Supplementary Online Content

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eTable 1. Key Data Limitations at the Time of Accelerated Approval

Agent	Excerpt from product label
Bevacizumab	No data available demonstrating improvement in disease-related symptoms or survival with [bevacizumab].
Pralatrexate	Clinical benefit such as improvement in progression free survival or overall survival has not been demonstrated.
Ofatumumab	No data demonstrate an improvement in disease related symptoms or increased survival with [ofatumumab].
Lapatinib	[Lapatinib] in combination with an aromatase inhibitor has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer.
Nilotinib	The study is ongoing and further data will be required to determine long-term outcome.
Dasatinib	The trial is ongoing and further data will be required to determine long-term outcome.
Everolimus	Clinical benefit such as improvement in disease-related symptoms or increase in overall survival has not been demonstrated.
Hydroxyprogesterone caproate	There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity.
Romidepsin	Clinical benefit such as improvement in overall survival has not been demonstrated.
Brentuximab vedotin	There are no data available demonstrating improvement in patient reported outcomes or survival with [brentuximab vedotin].
Brentuximab vedotin	There are no data available demonstrating improvement in patient reported outcomes or survival with [brentuximab vedotin].
Crizotinib	There are no data available demonstrating improvement in patient reported outcomes or survival with [crizotinib].
Deferiprone	There are no controlled trials demonstrating a direct treatment benefit, such as improvement in disease-related symptoms, functioning, or increased survival.
Everolimus	Further follow-up of patients is required to determine long-term outcomes.
Carfilzomib	Clinical benefit, such as improvement in survival or symptoms, has not been verified.
Vincristine sulfate liposome	Clinical benefit such as improvement in overall survival has not been verified.
Omacetaxine	There are no trials verifying an improvement in disease-related symptoms or increased survival with [omacetaxine mepesuccinate].
Ponatinib	There are no trials verifying an improvement in disease-related symptoms or increased survival with [ponatinib].
Bedaquiline	This indication is based on analysis of time to sputum culture conversion from two controlled Phase 2 trials in patients with pulmonary multidrug resistant tuberculosis.
Deferasirox	An improvement in survival or disease-related symptoms has not been established.
Pomalidomide	Clinical benefit, such as improvement in survival or symptoms, has not been verified.
Idursulfase	In patients 16 months to 5 years of age, no data are available to demonstrate improvement in disease-related symptoms or long term clinical outcome.
Pertuzumab	No data are available demonstrating improvement in event-free survival or overall survival.
Ibrutinib	An improvement in survival or disease-related symptoms has not been established.

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eTable 2. Confirmatory Study Details, Status and Associated Regulatory Outcomes

Agent	Confirmatory study description (according to regulatory letters sent to sponsors)	Status	Regulatory outcome
Bevacizumab	To submit an efficacy supplement containing the final study report, including summary analyses and datasets and revised labeling based on the results of study AVF4396g/BO20990 entitled "A Randomized, Double Blind, Placebo Controlled, Multicenter, Phase III Trial of Bevacizumab, Temozolomide and Radiotherapy, Followed by Bevacizumab and Temozolomide Versus Placebo, Temozolomide Followed by Placebo and Temozolomide in Patients with Newly Diagnosed Glioblastoma," which was accepted under a Request for Special Protocol Assessment on December 29, 2008. Protocol submitted: October 31, 2008, Complete accrual: June 30, 2013, Complete study: June 30, 2015, Supplement submission: December 31, 2015	Complete. FDA database: "Submitted" (no further detail provided) ClinicalTrials.gov identifier: NCT00943826 Trial results are published.[1]	Not available.
Pralatrexate	1547-1 A randomized trial of maintenance treatment with pralatrexate in previously untreated patients with PTCL who have demonstrated a response to CHOP or a CHOP-like regimen. Description of trial: This will be a Phase 3 multi-center, randomized clinical trial of sequential FOLOTYN versus observation in patients with newly diagnosed aggressive peripheral T-cell lymphoma who have responded following initial treatment with CHOP-based chemotherapy. The primary endpoint will be progression-free survival (PFS). The trial will also be sized to detect a realistic difference in survival. Patients will be enrolled prior to initiation of the CHOP-based regimen. Patients responding (CR or PR) after CHOP-based treatment will then be randomized 2:1 to FOLOTYN versus observation. The timetable you submitted on September 20, 2009, states that you will conduct this trial according to the following timetable: Final Protocol Submission Date: December 23, 2009 Trial Completion Date: December 31, 2016 Final Report Submission Date: June 30, 2017	Incomplete. Study has been terminated. FDA database: "Ongoing" (no further detail provided) ClinicalTrials.gov: "Study has been terminated." ClinicalTrials.gov identifier: NCT01420679	Not available.
Pralatrexate	1547-2 A randomized trial comparing pralatrexate in combination with systemic bexarotene versus systemic bexarotene alone in patients with cutaneous T-cell lymphoma (CTCL) who are refractory to at least one prior systemic therapy. Description of trial: This will be a Phase 3 multi-center, randomized clinical trial in patients with CTCL. The primary endpoint will be progression-free survival (PFS). Response rate will be a	Incomplete. Delayed by more than 12 months. FDA database: "Thirty evaluable patients are	Not available.

