Protocol 14D-MC-JTJH A Phase 2 Study of LY2606368 in Patients with Extensive Stage Disease Small Cell Lung Cancer

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Protocol I4D-MC-JTJH(a)
A Phase 2 Study of LY2606368 in Patients with Extensive Stage Disease Small Cell Lung Cancer

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LY2606368

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1. Synopsis

Protocol Title: A Phase 2 Study of LY2606368 in Patients with Extensive Stage Disease Small Cell Lung Cancer

Rationale:

Small-cell lung cancer patients with extensive stage disease (ED-SCLC) are commonly treated with cisplatin or carboplatin in combination with etoposide. While a majority of patients respond to initial treatment, nearly all patients relapse and die from their disease. Consequently, new agents are needed to improve clinical outcomes for ED-SCLC patients. Study I4D-MC-JTJH (Study JTJH) will evaluate the efficacy of LY2606368 in both platinum-sensitive and platinum-resistant/refractory patients.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• Cohort 1: To estimate the ORR when a dose of 105 mg/m^2 LY2606368 every 14 days is administered to patients with ED-SCLC that have platinum-sensitive disease • Cohort 2: To estimate the ORR when a dose of 105 mg/m^2 LY2606368 every 14 days is administered to in patients with ED-SCLC that have platinum resistant/refractory disease	• Best overall response (PR+CR) as determined per RECIST version 1.1
Secondary	
• To characterize the safety and toxicity profile of LY2606368	• The safety endpoints evaluated will include but are not limited to the following: AEs, SAEs, clinical laboratory tests, ECGs vital signs, and physical examinations
• To characterize the PK of LY2606368	• LY2606368 concentration in plasma
• To estimate secondary efficacy measures including DCR, DoR, PFS, and OS	• DCR: best overall response (CR, PR) and SD as determined per RECIST, version 1.1 • DoR: time from the date of an objective response until PD, per RECIST 1.1 or the date of death from any cause in the absence of PD • PFS: time from enrollment until the first radiographic documentation of progression or death from any cause in the absence of PD • OS: time from enrollment until death from any cause
• To evaluate the association between best tumor response and change from baseline in lung cancer-specific symptoms, symptomatic distress, activity status, overall quality of life, total LCSS score, and ASBI for patients who have platinum-sensitive or platinum-resistant/refractory SCLC	• Lung cancer symptoms (appetite loss, fatigue, cough, dyspnea, hemoptysis, and pain), summation items (symptomatic distress, activity level, and global quality of life), total LCSS, and ASBI

Abbreviations: AEs = adverse events; ASBI = Average Symptom Burden Index; CR = complete response; DCR = disease control rate; DoR = duration of response; ECG = electrocardiogram; ED-SCLC = extensive-stage disease small cell lung cancer; LCSS = Lung Cancer Symptom Scale; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; RECIST = Response Evaluation Criteria In Solid Tumors; SAEs = severe adverse events; SD = stable disease.

Overall Design:

Study I4D-MC-JTJH (JTJH) is a multicenter, Phase 2 study of LY2606368 in patients with ED-SCLC who have either platinum-sensitive or platinum-resistant/refractory disease. Cohort 1 will include patients with objective response to prior platinum-based therapy with subsequent progression ≥90 days after the last dose of platinum. Cohort 2 will include patients that either did not have an objective response to prior platinum-based therapy or had progression <90 days after the last dose of platinum. Patients cannot have received more than 2 prior therapies for ED-SCLC.

Number of Patients:

Approximately 134 patients will be entered into Study JTJH, and 116 patients will be enrolled and complete the trial.

Treatment Arms and Duration:

	Dose and Schedule (q 14 Days)	
Cohort	**LY2606368 D1**	**Number of Cycles**
1 and 2	105 mg/m^2	Treatment will continue until a discontinuation criterion is met.

Abbreviations: D = day; q = every.

2. Schedule of Activities

Table JTJH.2.1. Schedule of Screening Activities

	Study Period	Baseline		
	Cycle	BL		
	Visit	0		
	Duration	Up to 28 days		
	Relative Day	≤28	≤14	≤7
Procedure Category	**Procedure**			**Comments**
Study Entry/Enrollment	Informed Consent Form signed (prior to conducting any protocol specific tests/procedures)	X		
	Inclusion/Exclusion evaluation		X	
Medical History	Initial history/preexisting conditions		X	
	Historical illness		X	
	Habits assessment		X	Includes smoking history.
Physical Examination	Physical examination		X	Includes height and weight.
	ECOG performance status		X	
	Vital signs		X	
Tumor Assessment	Radiologic imaging according to RECIST 1.1	X		Baseline radiological tumor assessment per RECIST version 1.1 should be done (see Section 9.1). Radiologic assessments obtained previously as part of routine clinical care may be used as the baseline assessment provided that they were done no more than 28 days before the first dose of study drug.
	Tumor measurement (palpable or visible)	X		Performed at the same time as radiologic imaging.
Adverse Events Collection/CTCAE Grading		X		
Concomitant Medication Notation		X		
Laboratory/ Diagnostic Tests	Hematology		X	
	Chemistry		X	
	Urinalysis		X	
	Coagulation		X	
	Pregnancy test	X		Women of childbearing potential must have negative serum pregnancy tests at their baseline visits and have negative urine pregnancy tests within 7 days before their first doses of LY2606368 (see Section 6.1).
	ECG		X	Single local ECG
	Confirm availability of pretreatment tumor tissue	X		If archived tissue is not available, a fresh tumor biopsy should be obtained after all other study entry criteria have been confirmed, unless the sponsor and investigator document that the patient may be enrolled without pre-treatment tissue.
	Exploratory blood sample for biomarkers		X	
	Optional pretreatment biopsy	X		Optional and may be performed at any time before starting treatment with LY2606368. See Section 9.8.2.
Health Outcome Measure	Lung Cancer Symptom Scale		X	The LCSS should be administered prior to extensive interaction with site personnel.

Schedule of Screening Activities

Abbreviations: BL = baseline; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2009); ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); LCSS = Lung Cancer Symptom Scale; RECIST 1.1 = Response Evaluation Criteria In Solid Tumors Version 1.1 (Eisenhauer et al. 2009).

Table JTJH.2.2. On-Study-Treatment Schedule of Activities

	Study Period	Study Treatment Period						
	Cycle/Visit	1		2		3-n[a]		
	Duration	14 days		14 days		14 days		
	Relative Day within Dosing Cycle	1	8	1	8	1	8	
Procedure Category	**Procedure**							**Comments**
Physical Examination	Physical Exam	X		X		X		Includes weight and calculated BSA. May be completed up to 7 days prior to treatment infusion. In Cycle 4 and beyond may be completed every other cycle (for example, Cycle 4, 6, 8, etc.).
	Vital signs	X		X		X		Includes blood pressure, pulse, and temperature. Complete before treatment infusion.
	ECOG performance status	X		X		X		Complete before treatment infusion.
Laboratory/ Diagnostic Tests	Hematology	X	X	X	X	X	X	May be drawn up to 3 days before the planned assessment. In Cycles 4-n, the Day-8 sample may be collected at the discretion of the investigator.
	Chemistry	X		X		X		May be drawn up to 3 days before the planned assessment.
	Urinalysis					X		May be collected up to 3 days before the planned assessment.
	Urine pregnancy test					X		Day 1 of every other cycle. Only to be performed on women of childbearing potential.
	PK sampling	X	X	X		X	X	See PK Schedule for collection information.
	Stored sample for pharmacogenetics	X						Collect once. Sample can be collected at any time if not collected on Day 1 of Cycle 1.
	Exploratory blood sample for biomarkers					X		Only to be collected on the same day when the CT scan is obtained (every 3 cycles starting with Cycle 3).
	Plasma biomarker sample	X				X		Collect prior to dosing on Day 1 of Cycles 1 and 3 only.
	ECG	X		X		X		Single local ECG collected at each time point. Day 1: predose, 10 min after EOI (±5 min), 30 min after EOI (±10 min), and >1 hour after EOI. Cycle 2-X: predose. However, if QTcF >480 msec is observed on Day 1, then 10 min after EOI (±5 min), 30 min after EOI (±10 min), and >1 hour after EOI should also be collected in subsequent cycles.
	Optional Tumor Biopsy	X						Can occur at any time during patient's treatment.

		Study Period	Study Treatment Period						
		Cycle/Visit	1		2		3-n[a]		
		Duration	14 days		14 days		14 days		
		Relative Day within Dosing Cycle	1	8	1	8	1	8	
Tumor Assessment	Radiologic imaging according to RECIST 1.1							X	For the first 52 weeks following enrollment, perform approximately every 6 weeks starting at the end of Cycle 3 (eg, Days 8-14). Thereafter, perform approximately every 12 weeks. The scanning interval (6 or 12 weeks [±1 week]) should be maintained even if cycles are delayed. As a result, after Cycle 3, the scans may not always occur at the end of a cycle. The same method of imaging used at baseline should be used for each subsequent assessment. Scans should also be obtained as clinically indicated.
Tumor Assessment	Tumor measurement (palpable or visible)							X	Perform at least every 6 weeks starting in Cycle 3 on the same day as the radiologic imaging.
Adverse Events Collection/ CTCAE Grading			X		X		X		
Concomitant Medication Notation			X		X		X		
Lung Cancer Symptom Scale			X		X		X		The LCSS is to be administered prior to extensive interaction with site personnel and prior to administration of study drug.
Study Treatment	LY2606368		X		X		X		IV over approximately 60 (+10) min

Abbreviations: BSA = body surface area; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2009); ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); EOI = end of infusion; IV = intravenous; min = minute; LCSS = Lung Cancer Symptom Scale; PK = pharmacokinetic; QTcF = QT interval using Fridericia's correction; RECIST 1.1 = Response Criteria In Solid Tumors Version 1.1 (Eisenhauer et al. 2009).

Table JTJH.2.3. Post-Treatment Follow-Up Schedule of Activities

	Study Period	Post-discontinuation Follow-Up		
		Short-term Follow-Up	Long-term Follow-Up	
	Duration	30 ± 5 days	60 ± 14 days	
	Visit	801	802-X	
	Relative day within a cycle	Period begins the day after stopping of study treatment and lasts approximately 30 days	Period begins 1 day after short-term follow-up period is completed and continues until death, study withdrawal, or the patient is lost to follow-up	
Procedure Category	Procedure			Comments
Physical Examination	Physical examination (including weight)	X		
	Vital signs	X		Includes blood pressure, pulse, and temperature.
	ECOG performance status	X		
Tumor Assessment	Radiologic imaging according to RECIST 1.1	X		The same method of imaging (CT scan, spiral CT, etc.) used at baseline should be used for each subsequent assessment. Not required if progressive disease is documented while on treatment or if there are clear signs of clinical progression.
	Tumor measurement (palpable or visible)	X		Performed at the same time as radiologic imaging.
Adverse Events Collection/CTCAE Grading		X	X	After Visit 801, only study treatment-related serious events are reported.
Concomitant Medication Notation		X		
Lab/Diagnostic Tests	Hematology	X		
	Chemistry	X		
	ECG	X		
	Exploratory blood sample for biomarkers	X		
	Plasma biomarker sample	X		
	Optional posttreatment biopsy	X		See Section 9.8.2.
Health Outcome Measure	Lung Cancer Symptom Scale	X		The LCSS will need to be administered prior to extensive interaction with site personnel.
Follow-Up	Survival Assessment		X	Approximately every 60 (±14) days (telephone assessment is acceptable).

Abbreviations: CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2009); ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); LCSS = Lung Cancer Symptom Scale; RECIST 1.1 = Response Criteria In Solid Tumors Version 1.1 (Eisenhauer et al. 2009).

Table JTJH.2.4. Continued Access Schedule of Activities

	Study Treatment	Follow-Up[a]	
Visit	**501-5XX**	**901**	
Procedure[b]			**Comments**
AE collection	X	X	
Administer LY2606368	X		IV over approximately 60 (+10) minutes once every 14 days.

Abbreviations: AE = adverse event; IV = intravenously.

a Continued access follow-up begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days. No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

b Efficacy assessments will be done at the investigator's discretion based on the standard of care.

