for HER2-positive, unresectable and/or metastatic breast cancer patients previously treated with trastuzumab, to confirm clinical benefit and provide additional efficacy data that may inform product labeling for fam-trastuzumab deruxtecan (DS 8201a).	761139	12/20/2019	6/2023	Submitted 11/17/2021
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	6/2023	On-Going

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Product/ Compound	Description of Commitment	BLA Number	Agreement Date	Projected Completion Date	Status
ENHERTU (fam-trastuzumab deruxtecan-nxki), 100mg injection	3762-3 Provide the bioburden test method qualification report for two additional batches of and DS-8201a drug substance in-process and release samples by May 2020.	761139	12/20/2019	5/2020	Fulfilled Approved 09/28/2020
ENHERTU (fam-trastuzumab deruxtecan-nxki), 100mg injection	3762-4 . Perform the microbial ingress container closure integrity test to validate the maximum and minimum crimping pressures and include a positive control with a breach size of ≤ 20 microns. In addition, monitor the viability of the challenge microorganism at the end of testing.	761139	12/20/2019	1/2020	Fulfilled Approved 08/03/2020

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Product/ Compound	Description of Commitment	BLA Number	Agreement Date	Projected Completion Date	Status
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
ENHERTU (fam-trastuzumab deruxtecan-nxki), 100mg injection	3762-6 Provide endotoxin method qualification using two (2) additional drug product batches manufactured at	761139	12/20/2019	1/2020	Fulfilled Approved 9/9/2021
ENHERTU (fam-trastuzumab deruxtecan-nxki), 100mg injection	3762-7 Provide bioburden method qualification using 100 mL sample volumes from three (3) batches of DP manufactured at	761139	12/20/2019	3/2020	Fulfilled Approved 04/23/2020

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Product/ Compound	Description of Commitment	BLA Number	Agreement Date	Projected Completion Date	Status
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	6/2020	Submitted 06/24/2020; Pending FDA Response
ENHERTU (fam-trastuzumab deruxtecan-nxki), 100mg injection	3762-9 Improve the requalification procedures for the current MAAL-9001 primary reference standard (PRS) 159RS02 and secondary reference standard (SRS) ST01-01 by revising the requalification protocols to include numerical acceptance criteria for HER2 binding of the PRS and stability trending of additional quantitative quality attributes with pre-defined trending rules and criteria, to allow timely detection of changes in the quality attributes of the PRS and SRS and to inform when the current RSs should be replaced. The acceptance criteria for HER2 binding of the PRS, the selected quality attributes for trending, the trending rules and criteria, and the criteria for assessment of when the RSs should be replaced will be scientifically justified. The revised qualification protocol will be submitted to the Agency per 21 CFR 601.12.	761139	12/20/2019	3/2020	Fulfilled Approved 07/20/2020

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Product/ Compound	Description of Commitment	BLA Number	Agreement Date	Projected Completion Date	Status
ENHERTU (fam-trastuzumab deruxtecan-nxki), 100mg injection	3762-10 Improve the requalification procedures for the current DS-8201a primary reference standard (PRS) 164RS03 and secondary reference standard (SRS) 164WS01 by revising the requalification protocols to include numerical acceptance criteria for cell growth inhibition and HER2 binding activity, and stability trending of additional quantitative quality attributes with pre- defined trending rules and criteria, to allow timely detection of changes in the quality attributes of the PRS and SRS and to inform when the current RSs should be replaced. The numerical acceptance criteria for cell growth inhibition and HER2 binding activity, the selected quality attributes for trending, the trending rules and criteria, and the criteria for assessment of when the RSs should be replaced will be scientifically justified. The revised qualification protocols will be submitted to the Agency per 21 CFR 601.12.	761139	12/20/2019	3/2020	Fulfilled Approved 07/20/2020

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Product/ Compound	Description of Commitment	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	2/2020	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	2/2020	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	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	2/2020	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	2/2020	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	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	3/2020	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	6/2020	Submitted 06/19/2020 Pending FDA Response

US Post Marketing Commitments

Product/ Compound	Description of Commitment	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 Pending FDA Response