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	secondary endpoint. Prior to initiation of the Phase 3 trial, a Phase 1 trial will be conducted to determine the maximum tolerated dose (MTD) of the combination. The timetable you submitted on September 20, 2009, states that you will conduct this trial according to the following timetable: Protocol Submission Date for Phase 1 Trial: November 15, 2009 Phase 1 Trial Completion Date: August 31, 2011 Final Phase 3 Protocol Submission Date: September 30, 2011 Phase 3 Trial Completion Date: March 31, 2015 Phase 3 Trial Final Report Submission Date: September 30, 2015	enrolled in the study and the study is ongoing. The Phase 1 trial completion date (August 31, 2011) and the Phase 3 Protocol submission date (September 30, 2011) have been missed." ClinicalTrials.gov identifier: Could not be identified. (Non-randomized dose-finding component was completed. ClinicalTrials.gov identifier: NCT01134341)	
Ofatumumab	To submit a final report for ongoing clinical trial OMB110911, entitled, "A Phase III Open-label, Randomized, Multicenter Trial of Ofatumumab Added to Chlorambucil versus Chlorambucil Monotherapy in Previously Untreated Patients with Chronic Lymphocytic Leukemia" which is intended to verify the clinical benefit of ofatumumab through demonstration of a clinically meaningful effect on progression-free survival. The protocol for clinical trial OMB110911 was submitted to FDA on October 24, 2008 and began patient accrual on December 22, 2008. We also acknowledge receipt of the amended protocol submitted August 21, 2009. The timetable you submitted on October 6, 2009 states that you will conduct this trial according to the following milestones: Patient Accrual 50% Completed (222 patients) by August 30, 2010, Patient Accrual 75% Completed (333 patients) by March 30, 2011, Patient Accrual Completed by November 30, 2011, Trial Completion Date: by October 14, 2013, Final Report Submission: by June 30, 2014	Complete. FDA database: Could not be identified. ClinicalTrials.gov identifier: NCT00748189 Trial results are published.[2]	FDA letter dated 17 April 2014 confirms fulfilment of commitments made under 21 CFR 601.41.

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eTable 2. Confirmatory Study Details, Status and Associated Regulatory Outcomes

Agent	Confirmatory study description (according to regulatory letters sent to sponsors)	Status	Regulatory outcome
Lapatinib	1586-1. A randomized trial comparing lapatinib in combination with trastuzumab and an aromatase inhibitor versus trastuzumab in combination with an aromatase inhibitor versus lapatinib in combination with an aromatase inhibitor in postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor. Description of the trial: This will be a Phase 3 randomized clinical trial in postmenopausal women with hormone receptor positive metastatic breast cancer that overexpresses the HER2 receptor and who had prior neo-adjuvant/adjuvant trastuzumab and endocrine therapy. The primary endpoint will be superiority in overall survival comparing lapatinib in combination with trastuzumab and an aromatase inhibitor versus trastuzumab in combination with an aromatase inhibitor. The secondary efficacy endpoint will be overall survival comparing lapatinib in combination with trastuzumab and an aromatase inhibitor versus lapatinib in combination with an aromatase inhibitor. The timetable you submitted on January 21, 2010, states that you will conduct this trial according to the following timetable: Final Protocol Submission Date: May 31, 2010 Trial Completion Date: March 31, 2016 Final Report Submission Date: May 31, 2018	Incomplete. Delayed by more than 12 months. FDA database: "Difficulties in recruiting patients despite initiatives to increase enrolment." ClinicalTrials.gov identifier: NCT01160211	Not available.
Lapatinib	1586-2. EGF108919 is an ongoing collaborative trial between NCIC and GSK. It is a randomized trial comparing lapatinib in combination with a taxane versus trastuzumab in combination with a taxane in patients with metastatic breast cancer that overexpresses the HER2 receptor. Description of the trial: This will be a Phase 3, randomized clinical trial in patients with metastatic breast cancer that overexpresses the HER2 receptor. Patients will be stratified by prior trastuzumab or taxane therapy, planned taxane treatment on study and liver metastases. The primary endpoint will be superiority in overall survival comparing lapatinib in combination with a taxane versus trastuzumab in combination with a taxane. The timetable you submitted on January 21, 2010, states that you will conduct this trial according to the following timetable: Final Protocol Submission May 31, 2010, Trial Completion Date: June 15, 2011, Final Report Submission Date: PFS: April 30, 2013,	Complete. FDA database: Could not be identified. ClinicalTrials.gov identifier: NCT00667251 Trial results are published.[3]	Not available.