3. Introduction

3.1. Study Rationale

Lung cancer is the leading cause of cancer mortality worldwide, with an estimated rate of 1.8 million new cases per year, and is responsible for the majority of deaths due to cancer (1.59 million) (GLOBOCAN Population Fact Sheets page [WWW]). Small-cell lung cancer (SCLC) is a rapidly growing tumor, with approximately 60% to 70% of patients presenting with metastatic disease at diagnosis that accounts for 12% of new lung cancer cases (Wakuda et al. 2015). Approximately two-thirds of patients with SCLC present with extensive stage disease (ED-SCLC), which has traditionally been defined as disease beyond the ipsilateral hemithorax and may include malignant pleural effusion, pericardial effusion, or hematogenous metastases (Micke et al. 2002).

SCLC is highly sensitive to chemotherapy, with combination chemotherapy remaining the focus of treatment for patients with ED-SCLC. About 60% to 80% of patients with extensive stage disease respond to combination chemotherapy (Hann and Rudin 2008). Cisplatin or carboplatin in combination with etoposide are commonly used regimens in the first-line treatment of SCLC. After an initial response, however, nearly all patients with extensive disease will relapse and the majority of patients will eventually die from their disease (Sundstrom et al. 2002). Platinum-refractory disease shows progression during therapy or within <90 days of the last dose of platinum. Platinum-sensitive disease shows progression ≥90 days after the last dose of platinum. Patients with platinum-sensitive disease have a higher likelihood of response to second-line treatment. Their response rate is approximately 20% to 25% (Fruh et al. 2013; Kalemkerian et al. 2013). In contrast, patients with platinum-refractory disease have a ≤10% chance of response to a second-line treatment (Kalemkerian et al. 2013). If left untreated, a relapsed patient will typically live 2 months to 4 months (Wakuda et al. 2015).

Several other agents have been shown to have activity in SCLC, and many studies have compared 3-drug regimens to the standard 2-drug regimens with no improvement in efficacy. Topotecan is approved for patients that have ED-SCLC that have failed or relapsed after first line chemotherapy (Demedts et al. 2010). Patients receiving topotecan (1.5 mg/m^2 daily for 5 days every 21 days) had an overall response rate of 24.3% (von Pawel et al. 1999). The median time to progression was 13.3 weeks and median survival was 25.0 weeks (von Pawel et al. 1999). Adverse events (AEs) associated with this treatment included Grade 4 neutropenia (70.2%), Grade 3/4 anemia (42.3%), Grade 4 thrombocytopenia (28.8%), and documented infection within 2 days of Grade 4 neutropenia (28%) (von Pawel et al. 1999). Other agents, including paclitaxel, irinotecan, vinorelbine, and gemcitabine, have been tested in the second-line setting in an effort to improve on the efficacy and tolerability of topotecan. Despite the modest benefit of topotecan, they have not increased efficacy over topotecan (Chan and Coward 2013), demonstrating the clear need for new agents to improve outcomes for patients with ED-SCLC.

Checkpoint kinase 1 (CHK1), a multifunctional protein kinase, is a regulator of the deoxyribonucleic acid (DNA) damage response (Dai and Grant 2010). CHK1 is a key component of the checkpoint response following DNA damage and is essential for homologous

recombination repair of DNA double strand breaks. It also affects the initiation of DNA replication origin firing, stabilization of replication forks, resolution of replication stress, and coordination of mitosis, even in the absence of exogenous DNA damage (McNeely et al. 2014). Although CHK1 inhibitors previously have been developed as chemopotentiators, given the integral role that CHK1 plays in DNA replication and the regulation of the cell cycle, inhibitors of CHK1 may also have single-agent activity. In particular, replication stress is emerging as a factor that may play a sensitizing role for response to monotherapy with CHK1 inhibitors (Lecona and Fernandez-Capetillo 2014).

SCLC is a tumor associated with replication stress and may be sensitive to the effects of a CHK1 inhibitor (Byers et al. 2012; Thompson et al. 2012). Furthermore, tumors with MYC alterations, which occur in approximately 20% of patients with SCLC (Byers and Rudin 2015), may have increased replication stress and higher sensitivity to CHK1 inhibition (Cole et al. 2011; Hoglund et al. 2011). Short hairpin ribonucleic acid (shRNA)-mediated targeted CHK1 knockdown significantly decreased the proliferation of SCLC lines and increased the level of pH2AX, a marker of DNA damage (Sen et al. 2015), providing further evidence that CHK1 may be an attractive target for this disease.

3.2. Background

LY2606368 is an adenosine-5'-triphosphate-competitive inhibitor of CHK1. LY2606368 inhibits the enzymatic activity of CHK1 with a half-maximal inhibitory concentration (IC_{50}) of <1 nM and CHK2 with an IC_{50} of 8 nM in in vitro assays (King et al. 2015). In nonclinical studies, LY2606368 induced DNA damage as measured by pH2A.X, a marker of double-stranded DNA breaks, and replication catastrophe. LY2606368 inhibited tumor growth in cancer xenografts, including SCLC models, as monotherapy and in combination with other agents (Wu et al. 2012; McNeely et al. 2014; King et al. 2015; Sen et al. 2015). In vitro data from cell viability screens across a large panel of tumor lines representing different tumor histologies demonstrated increased sensitivity to growth inhibition by LY2606368 in SCLC compared to other lung subtypes as well as generally increased sensitivity in tumor cell lines that were MYC amplified (data on file). In a panel of 39 SCLC lines, proteomic analysis revealed that sensitivity to LY2606368 was associated with elevated basal expression of total and phosphor cMYC (p=.01) (Sen et al. 2015).

LY2606368 has been evaluated in human clinical trials as a monotherapy for patients with solid tumors (Study I4D-MC-JTJA [JTJA], NCT01115790) and in combination with either chemotherapy or targeted agents (I4D-MC-JTJF, NCT02124148). In these Phase 1 studies, LY2606368 has shown an acceptable safety/tolerability profile.

3.2.1. Prior Clinical Experience with LY2606368 as a Monotherapy: Study JTJA

LY2606368 was assessed as a monotherapy for patients with solid tumors and demonstrated an acceptable safety/tolerability profile, with transient neutropenia being the primary toxicity.

As of 27 August 2015, data were available from 146 patients who were treated with LY2606368 on Days 1, 2, and 3, or on Day 1 only of a 14-day schedule. The maximum tolerated dose (MTD) of LY2606368 administered on Days 1, 2, and 3 every 14 days was determined to be 40 mg/m^2, and the MTD of LY2606368 when administered on Day 1 every 14 days was determined to be 105 mg/m^2. A dose of 105 mg/m^2 once every 14 days was selected as the recommended Phase 2 dose for monotherapy.

In patients who have received 105 mg/m^2 of LY2606368, neutropenia was the most frequent and severe toxicity following treatment with LY2606368. Grade 4 decreases in neutrophils deemed related to LY2606368 treatment were observed in 71% of these patients. In general, neutrophil counts nadir on Day 8 and Grade 4 decreases were often less than 5 days. Grade 4 decreases in platelets were observed in 5.7% of patients. Grade 4 anemia was not observed. Nonhematologic toxicity occurred at a lower frequency than hematologic toxicity and was predominantly Grade 1 in severity.

In the 105 patients who received LY2606368 at a dose of 105 mg/m^2 once every 2 weeks, the treatment-related AEs most frequently reported following LY2606368 treatment in Study JTJA include neutrophil count decreased (93%), platelet count decreased (46%), anemia (33%), white blood cell decreased (30%), fatigue (28%), nausea (14%), febrile neutropenia (11%), and headache (11%).

Please see the Investigator's Brochure (IB) for additional information on the nonclinical and clinical experience with LY2606368.

3.3. Benefit/Risk Assessment

Given the high unmet need for additional therapies for patients with previously treated ED-SCLC, the mechanistic rationale that supports a role for CHK1 inhibition in improving outcomes for patients with SCLC, the nonclinical data with LY2606368 as a monotherapy in nonclinical models (including SCLC), and the clinical safety profile of LY2606368, the risk/benefit assessment supports assessing LY2606368 monotherapy in the proposed patient population.

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated AEs of LY2606368 are to be found in the IB.

3.4. Rationale for JTJH Amendment (a)

Amendment (a) was developed to address requests resulting from member states participating in the Voluntary Harmonisation Procedure during the assessment of the initial clinical trial application for Study JTJH in the European Union. At the member states' request, the protocol was modified to incorporate those states' recommendations in the inclusion and exclusion

criteria and to establish the actions to be taken in case of prolongation of the QT/QTc interval >480 msec. Because a protocol amendment was required, the opportunity was taken to also include several other minor protocol improvements and clarifications.

4. Objectives and Endpoints

Table JTJH.4.1 shows the objectives and endpoints of the study.

Table JTJH.4.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• Cohort 1: To estimate the ORR when a dose of 105 mg/m^2 LY2606368 every 14 days is administered to patients with ED-SCLC that have platinum-sensitive disease • Cohort 2: To estimate the ORR when a dose of 105 mg/m^2 LY2606368 every 14 days is administered to in patients with ED-SCLC that have platinum resistant/refractory disease	• Best overall response (PR+CR) as determined per RECIST version 1.1
Secondary	
• To characterize the safety and toxicity profile of LY2606368	• The safety endpoints evaluated will include but are not limited to the following: AEs, SAEs, clinical laboratory tests, ECGs, vital signs, and physical examinations.
• To characterize the PK of LY2606368	• LY2606368 concentration in plasma
• To estimate secondary efficacy measures including DCR, DoR, PFS, and OS	• DCR: best overall response (CR, PR) and SD as determined per RECIST, version 1.1 • DoR: time from the date of an objective response until PD, per RECIST 1.1 or the date of death from any cause in the absence of PD • PFS: time from enrollment until the first radiographic documentation of progression or death from any cause in the absence of PD • OS: time from enrollment until death from any cause
• To evaluate the association between best tumor response and change from baseline in lung cancer specific-symptoms, symptomatic distress, activity status, overall quality of life, total LCSS score, and ASBI for patients who have platinum-sensitive or platinum resistant/refractory SCLC	• Lung cancer symptoms (appetite loss, fatigue, cough, dyspnea, hemoptysis, and pain), summation items (symptomatic distress, activity level, and global quality of life), total LCSS, and ASBI
Tertiary/Exploratory	
• To explore biomarkers associated with the efficacy and safety of LY2606368, the exposure (PK) of LY2606368, the mechanism of action of CHK1, DNA damage response pathways or downstream effects, cell cycle markers, immune function, or cancer pathobiology	• Biomarker research on genetic and circulating factors may be assessed from tumor tissue, whole blood, and plasma samples, unless precluded by local regulations.
• To explore whether ongoing measurement of tumor shrinkage (such as changes in tumor size) correlate with efficacy measures	• Tumor measurements

Abbreviations: AEs = adverse events; ASBI = Average Symptom Burden Index; CHK1 = checkpoint kinase 1; CR = complete response; DCR = disease control rate; DoR = duration of response; ECG = electrocardiogram; ED-SCLC = extensive-stage disease small cell lung cancer; LCSS = Lung Cancer Symptom Scale; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; RECIST = Response Evaluation Criteria In Solid Tumors; SAEs = severe adverse events; SD = stable disease.

5. Study Design

5.1. Overall Design

Study I4D-MC-JTJH (JTJH) is a multicenter, nonrandomized, parallel-cohort Phase 2 study of LY2606368 in patients with ED-SCLC who have either platinum-sensitive or platinum-resistant/refractory disease.

5.2. Number of Patients

Approximately 116 patients (58 platinum-sensitive patients and 58 platinum-refractory/resistant patients) will be enrolled to receive LY2606368.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure for the last patient.

5.4. Scientific Rationale for Study Design

An open-label, single-arm, nonrandomized study without concurrent controls is appropriate for patients with second-line or greater ED-SCLC. There is not currently a uniform standard of treatment for patients with resistant/refractory disease, and clinical trials are recommended (Fruh et al. 2013; Kalemkerian et al. 2013). Historical response rates are reported to be approximately 10%, and so large improvements on these options can be detected using a single-arm design. Although topotecan is the standard for patients with platinum-sensitive disease, the response rates (approximately 20%-25%) are well established from historical controls (von Pawel et al. 1999; Fruh et al. 2013; Kalemkerian et al. 2013).

