Summary Table of Study Protocol

Title	Tarlatamab vs. real-world physicians' choice therapies in patients with relapsed or refractory small cell lung cancer after two or more prior lines of treatment: patient-level indirect treatment comparison (ITC) of DeLLphi-301 vs. Flatiron real-world data
Protocol version identifier	Version 1.0
Date of last version of the protocol	02 May 2024
EU Post Authorization Study (PAS) Register No	N/A
Active Substance	N/A
Medicinal Product	N/A
Device	N/A
Product Reference	N/A
Procedure Number	N/A
Joint PASS	No
Research Question and Objectives	To estimate the relative effect of tarlatamab vs. comparator therapies among patients with relapsed or refractory small cell lung cancer who have progressed or recurred following one platinum-based regimen and at least one other line of therapy (LOT). Primary objective: - To estimate the relative effect of tarlatamab vs. comparator therapies on overall survival (OS) Secondary objectives: - To estimate the relative effect of tarlatamab vs. comparator therapies on time to treatment discontinuation (TTD) - To estimate the relative effect of tarlatamab vs. comparator therapies on time to next treatment or death (TTNTD) Exploratory objectives: CCI [redacted]

Country of Study	United States
Author	PPD (Amgen Global HEOR) PPD (Amgen Global HEOR) PPD (Amgen Global HEOR) PPD (Amgen Global CfOR) PPD (Analysis Group, Inc.) PPD (Analysis Group, Inc.)

Marketing Authorization Holder

Marketing authorization holder(s)	N/A
MAH Contact	N/A

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

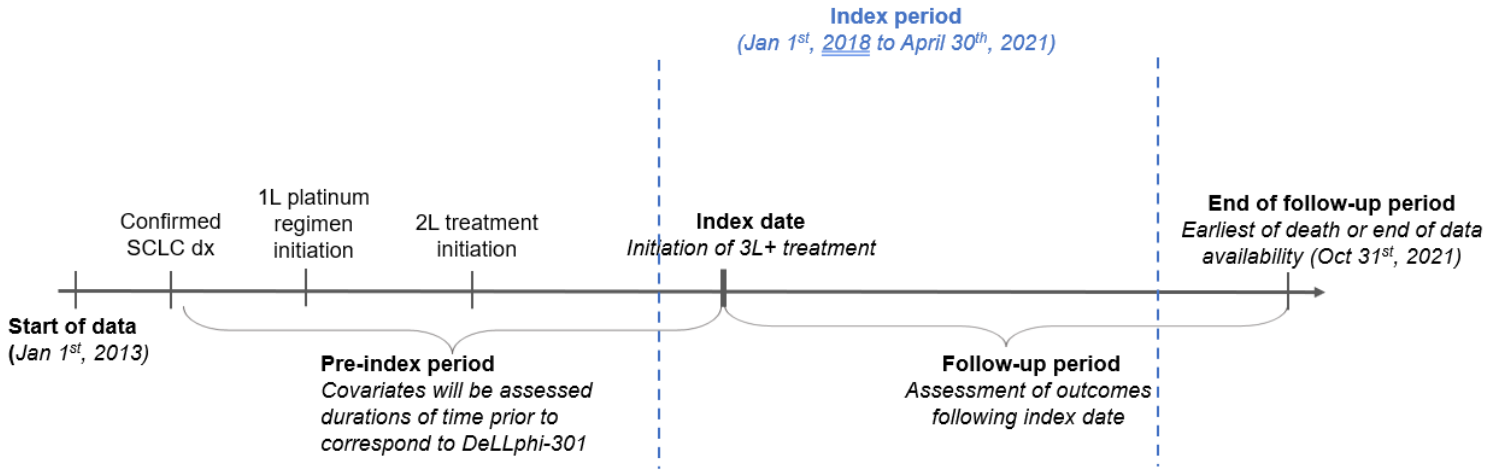
Protocol Version	Date of Protocol	Page Header Date
Original, Version 1.0	23 April 2024	23 April 2024
Original, Version 2.0	02 May 2024	02 May 2024

Confidentiality Notice

Study Design Schema

A patient-level ITC study will be conducted to estimate relative treatment effects of tarlatamab vs. comparator therapies among patients with relapsed or refractory SCLC who have progressed or recurred following one platinum-based regimen and at least one other line of therapy (LOT). Tarlatamab-treated patients will come from the phase 2 DeLLphi-301 trial. A cohort of patients receiving comparator therapies in third line or later (3L+) settings will be constructed by applying key inclusion/exclusion criteria of the Delphi-301 trial to patients with SCLC identified in the Flatiron Health Research Database. Efficacy outcomes will be compared between the tarlatamab and comparator therapies adjusting for baseline differences in the distributions of key prognostic factors between these two cohorts.