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eTable 2. Confirmatory Study Details, Status and Associated Regulatory Outcomes

Agent	Confirmatory study description (according to regulatory letters sent to sponsors)	Status	Regulatory outcome
	Final Survival Report Submission: July 31, 2016		
Nilotinib	1651-1 (S-005):Submit an interim report at 24 months and the completed report (at least 60 months of follow-up) from Trial 2303. Primary data will accompany each report. The timetable you submitted on June 4, 2010, states that you will conduct this trial according to the following schedule: Final Protocol Submitted: February 2007, Interim Report (at 24 months) Submission Date: March 2011 (Data Cut-off Date August 31, 2010), Final Report (at least 60 months Follow-Up) Submission Date: March 2014 (Data Cut-off Date September 30, 2013)	Complete. FDA database: Could not be identified. ClinicalTrials.gov identifier: NCT00471497 Trial results are published.[4]	FDA letter dated 27 January 2015 confirms receipt of clinical study report for 60 months of follow-up for study 2303, fulfilling commitments made under 21 CFR 314.510.
Dasatinib	1699-1 To submit the final report (at least 60 months of follow-up) and data from CA180056 entitled "An Open-Label, Randomized, Multicenter Phase III Trial of Dasatinib versus Standard Dose Imatinib in the Treatment of Subjects with Newly Diagnosed Chronic Phase Philadelphia Chromosome Positive Chronic Myelogenous Leukemia." The timetable you submitted on October 21, 2010, states that you will conduct this trial according to the following schedule: Protocol Submission: by September 2009, Trial Completion: by February 2014, Final Report and Dataset Submission: by November 2014	Complete. FDA database: Could not be identified. ClinicalTrials.gov identifier: NCT00481247 Trial results are published.[5]	FDA letter dated 12 August 2015 confirms fulfilment of commitments made under 21 CFR 314.510.
Everolimus	PMR 1700-1: Submit the final report (at least 4 years of follow-up) and datasets from M2301, a randomized, double-blind, placebo-controlled, multi-center phase 3 trial evaluating treatment with everolimus versus placebo in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS). The timetable you submitted on October 26, 2010, states that you will conduct this trial according to the following schedule: Final Protocol Submission: January 2011; Trial Completion: September 2014; Final Report and Dataset Submission: March 2015.	Complete. FDA database: Could not be identified. ClinicalTrials.gov identifier: NCT00789828 Trial results are published.[6]	FDA letter dated 29 January 2016 confirms receipt of final report (with 4-year follow-up data) from M2301, fulfilling commitments made under 21 CFR 314.510.

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eTable 2. Confirmatory Study Details, Status and Associated Regulatory Outcomes

Agent	Confirmatory study description (according to regulatory letters sent to sponsors)	Status	Regulatory outcome
Everolimus	PMR 1700-2: Submit the long-term (at least 5 years) follow-up efficacy and safety data from C2485, a single- arm, single-institution, phase 2 trial evaluating treatment with everolimus in patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS). The timetable you submitted on October 26, 2010, states that you will conduct this trial according to the following schedule: Final Protocol Submission: March 2011; Trial Completion: March 2014; Final Report and Dataset Submission: November 2014	Complete. FDA database: Could not be identified. ClinicalTrials.gov identifier: NCT00411619 Trial results are published.[7]	FDA letter dated 18 September 2015 confirms receipt of 5-year follow-up data from study C2485.
Hydroxyprogesterone caproate	1722-1 To complete the clinical trial of hydroxyprogesterone caproate in women with a singleton pregnancy who had a previous spontaneous preterm birth (Protocol #17P-ES-003): Revised Protocol Submission: March 2011 Trial Completion: June 2016 Final Report Submission: December 2016.	Incomplete. Delayed by more than 12 months. FDA database: "The sponsor continues to experience challenges with recruitment and therefore subject enrollment will not be completed as planned." ClinicalTrials.gov identifier: NCT01004029	Not available.
Hydroxyprogesterone caproate	1722-2 To complete the clinical follow-up study (Protocol #17P-FU-004) of children born to women who participated in Protocol #17P-ES-003: Revised Protocol Submission March 2011 Study Completion Date July 2018 Final Interim Report Submission December 2016 Final Report Submission October 2018	Incomplete. Delayed by more than 12 months. FDA database: "The sponsor continues to experience challenges with recruitment and therefore subject enrollment will not be completed as planned."	Not available.

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Agent	Confirmatory study description (according to regulatory letters sent to sponsors)	Status	Regulatory outcome
		ClinicalTrials.gov identifier: NCT01146990	
Romidepsin	1775-1 To perform a randomized, blinded, controlled trial of previously untreated PTCL patients randomized to treatment with CHOP or to romidepsin plus CHOP, with Progression Free Survival as the primary efficacy endpoint. Final Progression Free Survival (PFS) data will be available at Trial Completion. For efficacy, the final analysis of the primary endpoint, PFS, will be performed when the trial has experienced the planned number of events. Using the same data cutoff date, an interim analysis of Overall Survival will be performed and included in the study report. The timetable you submitted on May 27, 2011, states that you will conduct this trial according to the following timetable: Final Protocol: April 2012 Trial Completion: April 2018 Final Report: April 2019	Incomplete. Delayed by more than 12 months. FDA database: "Ongoing" (no further detail provided) ClinicalTrials.gov identifier: NCT01796002	Not available.
Brentuximab vedotin	A randomized phase 3, double-blind, placebo-controlled trial of SGN-35 (brentuximab vedotin) in combination with CH-P versus CHOP as frontline therapy in patients with CD30-positive mature T- and NK-cell lymphomas including systemic ALCL (sALCL). Enrollment of approximately 300 patients is expected with a primary endpoint of progression free survival as determined by an independent blinded review facility. Overall survival is a key secondary endpoint. Final Protocol Submission Date: 3/2013 Trial Completion Date: 3/2019 Final Report Submission Date: 9/2019	Incomplete. Underway according to planned timelines. FDA database: "Ongoing" (no further detail provided) ClinicalTrials.gov identifier: NCT01777152	Not available.
Brentuximab vedotin	A randomized phase 3 trial of SGN-35 (brentuximab vedotin) in combination with AVD versus ABVD as frontline therapy in patients with advanced Hodgkin Lymphoma. Enrollment of at least 880 patients is expected with a primary endpoint of progression free survival determined by an independent blinded review facility. Overall survival is a key secondary endpoint. Final Protocol Submission Date: 09/2012 Trial Completion Date: 12/2018 Final Report Submission Date: 06/2019	Incomplete. Underway according to planned timelines. FDA database: "Ongoing" (no further detail provided) ClinicalTrials.gov identifier:	Not available.