5.5. Justification for Dose

The LY2606368 monotherapy MTD when administered once every 14 days was determined to be 105 mg/m^2. This dose and schedule was selected as the recommended Phase 2 dose for monotherapy based on several factors including: the nonclinical LY2606368 monotherapy pharmacokinetic (PK)/pharmacodynamic model predicted exposure range for maximum tumor response coinciding with the observed clinical PK data; human pharmacodynamics simulations indicating a pharmacodynamic profile in a predicted efficacious range; and an acceptable safety profile. Please see the IB for additional details.

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria:

[1] have histological or cytological diagnosis of ED-SCLC (Edge et al. 2010) and have received a prior platinum-based regimen

- Cohort 1: had an objective response to prior platinum-based therapy with subsequent progression ≥90 days after the last dose of platinum
- Cohort 2: either did not have an objective response to prior platinum based therapy or had progression <90 days after the last dose of platinum

If a patient has had more than one line of platinum therapy, the platinum sensitivity should be determined from the last exposure to platinum.

[2] have a performance status of 0 to 1 on the Eastern Cooperative Oncology Group scale (Oken et al. 1982)

[3] have discontinued all previous treatments for cancer and recovered from the acute effects of therapy. Patients must have discontinued from previous treatments, as shown below:

Previous Treatment	**Length of Time Prior to First Dose of LY2606368**
Cytotoxic therapies or targeted agents that are small molecule inhibitors	≥14 days
Biologic agents	≥14 days
Immunotherapy	≥14 days
Radiotherapy	≥14 days
Major surgery, excluding biopsy	≥14 days

[4] have at least 1 measurable lesion using standard techniques by Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 (Eisenhauer et al. 2009)

[5] have given written informed consent/assent prior to any study-specific procedures

[6] are of an acceptable age to provide informed consent according to the local regulations and are at least 18 years of age

[7] have adequate organ function, as defined below:

System	Laboratory Value
Hematologic	
ANC	≥1.5 × 10^9/L
Platelets	≥100 × 10^9/L
Hemoglobin	≥8 g/dL or ≥5 mmol
	Transfusions to increase the patient's hemoglobin level to meet enrollment criteria are not allowed in the 14 days preceding the first dose of study drug.
Hepatic	
Direct bilirubin	≤1.5 × ULN
ALT and AST	≤2.5 × ULN **OR** ≤5 × ULN if the liver has tumor involvement
Renal	
Serum creatinine **OR** Measured creatinine clearance **OR** Calculated creatinine clearance (using the CKP-EPI equation - see Appendix 6)	<1.5 × ULN **OR** ≥50 mL/min/1.73 m^2

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CKP-EPI = Chronic Kidney Disease Epidemiology Collaboration; ULN = upper limit of normal.

[8] men must be sterile or agree to use an effective method of contraception or a highly effective method of contraception during the study and for at least 12 weeks following the last dose of LY2606368

Refer to Appendix 1 for definitions of fertile men, effective method of contraception, and highly effective method of contraception.

[9] women of childbearing potential must:

a. have a negative serum pregnancy test at the baseline visit
b. have a negative urine pregnancy test within 7 days prior to the first dose of LY2606368
c. agree to use a highly effective method of contraception (Appendix 1) during the study and for 12 weeks following the last dose of LY2606368
d. not be breast-feeding

Refer to Appendix 1 for definitions of women of childbearing potential and postmenopausal women.

6.2. Exclusion Criteria

Patients will be excluded from the study if they meet **any** of the following criteria:

[10] have received more than 2 prior therapies for ED-SCLC (including immunotherapy, targeted therapies, or chemotherapy)

Each line of therapy is preceded by disease progression. Discontinuation of a regimen without progression (for example, due to toxicity) or a switch of an agent within the same drug class (for example, cisplatin to carboplatin) within a regimen to manage toxicity does not define the start of a new line of therapy. Similarly, maintenance therapy (continuation maintenance or switch maintenance) will not be considered a new line of treatment.

[11] have symptomatic central nervous system (CNS) malignancy or metastasis. Asymptomatic patients with treated CNS metastases are eligible for this study if they are not currently receiving corticosteroids to treat CNS metastases. CNS metastases should be stable for at least 14 days by clinical assessment, and patients should not have received corticosteroids to treat CNS metastases within 14 days of the first dose of study drug.

[12] have a second primary malignancy that in the judgment of the investigator and Lilly may affect the interpretation of results

[13] are currently enrolled in a clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study

[14] have previously completed or withdrawn from this study or any other study investigating LY2606368 or a CHK1 inhibitor or have shown hypersensitivity to any of the components of the LY2606368 formulation

[15] have a known serious concomitant systemic disorder (for example, active infection or cardiac disease) that, in the opinion of the investigator, would compromise the patient's ability to adhere to the protocol

[16] have a symptomatic human immunodeficiency virus (HIV) infection or symptomatic activated/reactivated hepatitis A, B, or C (screening is not required). If the medical history, symptoms, and/or laboratory values suggest that the patient may have HIV or hepatitis A, B, or C, appropriate assessment should be conducted to determine whether the patient should be excluded.

[17] have a serious cardiac condition, such as:

- symptomatic congestive heart failure
- New York Heart Association Class III/IV heart disease
- unstable angina pectoris
- symptomatic or poorly controlled cardiac arrhythmia
- myocardial infarction within the last 3 months

- have a QT interval using Fridericia's correction (QTcF) of >470 msec on more than one screening electrocardiogram (ECG)
- a family history of long-QT syndrome

6.3. Lifestyle Restrictions

There are no specific lifestyle restrictions for this protocol.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened. Individuals may be re-screened a maximum of 2 times. The interval between re-screenings should be at least 2 weeks. Each time re-screening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number. Repeating of laboratory tests during the 28-day screening period does not constitute re-screening.

7. Treatments

7.1. Treatments Administered

Patients in both cohorts will receive 105 mg/m^2 LY2606368 as an approximately 60 (+10) minute intravenous (IV) infusion on Day 1 of a 14-day cycle.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the drug and planned duration of each individual's treatment to the patient/study site personnel/legal representative
- verifying that instructions are followed properly
- maintaining accurate records of LY2606368 dispensing and collection
- at the end of the study returning all unused medication to Lilly, or its designee, unless Lilly and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law

7.1.1. Packaging and Labelling

The drug product, LY2606368 for injection, is supplied for clinical trial use as a lyophilized, yellow to white solid, in glass vials and is composed of either LY2606368 mesylate monohydrate and the inactive ingredient sulfobutyl ether beta-cyclodextrin sodium (Captisol®) or LY2606368 lactate monohydrate and the inactive ingredients trehalose and mannitol. Table JTJH.7.1 below gives the available strengths for these 2 formulations. At the start of the study, only the mesylate monohydrate formulation will be available. However, during the study the formulation may be switched to the lactate monohydrate formulation. Sites will be notified in writing prior to this occurring. Please see the IB for additional information on these formulations.

Clinical trial materials will be labeled according to the country's regulatory requirements.

Table JTJH.7.1. LY2606368 for Injection Strengths

Formulation API	Primary Packaging (Nominal Vial size, mL)	Strength mg/vial (as free base)
LY2606368 mesylate monohydrate	50	40
LY2606368 lactate monohydrate	50	67

Abbreviation: API = active pharmaceutical ingredient.

7.2. Method of Treatment Assignment

Upon obtaining informed consent, the site will register the patient via the Interactive Web Response System (IWRS), which is accessible 24 hours a day, to assign a patient number. Patients who meet all criteria for enrollment will be assigned to receive LY2606368 in this study. The IWRS will be used to dispense LY2606368 to each patient.

7.2.1. Selection and Timing of Doses

A cycle is defined as an interval of 14 days. A delay of a cycle (Day 1) due to holiday, weekend, inclement weather, or other unforeseen circumstances will be permitted for a maximum of 7 days and not counted as a protocol deviation. An interval of at least 14 days must be maintained between LY2606368 doses, and if there is a delay the cycle length should be extended to accommodate the delay.

The actual doses of LY2606368 to be administered will be determined by calculating the patient's body surface area (BSA) at the beginning of each cycle. If the patient's weight does not fluctuate by more than ±10% from the weight used to calculate the prior dose, the BSA will not need to be recalculated. A ±10% variance in the calculated total dose will be allowed for ease of dose administration.

A patient may continue to receive LY2606368 until he or she meets 1 or more of the specified reasons for discontinuation (as described in Section 8).

7.3. Blinding

This is an open-label study.

7.4. Dosage Modification

Before the start of each cycle:

- Nonhematologic toxicities must resolve to Grade 0 or 1 or baseline, except AEs with no immediate medical consequence or those that can be controlled with adequate treatment (for example, alopecia, fatigue, nausea, vomiting, diarrhea, or asymptomatic changes in electrolytes).
- Neutropenia, thrombocytopenia, and anemia must resolve to Grade 0, 1, or 2, as shown in Table JTJH.7.2.

Table JTJH.7.2. Hematologic Parameters Required for the Start of Each Cycle

	Dose
Neutrophils	≥1000/mm^3
Platelets	≥75/mm^3
Hemoglobin	≥8 g/dL

Treatment may be delayed for a maximum of 14 days to allow a patient sufficient time for recovery from LY2606368-related toxicity. If a patient does not recover from the toxicity within 28 days from the time of last treatment, the patient should be discontinued from LY2606368. In exceptional circumstances, a longer delay is permitted upon agreement between the investigator and the Lilly clinical research physician (CRP).

If a patient, in the investigator's opinion, experiences a toxicity warranting a dose reduction, LY2606368 should be reduced as shown in Table JTJH.7.3.

Table JTJH.7.3. LY2606368 Dose Reductions

Reduction	Dose
1st LY2606368 dose reduction	80 mg/m^2
2nd LY2606368 dose reduction	60 mg/m^2
3rd LY2606368 dose reduction	Discontinue from LY2606368

Following a dose reduction, re-escalation is acceptable. If a subsequent LY2606368 dose reduction is again required, the patient's dose may not be re-escalated a second time.

7.5. Preparation/Handling/Storage/Accountability

LY2606368 will be administered as an IV infusion using a central or peripheral IV line and will be filtered through an in-line filter. LY2606368 should be handled according to standard procedures and precautions consistent with a cytotoxic anticancer drug. For the most current detailed formulation information and preparation instructions, refer to the IB and Pharmacy Binder.

7.5.1. LY2606368 Mesylate Monohydrate

The LY2606368 mesylate monohydrate drug product contains 40 mg/vial of the base compound LY2606368. The vial contains a 3% excess to facilitate the withdrawal of the label amount 40 mg/vial for use with an appropriate device, such as an infusion set. The drug product is stable when stored at room temperature.

Reconstituting the vial contents with 19 mL of water for injection yields a clear yellow solution with a concentration of 2 mg/mL of LY2606368 and an osmotic pressure ratio of 344 mOsm. The reconstituted formulation is stable for at least 24 hours at room temperature; however, since the reconstituted drug product does not contain a preservative, the unused solution must be discarded after 12 hours. The reconstituted solution may be diluted with dextrose 5% injection (D5W) prior to administration. LY2606368 is incompatible with solutions containing saline or lactated Ringer's and must **NOT** be mixed or administered simultaneously with other drugs through the same infusion line. The infusion line should be flushed with D5W before and after LY2606368 administration.

7.5.2. LY2606368 Lactate Monohydrate

A 67-mg strength of LY2606368 lactate monohydrate drug product is in development and may be used in Study JTJH. The vial will contain a slight excess to facilitate the withdrawal of the label amount 67 mg/vial for use with an appropriate device, such as an infusion set. Reconstituting the vial contents with water for injection yields a clear yellow solution with a concentration of 3.35 mg/mL of LY2606368. For the most current detailed information on this strength refer to the IB and Pharmacy Binder.

7.6. Treatment Compliance

The study medication will be administered only at the investigational sites by the authorized study site personnel. As a result, treatment compliance is ensured.