Figure 1. Study Design Schema for Flatiron database



1. Table of Contents

CCI

[redacted]

CCI

[redacted]


CCI

2. List of Abbreviations

Abbreviation	Definition
1L	First-line
2L	Second-line
3L	Third-line
3L+	Third line and beyond
BiTE	Bispecific T-cell engager
CFI	Chemotherapy-free interval
CI	Confidence interval
CNS	Central nervous system
CCI	
ECOG	Eastern Cooperative Oncology Group
ED	Extensive disease
EHR	Electronic health record
FDA	Food and Drug Administration
HTA	Health Technology Assessment
LOT	Line of therapy
ICD-9	International Classification of Diseases version 9
ICD-10	International Classification of Diseases version 10
ITC	Indirect treatment comparison
NCCN	National Comprehensive Cancer Network
NSCLC	Non-small cell lung cancer
SCLC	Small cell lung cancer
CCI	
OS	Overall survival
CCI	
PPV	Positive predictive value
CCI	
RECIST	Response Evaluation Criteria in Solid Tumors
TTD	Time to treatment discontinuation
TTNTD	Time to next treatment or death
US	United States

3. Responsible Parties

Party	Roles and Responsibilities
Amgen	Sponsor; participating in study design, analyzing data, and interpretation of results
Analysis Group	Vendor; participating in study design, analyzing data, and interpretation of results

4. Abstract

Study Title:

Tarlatamab vs. comparator therapies in patients with relapsed or refractory small cell lung cancer (SCLC) after two or more prior lines of treatment: patient-level indirect treatment comparison (ITC) of DeLLphi-301 vs. Flatiron real-world data

Study Background and Rationale:

Evaluation of the comparative effectiveness of tarlatamab vs. comparator therapies is required for upcoming health technology assessment (HTA) and payer submissions seeking reimbursement of tarlatamab in 3L+ settings for small-cell lung cancer (SCLC). DeLLphi-301, a phase 2 open-label study is currently the only clinical trial of tarlatamab in the 3L+ setting. As the DeLLphi-301 trial does not have a concurrent comparator arm, an external control arm is required for assessment of comparative effectiveness.

External control arms can come from previous clinical trials or real-world data. In the absence of relevant clinical trials of comparator treatments in the 3L+ setting for SCLC, an external control arm from a suitable real-world data source is needed. The Flatiron Health Research Database (hereafter referred to as Flatiron data) was deemed a suitable data source for construction of an external control arm for tarlatamab because of its high-quality clinical data, sufficient sample size and reflection of a contemporaneous SCLC patient population (see more details in section 6.3).

In this study, we will compare tarlatamab versus comparator therapies in 3L+ settings using patient-level data from DeLLphi-301 and Flatiron datasets. While rigorous methods based on aggregate data from Flatiron and other real-world sources of external controls have been used in previous ITC studies (study number: 20230204), analyses based entirely on patient-level data are recommended when feasible. Use of patient-level data offers several important advantages in this study, including: 1) applying key trial inclusion/exclusion criteria to select an external control arm that more closely matches the DeLLphi-301 trial population, 2) more comprehensively adjusting for differences in prognostic factors between tarlatamab and external control arms, and 3) conducting additional analyses to pressure test the conclusions of the previously conducted ITCs.

Therefore, the patient-level comparative study proposed here is critical to comprehensively address evidence needs for HTA submissions in this 3L+ setting.

Study Feasibility and Futility Considerations:

Feasibility considerations

The feasibility of conducting a patient-level ITC of tarlatamab versus comparator therapies using Flatiron data was assessed by reviewing DeLLphi-301 trial documentation and baseline characteristics, and the protocol and report of an Amgen retrospective cohort study using Flatiron data (study number: 20190488).

The data sourced from Flatiron that will be used here reflects a contemporaneous cohort of SCLC patients and provides a rich, patient-level dataset on demographics, disease characteristics, comorbidities, treatments, and outcomes for patients with SCLC. This extensive data availability allows for application of a broader set of DeLLphi-301 trial inclusion/exclusion criteria to the Flatiron data to create a more closely matched comparator cohort (section 8.2.3) than used in the previous aggregate-level ITC.