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eTable 2. Confirmatory Study Details, Status and Associated Regulatory Outcomes

Agent	Confirmatory study description (according to regulatory letters sent to sponsors)	Status	Regulatory outcome
		NCT01712490	
Crizotinib	1789-1 Clinical trial report and datasets from A8081007: Phase 3, Randomized, Open-label Study of the Efficacy and Safety of PF-02341066 vs. Standard of Care (Pemetrexed or Docetaxel) in Patients with Advanced Non-Small Cell Lung Cancer Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase Gene Locus Final Protocol Submission: 09/2009 (submitted) Trial Completion: 12/2013 Final Report Submission: 06/2014.	Complete. FDA database: Could not be identified. ClinicalTrials.gov identifier: NCT00932893 Trial results are published.[8]	FDA letter dated 20 November 2013 confirms fulfilment of commitments made under 21 CFR 314.510.
Crizotinib	1789-2 Clinical trial report and datasets from A8081014: Phase 3, Randomized, Open-label Study of the Efficacy and Safety of Crizotinib vs. Pemetrexed/Cisplatin or Pemetrexed/Carboplatin in Previously Untreated Patients with Non-Squamous Carcinoma of the Lung Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase Gene Locus Final Protocol Submission: 06/2010 (submitted) Trial Completion: 12/2015 Final Report Submission: 06/2016	Complete. FDA database: Could not be identified. ClinicalTrials.gov identifier: NCT01154140 Trial results are published.[9]	FDA letter dated 20 November 2013 (same as above) states: "Since we have determined that the data provided in this supplement verify that clinical benefit is conferred by crizotinib capsules, you are released from PMR 1789-2, also required under 21 CFR 314.510."

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Agent	Confirmatory study description (according to regulatory letters sent to sponsors)	Status	Regulatory outcome
Deferiprone	PMR 1828-1 Conduct a trial to determine the efficacy and safety of the use of deferiprone to treat iron overload in patients with sickle cell disease and transfusional hemosiderosis who have not been adequately treated with available chelating agents. Submit the protocol for review and concurrence prior to commencing. The trial will enroll a sufficient number of patients with sickle cell disease as described above, to provide sufficient evidence to assess the efficacy and safety in the sickle cell disease population described. The trial may enroll patients with other conditions who have developed transfusional iron overload. The trial will stratify for hematologic diagnosis for the randomization. The primary and secondary endpoints will measure changes in cardiac iron concentration and liver iron concentration. Final Protocol Submission: February 2012 Trial Completion: January 2016 Final Report Submission: July 2016	Incomplete. Delayed by more than 12 months. FDA database: "Recruitment is slow, but the FDA requested enrollment continued to obtain more clinical data. Revised milestones acknowledged Nov 14, 2014 to complete study 2/1017 and submit the final study report July 2017 Additional time requested to allow for the recruitment of the planned number of patients into the study." ClinicalTrials.gov identifier: NCT02041299	Not available.
Everolimus	PMR #1892-1 To complete the ongoing clinical trial CRAD001M2302 entitled "A Randomized, Double-blind, Placebo-controlled Study of RAD001 in the Treatment of Angiomyolipoma in Patients with either Tuberous Sclerosis Complex (TSC) or Sporadic Lymphangioleiomyomatosis (LAM)" to further verify and describe the ultimate clinical outcomes of the duration of objective responses, incidence of nephrectomy and of renal embolization four years after randomization of the last patient in the study, as specified in the original protocol. You will submit the final comprehensive clinical study report, inclusive of all data collected in the clinical trial, as described in ICH E3. The timetable you submitted on April 23, 2012, states you will conduct this trial according to the following schedule:, Final Protocol Submission:	Complete. FDA database: Could not be identified. ClinicalTrials.gov identifier: NCT00790400 Trial results are published.[10]	FDA letter dated 18 February 2016 confirms that receipt of 4-year follow up data, fulfilling commitments made under 21 CFR 314.510.