7.7. Concomitant Therapy

No other chemotherapy, immunotherapy, cancer-related hormone therapy, herbal drugs intended to treat cancer, or experimental drugs will be permitted while the patients are on this study. Radiotherapy (including palliative radiotherapy) will only be permitted if it is agreed upon by the both investigator and Lilly. If the lesion that is to be treated is a target lesion, the lesion will be censored at the time of treatment. However, the patient may be eligible to remain on study drug treatment provided there are other lesions that can be followed for progression. Treatment delays of LY2606368 may be required if radiotherapy is administered. In addition, any disease progression requiring other forms of specific antitumor therapy will also necessitate early discontinuation from the study. Replacement hormonal therapy initiated before study entry will be allowed.

Patients should receive full supportive care during the trial. American Society of Clinical Oncology (ASCO) guidelines (Smith et al. 2015) should be followed for patients requiring support with granulocyte-colony stimulating factor (G-CSF). Primary or secondary prophylactic G-CSF support is permitted at the discretion of the investigator. Per the National Comprehensive Cancer Network (NCCN) guidelines, Phase 2 data support the use of pegfilgrastim in regimens with a 2-week cycle, and there is uniform consensus that this is appropriate (Category 2A) (NCCN guidelines for myeloid growth factors [WWW]). As a result, filgrastim, filgrastim biosimilars, or pegfilgrastim may be used.

Prophylactic antibiotics should be considered for use in patients that have experienced neutropenic fever or patients deemed at higher risk for neutropenic fever by the investigators. The treatment should be consistent with ASCO guidelines (Flowers et al. 2013).

Transfusion of packed red blood cells (RBCs) within 14 days of study entry is not permitted. The initiation of erythropoietin therapy to meet eligibility criteria is not permitted. Patients who are stable on erythropoietin for >1 month before study entry may continue their treatment. Erythropoietin and packed RBC transfusion may be used according to ASCO guidelines (Rizzo et al. 2008) if clinically indicated at any time during the study.

In Study JTJA, no prolongations in average QTcF interval (Fridericia's formula) >480 msec or of ≥60 msec from baseline were observed with LY2606368 monotherapy (n=101) at any time point. A thorough corrected QT (QTc) study has not yet been conducted. On days when LY2606368 is administered, patients should avoid taking multiple concomitant medications that are known or suspected to cause prolonged QTc or Torsades de Points and, if possible, alternative agents should be considered.

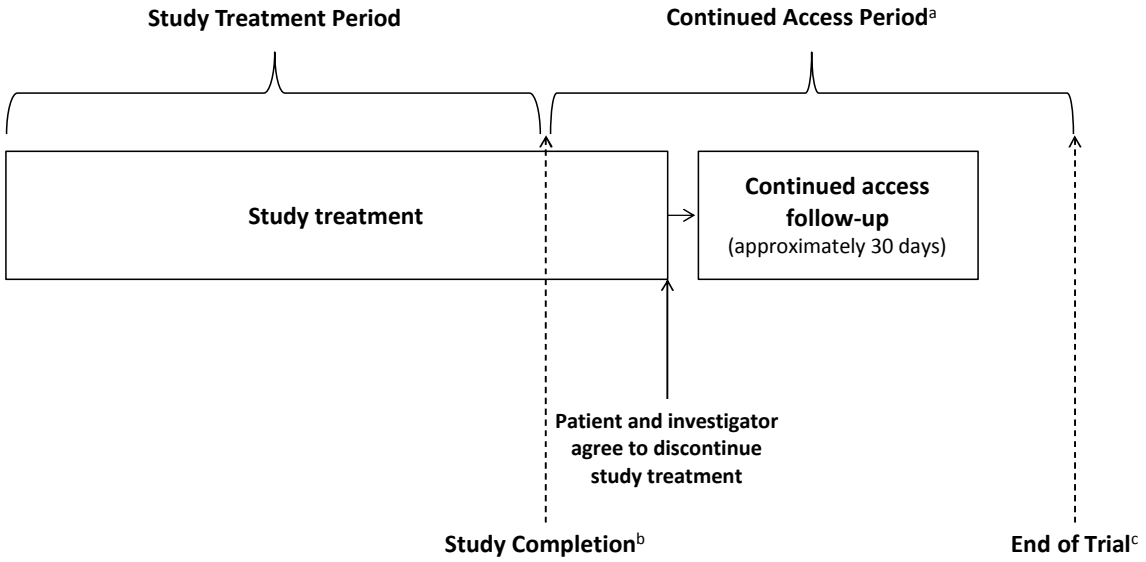
7.8. Treatment after the End of the Study

Study completion will occur no more than 1 year after the last patient enrolls in the trial, following the final analyses of progression-free survival (PFS) and overall survival (OS). Investigators will continue to follow Schedule of Activities (Section 2) for all patients until notified by Lilly that study completion has occurred.

7.8.1. Continued Access

Patients who are still on LY2606368 at the time of study completion may continue to receive LY2606368 if they are experiencing clinical benefit and no undue risks. The continued access period will apply to this study only if at least 1 patient is still on LY2606368 when study completion occurs. Lilly will notify investigators when the continued access period begins. Lilly may allow patients to enroll in a LY2606368 "rollover" protocol to provide long-term continued access for patients enrolled in this study. The continued access period is shown in Figure JTJH.7.1.

The patient's continued access to LY2606368 will end when a criterion for discontinuation is met (Section 8). Continued access follow-up will begin the day after the patient and the investigator agree to discontinue LY2606368 and lasts approximately 30 (±7) days. Follow-up procedures will be performed as shown in the Continued Access Schedule of Activities (Table JTJH.2.4).



[a] Lilly will notify sites when the continued access period begins and ends.
[b] Final analysis of overall survival. Lilly will notify sites when study completion occurs.
[c] End of trial occurs at the last visit or last scheduled procedure for the last patient.

Figure JTJH.7.1. Continued access diagram.

Patients who are in short-term follow-up when the continued access period begins will continue in short-term follow-up until the 30-day short-term follow-up visit is completed. Long-term follow-up does not apply.

Patients who are in long-term follow-up when the continued access period begins will be discontinued from long-term follow-up.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

Patients will be discontinued from study treatment in the fo llowing circumstances:

- the patient is enrolled in any other clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
- the patient becomes pregnant during the study
- the patient is significantly noncompliant with study procedures and/or treatment
- the patient has evidence of progressive disease
- the patient experiences unacceptable toxicity
- the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. Discontinuation from study treatment will occur prior to introduction of the new agent.
- the investigator decides that the patient should be discontinued from LY2606368
- the patient requests to be discontinued from LY2606368

Patients who are discontinued from LY2606368 will have follow-up procedures performed as shown in the Schedule of Activities (Section 2).

8.1.1. Discontinuation of Inadvertently Enrolled Patients

If Lilly or the investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly CRP and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without LY2606368.

8.2. Discontinuation from the Study

Patients will be discontinued from the study in the following circumstances:

- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- the investigator decides that the patient should be discontinued from the study
- the patient requests to be discontinued from the study

Patients who discontinue from the study early will have end-of-study procedures performed as shown in the Schedule of Activities (Section 2).

8.3. Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Study site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or who the site is otherwise unable to follow-up.

Study site personnel, or an independent third party, will attempt to collect the survival status for all enrolled patients who are lost to follow-up, within legal and ethical boundaries. Public sources may be searched for survival status information. If the patient's survival status is determined, the survival status will be documented, and the patient will not be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect survival status information.

9. Study Assessments and Procedures

Section 2 provides the Schedule of Activities for this study.

Appendix 3 provides a list of the laboratory tests that will be performed for this study.

Appendix 4 provides the schedule for collection of samples in this study.

Unless otherwise stated in the following subsections, all samples collected for specified laboratory tests will be destroyed within 60 days after receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

Tumor assessments will be performed for each patient at the times shown in the Schedule of Activities (Section 2).

Computed tomography (CT) scans, including spiral CT, are the preferred methods of measurement (CT scan thickness recommended to be ≤5 mm); however, magnetic resonance imaging (MRI) is also acceptable in certain situations, such as when body scans are indicated or if there is a concern about radiation exposure associated with CT. Intravenous and oral contrast is required unless medically contraindicated.

The CT portion of a positron emission tomography (PET)-CT scan may be used as a method of response assessment if the CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast). A PET scan alone or as part of a PET-CT may be performed for additional analyses but cannot be used to assess response according to RECIST v.1.1 (Eisenhauer et al. 2009).

Radiologic scans of the thorax and abdomen are required. A baseline intracranial evaluation with CT or MRI should be conducted. Scans of the pelvis or bone scans should be performed if clinically indicated. Copies of the scans may be requested by the sponsor for central review.

See Section 10.3.1 for definitions of the efficacy endpoints.

9.1.1. Appropriateness of Assessments

The measures used to assess safety and efficacy in this study are consistent with those used in most conventional oncology trials.

9.2. Adverse Events

The investigator will use Common Terminology Criteria for Adverse Events Version 4.0 (NCI 2009) to assign AE terms and severity grades.

Investigators are responsible for:

- monitoring the safety of patients in this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient
- the appropriate medical care of patients during the study
- documenting their review of each laboratory safety report
- following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to study treatment or the study, or that caused the patient to discontinue LY2606368 before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via case report form (CRF)/electronic data entry/designated data transmission methods the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, study site personnel will record via CRF/electronic data entry/designated data transmission methods any change in the preexisting conditions and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to study procedure or LY2606368 via CRF/electronic data entry/designated data transmission methods.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment or a study procedure, taking into account the disease, concomitant treatments, or pathologies. A "reasonable possibility" means that there is a cause and effect relationship between the study treatment and/or study procedure and the AE.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

Study site personnel must report any dose modifications or treatment discontinuations that result from AEs to Lilly or its designee via CRF/electronic data entry/designated data transmission methods, clarifying, if possible, the circumstances leading to the dose modification or discontinuation of treatment.

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity

- congenital anomaly/birth defect
- considered significant by the investigator for any other reason: important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious, based upon appropriate medical judgment.

Although all AEs after signing the ICF are recorded in the CRF/electronic data entry/designated data transmission methods, SAE reporting begins after the patient has signed the ICF and has received LY2606368. However, if an SAE occurs after signing the ICF, but prior to receiving LY2606368, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

Study site personnel must notify Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a Lilly-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Pregnancy (during maternal or paternal exposure to LY2606368) does not meet the definition of an AE but should be reported. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued and/or completed the study (the patient summary CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

Planned hospitalizations or procedures for preexisting conditions that were recorded in the patient's medical history at the time of enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study treatment or other protocol-required procedure) should not be considered an SAE.

Serious adverse events, including death, caused by disease progression should not be reported unless the investigator deems them to be possibly related to LY2606368.

9.2.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to study treatment or study procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidances.

9.2.3. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Patients should be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

9.3. Treatment of Overdose

Refer to the IB for the current guidance on overdose.

9.4. Safety

9.4.1. Other Safety Measures

For each patient, safety assessments, including ECGs, vital signs, and laboratory tests, should be collected as shown in the Schedule of Activities (Section 2). ECGs should be recorded according to the study-specific recommendations that will be provided separately.

As of 27 August 2015, no patients treated with LY2606368 monotherapy have had an average QTcF interval >480 msec at any time point. However, if a patient experiences a QTcF interval >480 msec, the patient should be monitored for signs of life-threatening arrhythmias such as torsades de pointes. It should be confirmed that the measurement is correct by repeating the ECG and ruling out other causes such as atrial fibrillation or the presence of a pacemaker. If the result is confirmed, institutional guidelines or standard of care measures for management of QTcF interval >480 msec and/or associated arrhythmias should be initiated. These actions may include the administration of IV magnesium sulfate and the assessment of clinical chemistry. If electrolytes are abnormal, they should be repeated as indicated. The QTcF value should be monitored until the interval has returned to <480 msec or at least to predose levels. It is recommended that the patient be assessed by a cardiologist before leaving the treating facility. For all subsequent doses, an ECG must be obtained at 10 minutes after the end of infusion (EOI) (±5 minutes), 30 minutes after EOI (±10 minutes), and >1 hour after EOI.

If a patient experiences a QTcF interval >500 msec and has an associated life-threatening arrhythmia, he/she should be discontinued from study treatment. If a patient experiences a QTcF interval >500 msec without an associated life-threatening arrhythmia and if the investigator deems it in the best interest of the patient, the patient may continue treatment with LY2606368. If a patient has a second occurrence of QTcF interval >500 msec, he/she should be discontinued from study treatment.