A summary of baseline characteristics among patients receiving tarlatamab in 3L+ settings from DeLLphi-301 and common comparators in 3L from the Flatiron natural history cohort (Protocol 20190488) is shown below. This table indicates that there are notable differences yet numerically reasonable overlaps in prognostic factors (e.g., sex, ECOG, brain metastases, platinum sensitivity after 1L treatment between these groups) between DeLLphi-301 and the Flatiron natural history cohorts. Adjustment to balance differences is necessary for subsequent indirect treatment comparisons.

Table 1. Baseline characteristics for tarlatamab and comparator therapies cohorts

Prognostic variables	**Tarlatamab N = 97**	**Comparator therapies (Flatiron study 20190488) N = 326**
Age(years) – mean (SD) at treatment initiation	63.48 (8.7)	66.7 (8.4)
Sex (female %)	26.8%	51.2%
History of smoking (%)	91.8%	96.3%
ECOG PS 0 at initiation of treatment	25.8%	19.9%
ECOG PS 1 at initiation of treatment	74.2%	41.4%
ECOG PS 2, 3+ or missing at initiation of treatment	0%	38.7%
Presence of brain metastases	22.7%	33.7%
Presence of liver metastases at initiation of treatment	38.1%	48.5%

Platinum resistant (CFI <90 days) after 1L treatment	27.3%	20.0%
Platinum sensitive (CFI 90 to <180 days) after 1L treatment	22.2%	33.5%
Platinum sensitive (CFI ≥180 days) after 1L treatment*	50.5%	46.5%
Disease stage – ES at initial diagnosis*	78.3%	67.5%
Time from diagnosis to start of line of treatment, days – mean (SD)	590.5 (304.4)	483.8 (293.7)

Note: *Includes missing data imputed to this category for Tarlatamab patients

Key clinical outcomes of interest (OS, CCI in the Flatiron data are available and have been well-validated in SCLC patients. Although some differences in outcome assessment exist given the trial setting of DeLLphi-301 versus the real-world care setting of Flatiron, comparisons of tarlatamab versus a comparator cohort of other therapies is feasible.

Finally, Flatiron data has been used as part of the evidence package in previous HTA submissions in lung cancer, which indicates its acceptability for this purpose.[1]

Futility considerations

The study will be stopped for futility if either of these criteria are met:

- **There remains inadequate balance between the tarlatamab and comparator therapy groups on the highest priority confounders (defined in section 8.3.3) after propensity score weighting:** As described below, standardized mean differences (SMD) will be reported to assess balance on confounding variables after propensity score weighting. The study will be stopped if SMD after weighting are greater than |0.25| for any of the following confounders: ECOG PS, age, disease stage, and number of previous lines of therapy
- **The effective sample size after propensity score weighting in the Flatiron comparator therapy cohort is less than 75 patients (see section 8.5 for detailed sample size and power estimation).**

Research Question and Objectives:

Objectives	Endpoints
Primary	
• To estimate the relative effect of tarlatamab vs. comparator therapies on overall survival (OS)	• OS

Secondary	
• To estimate the relative effect of tarlatamab vs. comparator therapies on time to treatment discontinuation (TTD)	• TTD
• To estimate the relative effect of tarlatamab vs. comparator therapies on time to next treatment or death (TTNTD)	• TTNTD
Exploratory	
CCI [redacted]	

Null hypothesis:

Null and alternative hypotheses for the primary outcome of OS are provide below.

Null hypothesis: There is no difference in overall survival between the tarlatamab and comparator therapy cohorts (HR=1).

Alternative hypothesis: There is a difference in overall survival between the tarlatamab and comparator therapy cohorts (HR≠1)

Study Design:

A patient-level ITC will be conducted to estimate relative treatment effects of tarlatamab vs. comparator therapies among patients with relapsed or refractory SCLC who have progressed or recurred following one platinum-based regimen and at least one other LOT. Key patient eligibility criteria from the DeLLphi-301 trial will be applied to Flatiron data to create an external control arm of patients receiving comparator therapies in the 3L+ setting for SCLC. Efficacy outcomes will be compared between the tarlatamab and comparator therapies cohorts utilizing a propensity score (PS) weighting approach to adjust for differences in the distributions of key prognostic factors between these two cohorts.

- **Study Population or Data Resource**

The target population for estimating relative effects of tarlatamab vs. comparator therapies are patients with relapsed or refractory SCLC who have progressed or recurred following one platinum-based regimen and at least one other LOT.

The study will use data from patients who received tarlatamab at a target dose of 10 mg in Parts 1 and 2 of the DeLLphi-301 trial and data from patients (meeting key DeLLphi-

301 eligibility criteria) in the Flatiron database who received comparator therapies for SCLC in 3L+ settings.