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eTable 2. Confirmatory Study Details, Status and Associated Regulatory Outcomes

Agent	Confirmatory study description (according to regulatory letters sent to sponsors)	Status	Regulatory outcome
	June 10, 2010, Study/Trial Completion: January 2015, Final Report Submission: August 2015		
Carfilzomib	PMR 1908-1 Conduct a randomized controlled trial per Protocol PX-171-009, as finalized, to compare carfilzomib-lenalidomide dexamethasone with lenalidomide dexamethasone in a population of patients with myeloma, whose disease has relapsed after previous response to at least one but not more than three prior therapies, to assess efficacy and safety. Patients' disease is required to show evidence of progression after prior therapy. The trial includes 792 patients. The randomization will balance known important prognostic factors. The goal of the trial is to evaluate the primary endpoint of progression-free survival (PFS) for the carfilzomib-containing arm, as determined by an independent review committee blinded to the treatment given. Final Protocol Submission: January 2010 Trial Completion: December 2013 Final Report Submission: June 2014	Complete. FDA database: Could not be identified. ClinicalTrials.gov identifier: NCT01080391 Trial results are published.[11]	FDA letter dated 24 July 2015 confirms fulfilment of PMR 1908-1.
Carfilzomib	* PMR 1908-2: Conduct a randomized clinical trial in patients receiving carfilzomib to identify and characterize the cardiac toxicities associated with carfilzomib. You have agreed to conduct this trial as a cardiac sub-trial within your ongoing Protocol 2011-003 (ENDEAVOR). The primary objective is to compare changes in cardiac function between the group receiving carfilzomib and a control group not receiving carfilzomib in a parallel group trial. The main trial protocol (2011-003) must require a baseline resting ECG and transthoracic ECHO to assess left ventricular (LV) function on all patients. If transthoracic ECHO is not available at some sites, MUGA will be acceptable for baseline screening LVEF evaluation. For the cardiac sub-trial, a subset of patients from the main trial will be assessed for LV and right ventricular (RV) function with	Complete. FDA database: Could not be identified. ClinicalTrials.gov identifier: NCT01568866 Trial results are published.[12]	FDA letter dated 21 January 2016 confirms completion of confirmatory study 2011-003 (ENDEAVOR), fulfilling commitments made under 21 CFR 314.510.

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Agent	Confirmatory study description (according to regulatory letters sent to sponsors)	Status	Regulatory outcome
	transthoracic ECHO (or MUGA for those sites using MUGA at baseline) periodically throughout trial treatment and at the time of the End-of-Treatment visit, using similar test procedures and equipment to allow serial intra-patient comparisons. This cardiac sub-trial must include a minimum of 100 patients and a maximum of 300 patients total (50 to 150 patients per treatment arm). Specific details regarding the interpretation of LVEF changes must be pre-specified and outlined in the SAP for this cardiac toxicity trial. For the sub-trial, readers of the ECHOs/MUGAs must be blinded to the protocol treatment given. In addition, any patient in the main trial who has a cardiac adverse event (AE) that is considered a clinically significant AE must have an ECHO performed to assess LV and RV function as part of the evaluation of that AE. Submit a complete cardiac sub-trial protocol for review and concurrence before commencing the sub-trial. The timetable you submitted on July 17, 2012, states that you will conduct this sub-trial according to the following schedule: 2011-003 (ENDEAVOR) Phase 3 Cardiac Sub-Trial Final sub-trial Protocol Submission: January 2013 Trial Completion: November 2015 Final Report Submission: May 2016 * *This requirement was not under the Accelerated Approval program. However, the FDA considered requirements made under 21 CFR 314.510 to be fulfilled once this trial was completed.*		
Vincristine sulphate liposome	1910-1 To perform and submit the trial, presently under SPA agreement, TTX404 "A Phase 3, Multicenter, Randomized Study to Evaluate the Substitution of Marqibo (Vincristine Sulfate Liposomes Injection, VSLI) Standard Vincristine Sulfate Injection (VSI) in the Induction, Intensification, and Maintenance Phases of Combination Chemotherapy in the Treatment of Subjects > 60 Years Old with Newly Diagnosed Acute Lymphoblastic Leukemia (ALL)" to address your subpart H commitment according to the timelines below. Any amendments to the SPA trial TTX404 must also be submitted to the PMR. Report of 1/3 enrollment 12/2014; Report of 2/3 enrollment 12/2015 Report of enrollment completion 12/2016 Study/Trial Completion: 8/2017 Final	Incomplete. Study has been terminated. FDA database: "Sponsor discontinued enrollment in the PMR study February 6, 2015. A meeting with the division was held January 6, 2016 to discuss a possible alternative study. A proposed protocol was	Not available.