Any clinically significant findings that result in a diagnosis and that occur after the patient receives the first dose of LY2606368 should be reported to Lilly or its designee as an AE via CRF/electronic data entry/designated data transmission methods.

9.4.2. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests. See Appendix 5.

- If a patient experiences elevated alanine aminotransferase (ALT) ≥5 × upper limit of normal (ULN) and elevated total bilirubin ≥2 × ULN, clinical and laboratory monitoring should be initiated by the investigator.
- For patients entering the study with ALT ≥3X ULN, monitoring should be triggered at ALT ≥2X baseline and elevated total bilirubin ≥2 × ULN.

9.5. Pharmacokinetics

Pharmacokinetic samples will be collected as specified in the Pharmacokinetic Sampling Schedule (Appendix 4).

At the visits and times specified in the Study Schedule, venous blood samples will be collected to determine the plasma concentrations of LY2606368. A maximum of 5 samples may be added or removed during the study if warranted and agreed upon between both the investigator and Lilly. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

These samples will be analyzed at a laboratory designated by the sponsor by using a validated liquid chromatography–mass spectrometry/mass spectrometry (LC-MS/MS) method.

The PK samples will be stored at a facility designated by the sponsor. Bioanalytical samples collected to measure LY2606368 concentrations will be retained for a maximum of 1 year following last patient visit for the study.

9.6. Pharmacodynamics

Pharmacodynamics samples will not be collected for this trial.

9.7. Pharmacogenomics

9.7.1. Whole Blood Sample for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in Section 2, where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to LY2606368 and to investigate genetic variants thought to play a role in SCLC. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the study site personnel. Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ethical review boards (ERBs)/institutional review boards (IRBs) impose shorter time limits, at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development of LY2606368 or after LY2606368 becomes commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing technologies include whole genome and exome sequencing, genome-wide association studies, multiplex assays, candidate gene studies, and epigenetic analyses. Regardless of the technology utilized, data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, mechanism of action, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including DNA, RNA, proteins, lipids, and other cellular elements.

As part of Lilly's ongoing efforts to understand the relationship between cancer, genetics, and response to therapy, this study will analyze biomarkers relevant to the mechanism of action of CHK1, DNA damage response pathways or downstream effects, cell cycle markers, immune function, and cancer pathobiology and/or for related research methods or validation of diagnostic tools or assays.

Samples for biomarker research will be collected as specified in Section 2 where local regulations allow. It is possible that biomarker data for patients in the study have already been generated from samples that were collected and analyzed before the patients' enrollment in this trial. This may include data generated from genetic analyses. If available, these data may be requested from medical records for use in the research described in Sections 9.8.1 and 9.8.2. Samples for biomarker research will be collected as specified Section 2, where local regulations allow.

9.8.1. Blood Samples

Plasma samples for biomarker research will be collected as specified in Section 2 where local regulations allow.

Samples will be examined for biomarkers related to SCLC, variable response to LY2606368, the mechanism of action of LY2606368, and/or for research-related methods or validating diagnostic tools or assays.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the study site personnel.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits, at a facility selected by Lilly. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development of LY2606368 or after LY2606368 becomes commercially available.

9.8.2. Tissue Samples

Tumor tissue will be examined for biomarkers related to the mechanism of action of CHK1, DNA damage response pathways or downstream effects, cell cycle markers, immune function, and cancer pathobiology. These markers may also be evaluated to assess any potential correlation with response to LY2606368.

Collection of the following tumor tissue sample(s) **is required** for all patients:

- an archived tumor sample (a block or slides) or a newly obtained biopsy specimen collected prior to treatment with LY2606368, if an archived tumor sample is not available, if not restricted by local regulations
- for patients who do not have archived tissue available and who have disease in technically challenging sites to obtain a fresh biopsy, the investigator and sponsor may agree to enroll the patient without tumor tissue. The joint decision must be documented in writing before the patient receives the first dose of LY2606368 and will not constitute a protocol violation.

Collection of the following tumor tissue sample(s) is **optional** for all patients:

- patients that have archived tumor tissue to meet the inclusion criteria for Study JTJH may also have an optional pre-treatment biopsy
- following treatment with LY2606368, patients may be asked to undergo collection of additional optional on-study, post-treatment, and/or post-progression biopsies for biomarker research from patients willing to consent. In particular, biopsies from lesions in patients who have received clinical benefit and subsequently progress may help identify molecular features that may explain treatment response and resistance mechanisms. Post-progression biopsies should be performed prior to the start of subsequent cancer treatment. However, the procedure should not impede or delay the planned cancer treatment.

Formalin-fixed paraffin-embedded tumor tissue obtained from the primary tumor or metastatic site should be provided as a block or unstained slides. Due diligence should be used to make sure that tumor sample (not a normal adjacent or a tumor margin sample) is provided. Pathology notes/report accompanying archival tissue may also be requested. The notes/report should be coded with the patient number. Personal identifiers, including the patient's name and initials, must be removed from the institutional pathology notes/report prior to submission. Archival

blocks will be sectioned and returned to the study site. Slides and tissue samples collected on-study will not be returned.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits, at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development of LY2606368 or after LY2606368 becomes commercially available.

Technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing technologies, including mutation profiling, copy number variability, gene expression, multiplex assays, and/or immunohisto chemistry, may be performed on these tissue samples to assess potential associations with these biomarkers and clinical outcomes.

9.9. Health Economics

The primary health outcomes research goal is to evaluate the association between best tumor response and change from baseline in lung cancer-specific symptoms, symptomatic distress, activity status, overall quality of life, total Lung Cancer Symptom Scale (LCSS) score, and Average Symptom Burden Index (ASBI) for patients who have platinum-sensitive or platinum-resistant/refractory SCLC. Patient-reported outcomes and symptoms will be assessed by the LCSS patient scale. The LCSS is a validated tool that has been broadly used in lung cancer research and is available in over 30 different languages.

The LCSS (Hollen et al. 1994) consists of 9 total items, each with a 100-mm line depicting the visual analog scale (VAS). Scores equal the length of line as marked by patient and range from 0 (for best outcome) to 100 (for worst outcome). Six items are symptom-specific measures for lung cancer (appetite loss, fatigue, cough, dyspnea, hemoptysis, and pain) that address 2 dimensions: physical and functional. There are also 3 summation items that describe symptomatic distress, activity status, and overall quality of life.

The LCSS will be administered as shown in the Schedule of Activities (Section 2). The LCSS will be completed by patients when a language translation is available in which the patient is fluent or literate. The recall period is 24 hours and the typical completion time is 8 minutes initially for demonstration of VAS; 3 to 5 minutes for subsequent administrations. To avoid biased responses, the questionnaires should be administered prior to extensive contact with study personnel and clinicians and prior to study drug administration.

10. Statistical Considerations

10.1. Sample Size Determination

The study will enroll approximately 116 patients (58 platinum-sensitive patients, 58 platinum-refractory/resistant patients).

For the platinum-sensitive cohort, it is assumed that a true overall response rate (ORR) of less than 20% indicates inadequate antitumor activity. Given that a futility interim analysis will be conducted on the first 29 patients' response data, then with a one-sided significance level of 0.1, a sample size of 58 patients will provide approximately 90% power to detect a true ORR of at least 35%, i.e. 16 or more confirmed overall responses (complete response [CR] or partial response [PR]) are observed in all 58 patients.

For the platinum-refractory/resistant cohort, it is assumed that a true ORR of less than 5% indicates inadequate anti-tumor activity. Given that a futility interim analysis will be conducted on the first 29 patients' response data, then with a one-sided significance level of 0.1, a sample size of 58 patients will provide approximately 90% power to detect a true ORR of at least 15%, i.e. 6 or more confirmed overall responses (CR or PR) are observed in all 58 patients.

For each cohort, the overall type II error rate, i.e. the probability of terminating an effective cohort, will be controlled using a Lan-DeMets spending function (Lan and DeMets 1983), which generates boundaries that are very similar, though not identical, to the classical stopping boundaries of O'Brien and Fleming (1979). The type II error rate spent at interim analysis after the first 29 patients for each cohort is approximately 2%; the cumulative type II error rates spent at final analysis for platinum-sensitive cohort and platinum-refractory/resistant cohort are 9.9% and 9.4%, respectively.

10.2. Populations for Analyses

The following populations will be defined for this study:

Intention-to-Treat (ITT) population: will include all enrolled patients. This population will be used for all baseline, efficacy, and health economics analyses. All patients in the ITT population will be considered to have completed the study.

Per-protocol population: will include all enrolled patients who receive at least one dose of study treatment and do not have any major protocol violations that could potentially affect the efficacy conclusions of the study. This population will be defined in detail in the statistical analysis plan (SAP) prior to database lock.

Safety population: will include all enrolled patients who received any quantity of study treatment, regardless of their eligibility for the study. The safety evaluation will be performed based on the first dose of study treatment a patient actually received. The safety population will be used for all dosing/exposure, and safety analyses.

Pharmacokinetic population: will include all enrolled patients who received at least 1 full infusion of LY2606368 and have evaluable PK samples collected.

Biomarker population: will include the subset of patients from the ITT population from whom a valid assay result has been obtained.

10.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of Lilly or its designee.

All tests of treatment effects will be conducted at a 1-sided alpha level of 0.1, unless otherwise stated. Unless otherwise stated, all confidence intervals (CIs) will be given at a 2-sided 95% level.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

10.3.1. Efficacy Analyses

Overall response rate (ORR) is defined as the number of patients who achieve a best overall response of CR or PR, divided by the total number of patients enrolled to the corresponding cohort (ITT population). Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point (greater than 4 weeks). The ORR, with 95% and 80% CIs, will be summarized for each cohort using the Clopper-Pearson method.

Disease control rate (DCR) is defined as the number of patients who achieve a best overall response of CR, PR, or stable disease (SD) divided by the total number of patients enrolled to the corresponding cohort (ITT population). The confirmation of CR and PR is required. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6 weeks). The DCR, with 95% CI, will be summarized for each cohort using the Clopper-Pearson method.

Duration of response is defined as the time from the date measurement criteria for CR or PR (whichever is first recorded) are first met until the first date that disease is recurrent or objective progression is observed, per RECIST 1.1 criteria, or the date of death from any cause in the absence of objectively determined disease progression or recurrence.

Overall survival is defined as the time from enrollment until death from any cause. If the patient is alive or lost to follow-up at the time of data analysis, OS data will be censored on the last date the patient is known to be alive. Overall survival curves, the median and survival rates at various time points with 95% CI, for each cohort will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958).

Progression-free survival is defined as the time from enrollment until the first radiographic documentation of progression or death from any cause in the absence of PD. Patients known to be alive and without disease progression will be censored at the time of the last adequate tumor assessment prior to study completion (a detailed PFS event/censoring scheme is provided in SAP). Progression-free survival curves, median PFS, and PFS rates at various time points with

95% CI for each cohort will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958).

Exploratory sensitivity analyses on efficacy endpoints may be conducted as described in the SAP.

10.3.2. Safety Analyses

All patients who receive at least 1 dose of any study therapy will be evaluated for safety and toxicity.

The Medical Dictionary for Regulatory Activities (MedDRA™) Version 18.0 (or higher) will be used when reporting AEs by MedDRA terms. The MedDRA Lower Level Term will be used in the treatment-emergent computation. Treatment-emergent adverse events will be summarized by System Organ Class (SOC) and by decreasing frequency of Preferred Term within SOC.

Safety analyses will include summaries of the following:

- AEs, including severity and possible relationship to study drug
- SAEs, including possible relationship to study drug
- AEs leading to dose adjustments
- discontinuations from study treatment due to AEs or death
- treatment-emergent abnormal changes in laboratory values
- treatment-emergent abnormal changes in vital signs and ECGs

10.3.3. Other Analyses

10.3.3.1. Patient Disposition

A detailed description of patient disposition will be provided, including a summary of the number and percentage of patients entered into the study and enrolled in the study, as well as number and percentage of patients completing the study, as defined in the SAP, or discontinuing (overall and by reason for discontinuation). A summary of all important protocol deviations will be provided.

10.3.3.2. Patient Characteristics

Demographic data are collected and reported to demonstrate that the study population represents the target patient population considered for regulatory approval.

A summary of baseline patient and disease characteristics, historical diagnoses, preexisting conditions, and prior therapies will be reported using descriptive statistics.

10.3.3.3. Concomitant Therapy

A summary of prior and concomitant medications by treatment cohort will be reported.

10.3.3.4. Poststudy-Treatment-Discontinuation Therapy

The numbers and percentages of patients receiving post study-treatment-discontinuation anticancer therapies will be provided by type of therapy (surgery, radiotherapy, or systemic therapy), and by drug class and/or name, overall and by line of therapy.

10.3.3.5. Treatment Compliance

The number of cycles received, dose omissions, dose reductions, dose delays, and dose intensity will be summarized for all treated patients by treatment cohort.

Study treatment will be administered at the investigator site, therefore treatment compliance is assured.

10.3.3.6. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic parameter estimates for LY2606368 will be estimated by standard population PK methods of analysis using validated PK software programs (for example, NONMEM) and that is approved for use by Global PK/pharmacodynamic management. The version of any software used for the analysis will be documented, and the program will meet the Lilly requirements of software validation.

Sparse LY2606368 PK data obtained from patients who receive at least 1 dose of LY2606368 and have had samples collected for PK analysis will be pooled with PK data from a previous study investigating LY2606368 as monotherapy (Study JTJA) and analyzed by population-based PK analysis methods to characterize the observed intra- and interpatient PK variability and identify the patient-specific covariates that contribute to the observed PK variability of LY2606368. Post-hoc LY2606368 PK parameters estimates will be calculated for each patient in this study and will include the maximum plasma concentration (C_{max}), area under the plasma concentration versus time curve (for example, $AUC_{[0\text{-}72]}$, $AUC_{[0\text{-}\infty]}$), terminal elimination half-life ($t_{1/2}$), systemic clearance, and the multi-compartmental volumes of distributions (for example, V_1, V_2, and V_{ss}]). A descriptive summary of LY2606368 plasma concentration data will also be provided for the LY2606368 C_{max}, minimum plasma concentration (C_{min}), and accumulation ratio across multiple cycles of treatment.

Additional exploratory analyses, such as population-based analyses that examine the relationship between LY2606368 exposure (PK) and response and/or safety, may be performed (if the data warrant).

Interim review of the clinical PK data after the first 29 patients enrolled in both Cohorts 1 and 2 may be conducted.

10.3.3.7. Biomarker Analyses

Descriptive summaries and statistical analyses results will be provided to support the biomarker research objectives outlined in Section 9.8.

Appropriate descriptive statistics for biomarker results based on pre-treatment, on-treatment, or post-progression samples will be reported. Each biomarker will be described using summary statistics at the study, treatment arm, and at the level of other patient subgrouping of interest. Any correlations or associations between the biomarkers measured on the same patient will also be looked at.

In particular, descriptive summaries of biomarkers obtained from biopsies done on lesions that regressed after treatment will be provided. Provided a sufficient number of patients with such

biopsies are available, additional analyses may be undertaken to investigate the correlation between the change in the status/level of the biomarker and the change in the size of the lesion.

All biomarkers deemed relevant may be specifically investigated with the aim of understanding the genetic profile of patients who receive the greatest clinical benefit from LY2606368. These investigations will look at the correlation/association between the baseline (archival or pre-treatment) status/level of the biomarker(s) and measures of clinical benefit such as objective clinical response status (CR/PR or no-CR/PR) or disease control status (CR/PR/SD or no-CR/PR/SD). Where a change in the status/level of a biomarker over time can be ascertained, additional exploratory analyses may be undertaken to assess the effect of the change or its magnitude on the same clinical efficacy endpoints. For secondary efficacy measures of PFS and OS, parametric and semi-parametric survival analysis will be undertaken to quantify the association between the biomarker status and the time-to-event efficacy measure.

For serially measured plasma-based biomarkers, change from baseline to subsequent time points may be associated with clinical response outcomes. In addition, the time-course relationship of these biomarkers with safety and/or PK outcomes may also be investigated.

Biomarker results may also be analyzed to elucidate the associations between the baseline status/level, or change in status/level and including, but not limited to, the mechanism of action of LY2606368, sensitivity to CHK1 inhibition, and sensitivity or resistance to platinum-based therapies.

10.3.3.8. Health Outcome/Quality of Life Analyses

For the LCSS, the compliance rate by cohort will be calculated as the number of completed assessments divided by the number of expected assessments (that is, patients still on study). Compliance rates, reasons for noncompliance, and data collected will be summarized by cohort. Descriptive statistics for each of the domain scores/items of interest by category of best overall response (that is, CR, PR, SD, PD) will be summarized and a linear model will be fitted for each cohort in order to evaluate the association between best overall response and change from baseline/the maximum improvement from baseline in lung cancer-specific symptoms, symptomatic distress, activity status, overall quality of life , total LCSS score, and ASBI for patients who have platinum-sensitive or platinum- resistant/refractory SCLC. The model will include change from baseline/maximum change from baseline as the response variable and category of best overall response as an independent variable. The ASBI will be calculated as the mean of 6 symptom-specific questions; the total LCSS score will be calculated as the mean of 9 questions from the LCSS. For a given assessment, if any of the 6 symptom-specific questions have not been completed, the ASBI will not be calculated. Similarly, if any of the 9 LCSS questions have not been completed, the total LCSS score will not be calculated.

10.3.4. Interim Analyses

For each cohort, one interim analysis of futility will be conducted after the 29th patient in the cohort has completed Cycle 3, and, if required, the response is confirmed. The interim analysis will be conducted to assess whether the respective cohort is unlikely to achieve statistical

significance on its primary endpoint and may also include PK data in order to confirm that patients are in the expected exposure range.

The stopping rule for interim analysis is defined as follows:

- Platinum-sensitive cohort:
    - If 4 or fewer confirmed overall responses (CR or PR) are observed in the first 29 patients, then the cohort will be terminated; otherwise, the cohort will continue.
- Platinum-refractory/resistant cohort:
    - If 0 confirmed overall responses (CR or PR) are observed in the first 29 patients, then the cohort will be terminated; otherwise, the cohort will continue.

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Appendix 1. Abbreviations and Definitions

Term	Definition
AE	Adverse event: any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ASBI	Average Symptom Burden Index
$AUC_{(0-72)}$	area under the plasma concentration-time curve from time zero to 72 hours (3 days)
$AUC_{(0-\infty)}$	area under the plasma concentration-time curve from time zero to infinity
BSA	body surface area
CHK1	checkpoint kinase 1
CI	confidence interval
C_{max}	maximum plasma concentration
collection database	a computer database where clinical trial data are entered and validated.
CR	complete response
CRF	case report form
CRP	Clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DoR	duration of response
ECG	electrocardiogram
ED-SCLC	extensive stage disease small cell lung cancer
effective method of contraception	Effective method of contraception means male condom with spermicide, female condom with spermicide, diaphragm with spermicide, cervical sponge, or cervical cap with spermicide.

Enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment and have received at least one dose of study treatment
Enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB/IRB	ethical review board / institutional review board
fertile men	A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.
GCP	good clinical practice
G-CSF	granulocyte-colony stimulating factor
highly effective method of contraception	combined oral contraceptive pill and mini-pill, NuvaRing®, implantable contraceptives, injectable contraceptives (such as Depo-Provera®), intrauterine device (such as Mirena® and ParaGard®), contraceptive patch for women <90 Kg (<198 pounds), total abstinence, or vasectomy.
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
interim analysis	An interim analysis is an analysis of clinical trial data conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial.
ITT	intent-to-treat
LCSS	Lung Cancer Symptom Scale
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participants are aware of the drug therapy received during the study.
ORR	overall response rate
OS	overall survival
PD	pharmacodynamics
PFS	progression-free survival

PK	pharmacokinetic
PR	partial response
QTc	corrected QT interval
QTcF	corrected QT interval (Fridericia's formula)
RECIST	Response Evaluation Criteria in Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	to screen a patient who was previously declared a screen failure for the same study
SAE	serious adverse event
SAP	Statistical Analysis Plan
Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
screen failure	patient who does not meet one or more criteria required for participation in a trial
SD	stable disease
SUSARs	Suspected unexpected serious adverse reactions
$t_{1/2}$	half-life
TEAE: Treatment-emergent adverse event	An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
V1	volume of distribution of the central compartment
V2	volume of distribution of the peripheral compartment
Vss	volume of distribution at steady state
women of childbearing potential	A woman is considered of childbearing potential (ie, fertile) after menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy; however, in the absence of 12 months of amenorrhea, a single follicle-stimulating hormone measurement is insufficient.

Appendix 2. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the potential risks and benefits of participating in the study
- ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any study procedures and prior to the administration of LY2606368.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial

Ethical Review

Documentation of ERB/IRB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs/IRBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP. The study site's ERBs/IRBs should be provided with the following:

- the current IB and updates during the course of the study
- the ICF
- relevant curricula vitae

Regulatory Considerations

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations.

Some obligations of Lilly may be assigned to a third-party organization.

Investigator Information

Physicians with a specialty in oncology will participate as investigators in this clinical trial.

Protocol Signatures

Lilly's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Final Report Signature

The clinical study report coordinating investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The investigator with the most enrolled patients will serve as the clinical study report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the clinical study report coordinating investigator.

The Lilly responsible medical officer and statistician will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide Lilly, applicable regulatory agencies, and applicable ERBs/IRBs with direct access to original source documents.

Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the Lilly provided electronic data capture system.

Electronic patient-reported outcome (ePRO) measures (LCSS) are entered into an ePRO instrument (tablet) at the time that the information is obtained. In these instances where there is no prior written or electronic source data at the site, the ePRO instrument record will serve as the source.

ePRO records are stored at a third-party site; therefore, investigator sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention.

Any data for which the ePRO instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

Case report form data collected via InForm, the clinical trial database, will be encoded by a third-party organization and stored electronically in the third-party organization's database system. Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. Validated data will be transferred from these systems to the Lilly data warehouse, using standard Lilly file transfer processes. Any data for which the paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

Study and Site Closure

Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB/IRB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology - local or investigator-designated laboratory[a]

Leukocytes (WBC)	Erythrocytes (RBC)
Neutrophils[b]	Hemoglobin (HGB)
Lymphocytes	Hematocrit (HCT)
Monocytes	
Eosinophils	
Basophils	Platelets (PLT)

Coagulation- local or investigator-designated laboratory

Activated partial thromboplastin time (aPTT)
International normalized ratio (INR) or Prothrombin time (PT)

Clinical Chemistry - central laboratory. In addition, local labs may be collected at investigator discretion.

Serum Concentrations of:	
Alanine aminotransferase (ALT)	Creatinine
Albumin	Glucose random
Alkaline phosphatase	Potassium
Aspartate aminotransferase (AST)	Sodium
Bilirubin, direct	Uric acid
Bilirubin, total	Total protein
Blood urea nitrogen (BUN) or blood urea	Lactate dehydrogenase
Calcium	

Clinical Laboratory Tests

Urinalysis - local or investigator-designated laboratory

Blood	Protein
Glucose	Specific gravity
Ketones	Urine leukocyte esterase
pH	

Pregnancy Test (for female patients of childbearing potential) – local or investigator-designated laboratory

Serum pregnancy test or
Urine pregnancy test

Abbreviations: CRF = case report form; RBC = red blood cells; WBC = white blood cells.

[a] Treatment decisions will be based on local laboratory results.

[b] Neutrophils reported by automated differential hematology instruments include both segmented and band forms. When a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

Appendix 4. Sampling Schedule for Pharmacokinetics

Pharmacokinetic samples will be collected for LY2606368 in Cohorts 1 and 2 of this study. It is essential that the exact infusion start and stop times are recorded using actual clock readings, as well as infusion parameters (such as, total dose infused and if intended dose was administered). The exact time of collection of each venous blood sample will be based on the clock used to record infusion times. The PK blood samples should not be withdrawn from the same IV site as the drug infusion.