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Agent	Confirmatory study description (according to regulatory letters sent to sponsors)	Status	Regulatory outcome
	Report Submission: 4/2018	submitted and not found to be acceptable. Sponsor is in the process of evaluating additional options for a replacement clinical study." ClinicalTrials.gov identifier: NCT01439347	
Omacetaxine mepesuccinate	* 1930-1 Continue follow-up of patients (on treatment and in protocol defined posttreatment follow-up) and submit a final analysis report of CGX-635-CML-300 with 24 months of minimum follow-up data for each patient. If 24 months of follow-up is not possible for certain patients, justification should be provided. Preliminary Protocol Submission: N/A Final Protocol Submission: N/A 24 Month Follow-up Completion: 03/2012 Final Report Submission: 04/2013 ** According to FDA medical review report, CGX-635-CML-300 refers to subset analysis of 2 pivotal trials.*	Complete. FDA database: Could not be identified. ClinicalTrials.gov identifier: NCT00375219 and NCT00462943 Trial results are published.[13]	FDA letter dated 10 February 2014 confirms receipt of PMR 1930-1, fulfilling commitments made under 21 CFR 314.510.
Ponatinib	PMR 1984-1 Collect sparse PK from ponatinib treated patients in the ongoing trial AP24534-12-301 to characterize exposure-response for Iclusig™ (ponatinib). The exposure-response analysis should be conducted for both efficacy and safety endpoints. Based on the results of these analyses, a trial to evaluate lower dose or an alternate dosing regimen of ponatinib may be necessary. Draft Protocol Submission: 02/2013 Final Protocol Submission: 04/2013 Trial Completion: 08/2015 Final Report Submission: 02/2016	Complete. Terminated due to safety concerns. FDA database: Could not be identified. ClinicalTrials.gov identifier: NCT01650805 "Study was terminated based on evaluation of safety data." Terminated trial results are published.[14]	FDA letter dated 2 June 2016 mentions receipt of safety results from Study AP24534-12-301 (not clearly concluding that this PMR is fulfilled).

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Agent	Confirmatory study description (according to regulatory letters sent to sponsors)	Status	Regulatory outcome
Ponatinib	PMR 1984-2 Conduct a dedicated drug interaction trial in humans to determine the effect of coadministration of the strong CYP3A4 inducer, rifampin, on the pharmacokinetics of Iclusig™ (ponatinib) in healthy subjects. Final Protocol Submission: 06/2012 Trial Completion: 06/2013 Final Report Submission: 12/2013	Complete. FDA database: Could not be identified. ClinicalTrials.gov identifier: Could not be identified. Trial results are published.[15]	FDA letter dated 24 July 2014 confirms receipt of final reports for the PMR 1982-2 postmarketing requirement.
Ponatinib	PMR1984-3 Conduct a dedicated clinical trial in humans to determine the effect of multiple doses of lansoprazole on the pharmacokinetics of Iclusig™ (ponatinib) in healthy subjects. Final Protocol Submission: 06/2012 Trial Completion: 06/2013 Final Report Submission: 12/2013	Complete. FDA database: Could not be identified. ClinicalTrials.gov identifier: Could not be identified. Trial results are published.[16]	FDA letter dated 24 July 2014 confirms receipt of final reports for the PMR 1982-3 postmarketing requirement.
Ponatinib	PMR 1984-4 Longer duration follow-up: Continue follow-up of patients (on treatment and in protocol defined post-treatment follow-up) and submit a final analysis report of trial AP24534-10-201 with 24 months of minimum follow-up for each patient. If 24 months of follow-up is not possible for certain patients, provide justification for each patient. Final Protocol Submission: 06/2012 Trial Completion: 12/2013 Final Report Submission: 06/2014	Complete. FDA database: "Fulfilled" (no further detail provided) ClinicalTrials.gov identifier: NCT01207440 Trial results (3-year analysis) are published.[17]	FDA letter dated 28 November 2016 confirms receipt of safety and efficacy data results from the 4-year updated clinical study report for Study AP24534-10-201 (PACE Trial), fulfilling commitments made under 21 CFR 314.510.

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Bedaquiline	1988-001: Conduct a confirmatory randomized double blind placebo controlled multicenter Phase 3 trial in subjects with sputum smear-positive pulmonary multidrug resistant tuberculosis (MDR-TB). This trial should assess long term outcomes of failure or relapse or death at least 6 months after all MDR-TB treatment is completed. Final Protocol Submission: 06/2013 Trial Completion: 08/2021 Final Report Submission: 03/2022	Incomplete. Underway according to planned timelines. FDA database: "Pending" (no further detail provided) ClinicalTrials.gov identifier: NCT02409290	Not available.
Deferasirox	PMR 1994-1 Conduct a trial to assess the long-term efficacy of Exjade® (deferasirox) in patients with NTDT and high LIC. The trial should assess response rates in the subset of patients with baseline LIC values >15 mg Fe/g dw (proportion of patients achieving an LIC <5 mg Fe/g dw and time to achieving an LIC <5 mg Fe/g dw). Follow-up of all subjects for up to 5 years is necessary. Final Protocol Submission: 09/2013 Trial Completion: 05/2019 Final Report Submission: 11/2019	Incomplete. Underway according to planned timelines. FDA database: "Ongoing" (no further detail provided) ClinicalTrials.gov identifier: NCT01709838	Not available.
Deferasirox	PMR 1994-2 Assess the long-term efficacy (and safety) of Exjade® (deferasirox) treatment to a target LIC of 3 mg Fe/g dw followed by one or more treatment holidays until the LIC is ≥5 mg Fe/g dw in patients with NTDT. Follow-up of all subjects for up to 5 years is necessary. Final Protocol Submission: 09/2013 Trial Completion: 05/2019 Final Report Submission: 11/2019	Incomplete. Underway according to planned timelines. FDA database: "Ongoing" (no further detail provided) ClinicalTrials.gov record could not be identified.	Not available.