Predose samples should be taken as close as possible to the start of first infusion (<10 minutes), and the exact clock reading should be recorded. Postdose (that is, end of infusion) PK samples should be drawn immediately after end of infusion (range = after end of infusion +10 minutes), and exact clock reading should be recorded.

PK Sampling Schedule – Cohorts 1 and 2

Sample Series	Cycle	Day	LY2606368 PK Sampling Times[a]
1	1	1	Prior to start of LY2606368 infusion (<10 min)
2	1	1	End of LY2606368 infusion (+10 min)[b]
3	1	8	Anytime[b]
4	2	1	Prior to start of LY2606368 infusion (<10 min)
5	3	1	Prior to start of LY2606368 infusion (<10 min)
6	3	1	End of LY2606368 infusion (+10 min)[b]
7	3	8	Anytime[b]
8	4	1	Prior to start of LY2606368 infusion (<10 min)
9	5	1	Prior to start of LY2606368 infusion (<10 min)
10	5	1	End of LY2606368 infusion (+10 min)[b]
11	5	8	Anytime[b]
12	6	1	Prior to start of LY2606368 infusion (<10 min)
13	7	1	Prior to start of LY2606368 infusion (<10 min)
14	7	1	End of LY2606368 infusion (+10 min)[b]

Abbreviations: min = minute; PK = pharmacokinetic.

[a] The sampling schedule is relative to the LY2606368 infusion times as noted in the table. The actual timing of the samples may be adjusted at the discretion of Lilly and the investigators as pharmacokinetic data become available. The total number or volume of samples will either remain the same or be reduced.

[b] PK samples that are collected after the start of the infusion will need to be drawn from a clean site, unless an adequately flushed vascular access catheter is the only option.

Appendix 5. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin (HGB)	
Hematocrit (HCT)	**Hepatic Coagulation[a]**
Erythrocytes (RBC)	Prothrombin time (PT)
Leukocytes (WBC)	Prothrombin time, INR
Neutrophils[b]	
Lymphocytes	**Hepatic Serologies[a,c]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets (PLT)	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
Alanine aminotransferase (ALT)	**Recommended Autoimmune Serology:**
Aspartate aminotransferase (AST)	Anti-nuclear antibody[a]
Gamma-glutamyl transferase (GGT)	Anti-smooth muscle antibody[a]
Creatine phosphokinase (CPK)	Anti actin antibody[a]

Abbreviations: CRF = case report form; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated laboratory.

[b] Neutrophils reported by automated differential hematology instruments include both segmented and band forms. Whenever a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

[c] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Appendix 6. Creatinine Clearance Formula

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation (2009)

The CKD-EPI creatinine equation is based on the same 4 variables as the Modification of Diet in Renal Disease (MDRD) Study equation, but uses a 2-slope spline to model the relationship between estimated glomerular filtration rate (GFR) and serum creatinine, and a different relationship for age, sex, and race. The equation was reported to perform better and with less bias than the MDRD Study equation, especially in patients with higher GFR. This results in reduced misclassification of CKD. As of November 2009, very few clinical laboratories report the estimated GFR using the CKD-EPI creatinine equation. In the future, other GFR-estimating equations may outperform CKD-EPI.

The CKD-EPI creatinine equation is:

$$GFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018[\text{if female}] \times 1.159[\text{if black}]$$

$\kappa = 0.7$ if female
$\kappa = 0.9$ if male

$\alpha = -0.329$ if female
$\alpha = -0.411$ if male

min = The minimum of Scr/κ or 1
max = The maximum of Scr/κ or 1

Scr = serum creatinine (mg/dL)

Source: Levey et al. 2009.

Appendix 7. Protocol Amendment I4D-MC-JTJH(a) Summary
A Phase 2 Study of LY2606368 in Patients with Extensive Stage Disease Small Cell Lung Cancer

Overview

Protocol I4D-MC-JTJH, A Phase 2 Study of LY2606368 in Patients with Extensive Stage Disease Small Cell Lung Cancer, has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

This amendment was developed to address requests resulting from member states participating in the Voluntary Harmonisation Procedure during the assessment of the initial clinical trial application for Study JTJH in the European Union. The request resulted in the following changes:

- Inclusion criterion #8 was updated to include a definition for fertile men.
- Inclusion criterion #9 was updated to include a definition of women of childbearing potential and postmenopausal women.
- Exclusion criterion #14 was updated to include known hypersensitivity to LY2606368.
- Exclusion criterion #16 was updated to clarify how patients with HIV or symptomatic activated or reactivated hepatitis A, B, or C would be excluded.
- Text was added to Section 9.4.1 to establish additional actions to be taken in case of prolongation of the QTcF interval >480 msec. Text was also added to provide guidance on patient management if a patient experiences a QTcF interval of >500 sec.

In addition, several other changes were made to the protocol as follows:

- Minor wording changes and clarifications were made to the Schedule of Activities in Section 2.
- A clarification to time to progression was made in Section 3.1.
- Adverse events were corrected for a literature reference in the rationale section.
- The wording for exclusion criterion#11 was clarified.
- A table was added to clarify the parameters required to start each cycle.
- Section 7.5.2 was modified to remove the stability information in the lactate monohydrate formulation.
- Section 7.8.1 was modified to remove the provision that patients must sign new ICFs to enter the continued access period.
- A clarification to the radiologic scans required was made in Section 9.1.
- A clarification to the PK analysis was made in Section 9.5

- A clarification to the biomarker collection was made in Section 9.8.
- Section 10.3.4 was modified to remove the final analysis from the stopping rules.
- Minor editing and formatting changes were made.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

Table JTJH.2.1. Schedule of Screening Activities

	Study Period	Baseline			
	Cycle	BL			
	Visit	0			
	Duration	Up to 28 days			
	Relative Day	≤28	≤14	≤7	
Procedure Category	**Procedure**				**Comments**
Study Entry/Enrollment	Informed Consent Form signed (prior to conducting any protocol specific tests/procedures)	X			
	Inclusion/Exclusion evaluation		X		
Medical History	Initial history/preexisting conditions		X		
	Historical illness		X		
	Habits assessment		X		Includes smoking history
Physical Examination	Physical examination		X		Includes height and weight
	ECOG performance status		X		
	Vital signs		X		
Tumor Assessment	Radiologic imaging according to RECIST 1.1	X			Baseline radiological tumor assessment per RECIST version 1.1 should be done (see Section 9.1). ~~during screening.~~ Radiologic assessments obtained previously as part of routine clinical care may be used as the baseline assessment provided that they were done no more than 28 days before the first dose of study drug.
	Tumor measurement (palpable or visible)	X			Performed at the same time as radiologic imaging
Adverse Events Collection/CTCAE Grading		X			
Concomitant Medication Notation		X			
Laboratory/ Diagnostic Tests	Hematology		X		
	Chemistry		X		
	Urinalysis		X		
	Coagulation		X		
	~~Serum or urine p~~Pregnancy test	X		~~X~~	Women of childbearing potential must have negative serum pregnancy tests at their baseline visits and have negative urine pregnancy tests within 7 days before their first doses of LY2606368 (see Section 6.1). ~~As required by local regulations~~
	ECG		X		Single local ECG
	Confirm availability of pretreatment tumor tissue	X			If archived tissue is not available, a fresh tumor biopsy should be obtained after all other study entry criteria have been confirmed, unless the sponsor and investigator document that the patient may be enrolled without pre-treatment tissue.
	Exploratory blood sample for biomarkers			X	
	Optional pretreatment biopsy	X			Optional and may be performed at any time before starting treatment with LY2606368. See Section 9.8.2.
Health Outcome Measure	Lung Cancer Symptom Scale			X	The LCSS should be administered prior to extensive interaction with site personnel.

Table JTJH.2.2. On-Study-Treatment Schedule of Activities

Procedure Category	Procedure	Study Treatment Period: Cycle 1, 14 days, Day 1	Cycle 1, 14 days, Day 8	Cycle 2, 14 days, Day 1	Cycle 2, 14 days, Day 8	Cycle 3-n[a], 14 days, Day 1	Cycle 3-n[a], 14 days, Day 8	Comments
Physical Examination	Physical Exam	X		X		X		Includes weight and calculated BSA. May be completed up to 7 days prior to treatment infusion. In Cycle 4 and beyond may be completed every other cycle (for example, Cycle 4, 6, 8, etc.).
	Vital signs	X		X		X		Includes blood pressure, pulse, and temperature. Complete before treatment infusion.
	ECOG performance status	X		X		X		Complete before treatment infusion
Laboratory/ Diagnostic Tests	Hematology	X	X	X	X	X	X	May be drawn up to 3 days before the planned assessment. In Cycles 4-n, the Day-8 sample may be collected at the discretion of the investigator.
	Chemistry	X		X		X		May be drawn up to 3 days before the planned assessment
	Urinalysis					X		May be collected up to 3 days before the planned assessment
	Urine pregnancy test					X		Day 1 of every other cycle. Only to be performed on women of childbearing potential
	PK sampling	X	X	X		X	X	See PK Schedule for collection information.
	Stored sample for pharmacogenetics	X						Collect once. Sample can be collected at any time if not collected on Day 1 of Cycle 1.
	Exploratory blood sample for biomarkers					X		Only to be collected on the same day when the CT scan is obtained (every 3 cycles starting with Cycle 3).
	Plasma biomarker sample	X				X		Collect prior to dosing on Day 1 of Cycles 1 and 3 only
	ECG	X		X		X		Single local ECG collected at each time point. Day 1: predose, 10 min after EOI (±5 min), 30 min after EOI (±10 min), and >1 hour after EOI. Cycle 2-X: predose. However, if QTcF >480 msec is observed on Day 1, then 10 min after EOI (±5 min), 30 min after EOI (±10 min), and >1 hour after EOI should also be collected in subsequent cycles.
	Optional Tumor Biopsy	X						Can occur at any time during patient's treatment.

Study Period		Study Treatment Period						
Cycle/Visit		1		2		3-n[a]		
Duration		14 days		14 days		14 days		
Relative Day within Dosing Cycle		1	8	1	8	1	8	
Tumor Assessment	Radiologic imaging according to RECIST 1.1						X	For the first 52 weeks following enrollment, perform approximately every 6 weeks ~~(that is, every 3 cycles)~~ starting at the end of Cycle 3 (eg, Days 8-14). Thereafter, perform approximately every 12 weeks. The scanning interval (6 or 12 weeks [±1 week]) should be maintained even if cycles are delayed. As a result, after Cycle 3, the scans may not always occur at the end of a cycle. The same method of imaging used at baseline should be used for each subsequent assessment. Scans should also be obtained as clinically indicated.
Tumor Assessment	Tumor measurement (palpable or visible)						X	Perform at least every 6 weeks ~~(that is, every 3 cycles)~~ starting in Cycle 3 on the same day as the radiologic imaging.
Adverse Events Collection/ CTCAE Grading		X		X		X		
Concomitant Medication Notation		X		X		X		
Lung Cancer Symptom Scale		X		X		X		The LCSS is to be administered prior to extensive interaction with site personnel and prior to administration of study drug.
Study Treatment	LY2606368	X		X		X		IV over approximately 60 (+10) min

Table JTJH.2.3. Post-Treatment Follow-Up Schedule of Activities

	Study Period	Post-discontinuation Follow-Up		
		Short-term Follow-Up	Long-term Follow-Up	
	Duration	30 ± 5 days	60 ± 14 days	
	Visit	801	802-X	
	Relative day within a cycle	Period begins the day after stopping of study treatment and lasts approximately 30 days	Period begins 1 day after short-term follow-up period is completed and continues until death, study withdrawal, or the patient is lost to follow-up	
Procedure Category	**Procedure**			**Comments**
Physical Examination	Physical examination (including weight)	X		
	Vital signs	X		Includes blood pressure, pulse, and temperature
	ECOG performance status	X		
Tumor Assessment	Radiologic imaging according to RECIST 1.1	X		The same method of imaging (CT scan, spiral CT, etc.) used at baseline should be used for each subsequent assessment. Not required if progressive disease is documented while on treatment or if there are clear signs of clinical progression.
	Tumor measurement (palpable or visible)	X		Performed at the same time as radiologic imaging
Adverse Events Collection/CTCAE Grading		X	X	After Visit 801, only study treatment-related serious events are reported.
Concomitant Medication Notation		X		
Lab/Diagnostic Tests	Hematology	X		
	Chemistry	X		
	ECG	X		
	Exploratory blood sample for biomarkers	X		
	Plasma biomarker sample	X		
	Optional posttreatment biopsy	X		~~The optional post-treatment biopsy must be taken prior to the patient starting a new treatment for their cancer.~~ See Section 9.8.2
Health Outcome Measure	Lung Cancer Symptom Scale	X		The LCSS will need to be administered prior to extensive interaction with site personnel.
Follow-Up	Survival Assessment		X	Approximately every 60 (±14) days (telephone assessment is acceptable)

Section 3.1 Study Rationale

…

SCLC is highly sensitive to chemotherapy, with combination chemotherapy remaining the focus of treatment for patients with ED-SCLC. About 60% to 80% of patients with extensive stage disease respond to combination chemotherapy (Hann and Rudin 2008). Cisplatin or carboplatin in combination with etoposide are commonly used regimens in the first-line treatment of SCLC. After an initial response, however, nearly all patients with extensive disease will relapse and the majority of patients will eventually die from their disease (Sundstrom et al. 2002). Platinum-refractory disease shows progression during therapy or within ~~≤~~≤90 days of the last dose of platinum. Platinum-sensitive disease shows progression ~~≥~~≥90 days after the last dose of platinum. Patients with platinum-sensitive disease have a higher likelihood of response to second-line treatment. Their response rate is approximately 20% to 25% (Fruh et al. 2013; Kalemkerian et al. 2013). In contrast, patients with platinum-refractory disease have a ≤10% chance of response to a second-line treatment (Kalemkerian et al. 2013). If left untreated, a relapsed patient will typically live 2 months to 4 months (Wakuda et al. 2015).