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eTable 2. Confirmatory Study Details, Status and Associated Regulatory Outcomes

Agent	Confirmatory study description (according to regulatory letters sent to sponsors)	Status	Regulatory outcome
Deferasirox	PMR 1994-3 Conduct a prospective, randomized trial in at least 210 patients with low to intermediate risk myelodysplastic syndromes (MDS) receiving Exjade® (deferasirox) for transfusional iron overload (approximately 140) or placebo (approximately 70) to determine the efficacy and safety of Exjade® (deferasirox) in this population. The trial will continue for 3 years from the date the last patient is enrolled. Final Protocol Submission: 07/2013 Trial Completion: 03/2018 Final Report Submission: 09/2018	Incomplete. Underway according to planned timelines. FDA database: "Ongoing" (no further detail provided) ClinicalTrials.gov identifier: NCT00940602	Not available.
Pomalidomide	PMR 2006-1 Conduct a randomized controlled trial (CC-4047-MM-007) that isolates and demonstrates the efficacy and safety of Pomalyst (pomalidomide) in patients with previously treated multiple myeloma. Final Protocol Submission: 12/2012 (completed) Trial Completion: 4/2018 Final Report Submission: 1/2019	Incomplete. Underway according to planned timelines. FDA database: Could not be identified. ClinicalTrials.gov identifier: NCT01734928	FDA letter dated 23 April 2015 confirms that FDA concluded that the approval of Supplement S-006 and the fulfilment of PMR 2006-2 addressed PMR 2006-1, fulfilling commitments made under 21 CFR 314.510.
Pomalidomide	PMR 2006-2 Conduct a clinical trial, per FDA guidance [Drug Interaction Studies—Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations], to determine the effect of CYP3A induction, which may decrease drug exposure, on the PK of Pomalyst (pomalidomide). Final Report Submission: 9/2013	Complete. FDA database: Could not be identified. ClinicalTrials.gov identifier: NCT01707407	FDA letter dated 13 March 2014 confirms receipt of data from the study entitled "A Phase 1 Open-Label Study to Evaluate the Effect of CYP450 and P-gp Inhibition and Induction of the Pharmacokinetics of Pomalidomide (CC-4047) in Healthy Male Subjects" addressing PMR 2006-2.

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eTable 2. Confirmatory Study Details, Status and Associated Regulatory Outcomes

Agent	Confirmatory study description (according to regulatory letters sent to sponsors)	Status	Regulatory outcome
Idursulfase	To conduct a verification trial to describe clinical benefit attributable to Elaprase (idursulfase) in a cohort of Hunter syndrome patients 5 years of age and younger. At a minimum, this trial will assess longitudinal changes in anthropometric measures (i.e., length/height z-scores, annual growth velocity z-scores, weight z- scores) and the progression of skeletal deformities (i.e. joint stiffness, joint contractures) in children being treated with Elaprase (idursulfase). The growth parameters will be followed in these children for a minimum of 5 years from initiation of Elaprase (idursulfase) treatment or until they have reached at least 10 years of age, whichever is longer. The trials will monitor antibody response (binding, neutralizing, and IgE) at least every 6 months. Additionally, the trial will evaluate the relationship between development of immune tolerance and genetic mutations, endogenous enzyme activity level, and anthropometric measures. The trial may be conducted as a separate trial or as a sub-trial under a special protocol within the Hunter Outcome Survey. Final Protocol Submission: 06/2014 Trial Completion: 03/2022 Final Report Submission: 09/2022	Incomplete. Underway according to planned timelines. FDA database: "Ongoing" (no further detail provided) ClinicalTrials.gov identifier: NCT02455622	Not available.
Idursulfase	To evaluate a prophylactic immune tolerance regimen in a cohort of Hunter syndrome patients treated with Elaprase (idursulfase) who are at high risk of developing persistent neutralizing antibody that could result in diminished clinical benefit. This immune tolerance regimen will be implemented before or concomitant with onset of therapy. The trial will monitor antibody status (binding, neutralizing, and IgE), urinary GAG, and hypersensitivity reactions in patients at regular intervals. Additionally, the trial will evaluate the relationship between development of immune tolerance and genetic mutations, endogenous enzyme activity level, and clinical outcome. Completion of this PMR is pending the outcome of an Advisory Committee Meeting and completion of PMR 3. Final Protocol Submission: 06/2017 Trial Completion: 03/2022 Final Report Submission: 09/2022	Incomplete. FDA database: "Pending" (no further detail provided) ClinicalTrials.gov identifier: Could not be identified.	Not available.
Pertuzumab	Submit the final efficacy (disease-free survival) and safety results from Trial BO25126 (APHINITY) as defined in your protocol and Statistical Analysis Plan (SAP).	Incomplete. Underway according to planned timelines.	Not available.