Several other agents have been shown to have activity in SCLC, and many studies have compared 3-drug regimens to the standard 2-drug regimens with no improvement in efficacy. Topotecan is approved for patients that have ED-SCLC that have failed or relapsed after first line chemotherapy (Demedts et al. 2010). Patients receiving topotecan (1.5 mg/m^2 daily for 5 days every 21 days) had an overall response rate of 24.3% (von Pawel et al. 1999). The median time to progression was 13.3 weeks and median survival was 25.0 weeks (von Pawel et al. 1999). ~~Grade 4 neutropenia occurred in 37.8% of patients, while Grade 4 thrombocytopenia occurred in 9.8% of patients~~ Adverse events (AEs) associated with this treatment included Grade 4 neutropenia (70.2%), Grade 3/4 anaemia (42.3%), Grade 4 thrombocytopenia (28.8%), and documented infection within 2 days of Grade 4 neutropenia (28%) (von Pawel et al. 1999). Other agents, including paclitaxel, irinotecan, vinorelbine, and gemcitabine, have been tested in the second-line setting in an effort to improve on the efficacy and tolerability of topotecan. Despite the modest benefit of topotecan, they have not increased efficacy over topotecan (Chan and Coward 2013), demonstrating the clear need for new agents to improve outcomes for patients with ED-SCLC.

…

3.4. Rationale for JTJH Amendment (a)

Amendment (a) was developed to address requests resulting from member states participating in the Voluntary Harmonisation Procedure during the assessment of the initial clinical trial application for Study JTJH in the European Union. At the member states' request, the protocol was modified to incorporate those states' recommendations in the inclusion and exclusion criteria and to establish the actions to be taken in case of prolongation of the QT/QTc interval >480 msec. Because a protocol amendment was required, the opportunity was taken to also include several other minor protocol improvements and clarifications.

6.1 Inclusion Criteria

…

[8] men must be sterile or agree to use an effective method of contraception or a highly effective method of contraception during the study and for at least 12 weeks following the last dose of LY2606368

Refer to Appendix 1 for definitions of fertile men, effective method of contraception, and highly effective method of contraception.

[9] women of childbearing potential must:

a. have a negative serum pregnancy test at the baseline visit
b. have a negative urine pregnancy test within 7 days prior to the first dose of LY2606368
c. agree to use a highly effective method of contraception (Appendix 1) during the study and for 12 weeks following the last dose of LY2606368
d. not be breast-feeding

Refer to Appendix 1 for definitions of women of childbearing potential and postmenopausal women.

6.2 Exclusion Criteria

…

[11] have symptomatic central nervous system (CNS) malignancy or metastasis. Asymptomatic ~~P~~patients with treated CNS metastases are eligible for this study if they are not currently receiving corticosteroids to treat CNS metastases. ~~and/or anticonvulsants.~~ CNS metastases should be stable for at least 14 days by clinical assessment, and patients should not have received corticosteroids to treat CNS metastases within 14 days of the first dose of study drug.

…

[14] have previously completed or withdrawn from this study or any other study investigating LY2606368 or a CHK1 inhibitor or have shown hypersensitivity to any of the components of the LY2606368 formulation

…

[16] have a symptomatic human immunodeficiency virus (HIV) infection or symptomatic activated/reactivated hepatitis A, B, or C (screening is not required). If the medical history, symptoms, and/or laboratory values suggest that the patient may have HIV or hepatitis A, B, or C, appropriate assessment should be conducted to determine whether the patient should be excluded.

7.4 Dosage Modification

Before the start of each cycle:

- Nonhematologic toxicities must resolve to Grade 0 or 1 or baseline, except AEs with no immediate medical consequence or those that can be controlled with adequate treatment (for example, alopecia, fatigue, nausea, vomiting, diarrhea, or asymptomatic changes in electrolytes).
- Neutropenia, thrombocytopenia, and anemia must resolve to Grade 0, 1, or 2, as shown in Table JTJH.7.2.

Table JTJH.7.2. Hematologic Parameters Required for the Start of Each Cycle

	Dose
Neutrophils	≥1000/mm^3
Platelets	≥75/mm^3
Hemoglobin	≥8 g/dL

Treatment may be delayed for a maximum of 14 days to allow a patient sufficient time for recovery from LY2606368-related toxicity. If a patient does not recover from the toxicity within 28 days from the time of last treatment, the patient should be discontinued from LY2606368. In exceptional circumstances, a longer delay is permitted upon agreement between the investigator and the Lilly clinical research physician (CRP).

If a patient, in the investigator's opinion, experiences a toxicity warranting a dose reduction, LY2606368 should be reduced as shown in Table JTJH.7.3.~~2.~~

Table JTJH.7.~~2~~.3. LY2606368 Dose Reductions

Reduction	**Dose**
1st LY2606368 dose reduction	80 mg/m^2
2nd LY2606368 dose reduction	60 mg/m^2
3rd LY2606368 dose reduction	Discontinue from LY2606368

7.5.2. LY2606368 Lactate Monohydrate

A 67-mg strength of LY2606368 lactate monohydrate drug product is in development and may be used in Study JTJH. The vial will contain a slight excess to facilitate the withdrawal of the label amount 67 mg/vial for use with an appropriate device, such as an infusion set. ~~The drug product is stable when stored at room temperature.~~ Reconstituting the vial contents with water for injection yields a clear yellow solution with a concentration of 3.35 mg/mL of LY2606368. For the most current detailed information on this strength refer to the IB and Pharmacy Binder.

7.8.1 Continued Access

Patients who are still on LY2606368 at the time of study completion may continue to receive LY2606368 if they are experiencing clinical benefit and no undue risks. The continued access period will apply to this study only if at least 1 patient is still on LY2606368 when study completion occurs. Lilly will notify investigators when the continued access period begins. Lilly may allow patients to enroll in a LY2606368 "rollover" protocol to provide long-term continued access for patients enrolled in this study. ~~Patients must sign a new ICF before continued access is provided.~~ The continued access period is shown in Figure JTJH.7.1.

9.1 Efficacy Assessments

Tumor assessments will be performed for each patient at the times shown in the Schedule of Activities (Section 2).

Computed tomography (CT) scans, including spiral CT, are the preferred methods of measurement (CT scan thickness recommended to be ≤5 mm); however, magnetic resonance imaging (MRI) is also acceptable in certain situations, such as when body scans are indicated or if there is a concern about radiation exposure associated with CT. Intravenous and oral contrast is required unless medically contraindicated.

The CT portion of a positron emission tomography (PET)-CT scan may be used as a method of response assessment if the CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast). A PET scan alone or as part of a PET-CT may be performed for additional analyses but cannot be used to assess response according to RECIST v.1.1 (Eisenhauer et al. 2009).

Radiologic scans of the thorax and abdomen are required. A baseline intracranial evaluation with CT or MRI should be conducted. Scans of the pelvis or bone scans should be performed if clinically indicated. Copies of the scans may be requested by the sponsor for central review.

See Section 10.3.1 for definitions of the efficacy endpoints.

9.4.1 Other Safety Measures

For each patient, safety assessments, including ECGs, vital signs, and laboratory tests, should be collected as shown in the Schedule of Activities (Section 2). ECGs should be recorded according to the study-specific recommendations that will be provided separately.

As of 27 August 2015, no patients treated with LY2606368 monotherapy have had an average QTcF interval >480 msec at any time point. However, if a patient experiences a QTcF interval >480 msec, the patient should be monitored for signs of life-threatening arrhythmias such as torsades de pointes. It should be confirmed that the measurement is correct by repeating the ECG and ruling out other causes such as atrial fibrillation or the presence of a pacemaker. If the result is confirmed, institutional guidelines or standard of care measures for management of QTcF interval >480 msec and/or associated arrhythmias should be initiated. These actions may include the administration of IV magnesium sulfate and the assessment of clinical chemistry. If electrolytes are abnormal, they should be repeated as indicated. The QTcF value should be

monitored until the interval has returned to <480 msec or at least to predose levels. It is recommended that the patient be assessed by a cardiologist before leaving the treating facility. For all subsequent doses, an ECG must be obtained at 10 minutes after the end of infusion (EOI) (±5 minutes), 30 minutes after EOI (±10 minutes), and >1 hour after EOI.

If a patient experiences a QTcF interval >500 msec and has an associated life-threatening arrhythmia, he/she should be discontinued from study treatment. If a patient experiences a QTcF interval >500 msec without an associated life-threatening arrhythmia and if the investigator deems it in the best interest of the patient, the patient may continue treatment with LY2606368. If a patient has a second occurrence of QTcF interval >500 msec, he/she should be discontinued from study treatment.

Any clinically significant findings that result in a diagnosis and that occur after the patient receives the first dose of LY2606368 should be reported to Lilly or its designee as an AE via CRF/electronic data entry/designated data transmission methods.

9.5 Pharmacokinetics

…

These samples will be analyzed at a laboratory designated by the sponsor by using a validated liquid chromatography–mass spectrometry/mass spectrometry (LC-MS/MS) method.

…

9.8 Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, mechanism of action, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including DNA, RNA, proteins, lipids, and other cellular elements.

As part of Lilly's ongoing efforts to understand the relationship between cancer, genetics, and response to therapy, this study will analyze biomarkers relevant to the mechanism of action of CHK1, DNA damage response pathways or downstream effects, cell cycle markers, immune function, and cancer pathobiology and/or for related research methods or validation of diagnostic tools or assays.

Samples for biomarker research will be collected as specified in Section 2 where local regulations allow. It is possible that biomarker data for patients in the study have already been generated from samples that were collected and analyzed before the patients' enrollment in this trial. This may include data generated from genetic analyses. If available, these data may be requested from medical records for use in the research described in Sections 9.8.1 and 9.8.2.

Samples for biomarker research will be collected as specified Section 2, where local regulations allow.

10.3.4. Interim Analyses

For each cohort, one interim analysis of futility will be conducted after the 29th patient in the cohort has completed Cycle 3, and, if required, the response is confirmed. The interim analysis will be conducted to assess whether the respective cohort is unlikely to achieve statistical significance on its primary endpoint and may also include PK data in order to confirm that patients are in the expected exposure range.

The stopping rule for interim analysis ~~and final analysis~~ is defined as follows:

…

Appendix 1 Abbreviations and Definitions

fertile men	A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.
women of childbearing potential	A woman is considered of childbearing potential (ie, fertile), after menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy; however, in the absence of 12 months of amenorrhea, a single follicle-stimulating hormone measurement is insufficient.