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eTable 2. Confirmatory Study Details, Status and Associated Regulatory Outcomes

Agent	Confirmatory study description (according to regulatory letters sent to sponsors)	Status	Regulatory outcome
	The timetable you submitted on September 24, 2013, states that you will conduct this trial according to the following schedule: Final Protocol Submission: 10/13 Trial Completion: 11/16 Final Report Submission: 05/17	FDA database: "The study completion date has passed and the study has not yet been completed." ClinicalTrials.gov identifier: NCT01358877	
Ibrutinib	PMR 2060-1 Continue follow-up of patients (on treatment and in protocol defined post-treatment follow-up) and submit a final analysis report of trial PCYC-1104-CA with a minimum follow-up of 24 months for each patient. If 24 months follow-up is not possible for certain patients, provide justification for each patient. In addition, submit detailed assessment information regarding all sites of extranodal disease at baseline and follow-up, including assessments for response and progression. Summarize extranodal disease characteristics at baseline and at time of progression. Request further documentation as necessary from clinical trial sites in order to summarize the details of the extranodal disease progression. Final Protocol Submission: Complete 01/2013 Trial Completion: 09/2014 Final Report Submission: 03/2015	Complete. FDA database: Could not be identified. ClinicalTrials.gov identifier: NCT01236391 Trial results are published.[18]	Not available.
Ibrutinib	PMR 2060-2 Complete and submit the final results of the ongoing randomized, double-blind, placebo-controlled Phase 3 clinical trial (PCI-32765MCL3002) of ibrutinib in combination with bendamustine and rituximab in patients with newly diagnosed mantle cell lymphoma. Enrollment of approximately 520 patients is expected. The primary endpoint is progression-free survival as assessed by investigators. Overall survival is a key secondary endpoint. Final Protocol Submission: Completed 04/2013 Trial Completion: 12/2018 Final Report Submission: 03/2019	Incomplete. Underway according to planned timelines. FDA database: "Ongoing" (no further detail provided) ClinicalTrials.gov identifier: NCT01776840	Not available.

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eReferences for eTable 2

1. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus Radiotherapy–Temozolomide for Newly Diagnosed Glioblastoma. *New England Journal of Medicine.* 2014;370(8):709-722.

2. Hillmen P, Robak T, Janssens A, et al. Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukaemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial. *Lancet (London, England).* 2015;385(9980):1873-1883.

3. Gelmon KA, Boyle FM, Kaufman B, et al. Lapatinib or Trastuzumab Plus Taxane Therapy for Human Epidermal Growth Factor Receptor 2–Positive Advanced Breast Cancer: Final Results of NCIC CTG MA.31. *Journal of Clinical Oncology.* 2015;33(14):1574-1583.

4. Hochhaus A, Saglio G, Hughes TP, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. *Leukemia.* 2016;30(5):1044-1054.

5. Cortes JE, Saglio G, Kantarjian HM, et al. Final 5-Year Study Results of DASISION: The Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients Trial. *Journal of Clinical Oncology.* 2016;34(20):2333-2340.

6. Franz DN, Belousova E, Sparagana S, et al. Long-Term Use of Everolimus in Patients with Tuberous Sclerosis Complex: Final Results from the EXIST-1 Study. *PloS one.* 2016;11(6):e0158476.

7. Franz DN, Agricola K, Mays M, et al. Everolimus for subependymal giant cell astrocytoma: 5-year final analysis. *Annals of neurology.* 2015;78(6):929-938.

8. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *The New England journal of medicine.* 2013;368(25):2385-2394.

9. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *The New England journal of medicine.* 2014;371(23):2167-2177.

10. Bissler JJ, Kingswood JC, Radzikowska E, et al. Everolimus for renal angiomyolipoma in patients with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis: extension of a randomized controlled trial. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* 2016;31(1):111-119.

11. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *The New England journal of medicine.* 2015;372(2):142-152.

12. Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple

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myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. *The Lancet Oncology*. 2016;17(1):27-38.

13. Cortes JE, Kantarjian HM, Rea D, et al. Final analysis of the efficacy and safety of omacetaxine mepesuccinate in patients with chronic- or accelerated-phase chronic myeloid leukemia: Results with 24 months of follow-up. *Cancer*. 2015;121(10):1637-1644.

14. Lipton JH, Chuah C, Guerci-Bresler A, et al. Ponatinib versus imatinib for newly diagnosed chronic myeloid leukaemia: an international, randomised, open-label, phase 3 trial. *The Lancet Oncology*. 2016;17(5):612-621.

15. Narasimhan NI, Dorer DJ, Davis J, Turner CD, Sonnichsen D. Evaluation of the effect of multiple doses of rifampin on the pharmacokinetics and safety of ponatinib in healthy subjects. *Clinical pharmacology in drug development*. 2015;4(5):354-360.

16. Narasimhan NI, Dorer DJ, Davis J, Turner CD, Sonnichsen D. Evaluation of the effect of multiple doses of lansoprazole on the pharmacokinetics and safety of ponatinib in healthy subjects. *Clinical drug investigation*. 2014;34(10):723-729.

17. Cortes JE, Kim D-W, Pinilla-Ibarz J, et al. Long-Term Follow-up of Ponatinib Efficacy and Safety in the Phase 2 PACE Trial. *Blood*. 2014;124(21):3135-3135.

18. Wang ML, Blum KA, Martin P, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. *Blood*. 2015;126(6):739-745.

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