Eligibility Criteria

Key inclusion and exclusion criteria from DeLLphi-301 are described below, along with the operationalizations of these criteria in the Flatiron data that will be used to select the external control arm.

Inclusion criteria

DeLLphi-301 trial	**Flatiron**
○ Initiated tarlatamab 10 mg	○ Initiated comparator therapies (any systematic therapies used in the 3L+ settings, including: cyclophosphamide/doxorubicin/vincristine (CAV), topotecan, irinotecan, lurbinectedin, platinum-based regimens with or without immunotherapy, immunotherapy only regimens, taxanes (paclitaxel and docetaxel), and others)
○ Male or female 18 years of age or older at screening	○ Male or female 18 years of age or older at initiation of 3L+ treatment *(index date)*
○ Histologically or cytologically confirmed SCLC	○ Diagnosis of lung cancer (ICD-9 162.x or ICD-10 C34x, or C39.9) ○ Pathology consistent with SCLC (i.e., based on biopsy findings and/or that the provider explicitly documents a SCLC diagnosis.); not diagnosed with NSCLC on or before the time a patient was first extracted for the SCLC cohort
○ Relapsed or refractory SCLC; progressed or recurred following 1 platinum-based regimen and at least 1 other prior LOT prior to tarlatamab initiation (i.e., patients are 3L or later at tarlatamab initiation)	○ Evidence of treatment with a platinum-based regimen as front-line systemic (non-maintenance) therapy for SCLC, and at least 1 immediate subsequent (non-maintenance) line of therapy for SCLC after 1L treatment; ○ Initiated a 3L+ systemic treatment

	○ No gap of greater than ≥90 days from initial SCLC diagnosis date to the start of structured data activity after diagnosis
○ Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 at screening	○ ECOG PS of 0 or 1 within a window of 28 days before or 7 days after initiation of 3L+ treatment
○ No brain metastases at screening, or ○ Treated brain metastases, if definitive therapy was completed at least 2 weeks prior to first dose of tarlatamab, no evidence of CNS progression or only psuedoprogression at time of screening, and asymptomatic	○ No brain metastases prior to initiation of 3L+ therapy, or ○ Evidence of treatment for brain or CNS metastases that was completed at least 2 weeks prior to initiation of 3L+ therapy ○ Patients with brain metastases and initiated 3L treatment. Initiating 3L treatment is served as an evidence that active management was in place or a justification for not actively treating brain metastases was made prior to initiating anti-cancer treatment.
○ Adequate organ function, defined based on laboratory/test values for markers of hematological, coagulation, renal, hepatic, pulmonary and cardiac function	○ Proxied by patients initiating 3L+ treatment, given that adequate organ function is required before initiating any anti-cancer therapies in clinical practice

Exclusion criteria

DeLLphi-301 trial	**Flatiron**
○ Untreated or symptomatic central nervous system (CNS) metastases or leptomeningeal disease	○ Untreated brain or CNS metastases as proxied by no record of treatment for brain metastases nor initiating 3L+ SCLC treatment
○ Evidence of interstitial lung disease or active, non-infectious pneumonitis	○ Evidence of pneumonitis
○ History of other malignancies within the past 2 years (with exceptions)	○ Evidence of other malignancies prior to 3L+ treatment initiation
○ History of myocardial infarction (MI), symptomatic congestive heart failure	○ History of MI, CHF, or arterial thrombosis within 12 months of 3L+ treatment initiation

(CHF), or arterial thrombosis within 12 months of first dose of tarlatamab	
○ Evidence of hepatitis B	○ This criterion will not be applied to the Flatiron cohort based on clinical input
○ Evidence of hepatitis C	○ This criterion will not be applied to the Flatiron cohort based on clinical input
○ Diagnosis of immunodeficiency (e.g., HIV/AIDS) or receiving systemic steroids or immunosuppressive therapy within 7 days prior to first dose of tarlatamab	○ This criterion will not be applied to the Flatiron cohort based on clinical input
○ Prior therapy with tarlatamab	○ Not applicable
○ Prior anti-cancer therapy within 28 days prior to first dose of tarlatamab (except conventional chemotherapy or radiotherapy)	○ Anti-cancer therapies other than chemotherapies within 28 days prior to first dose of physicians' choice of therapy
○ Currently receiving or recently ended treatment in another investigational device or drug study	○ Received any investigative agents as part of a clinical trial during any line of therapy (including 3L+)

- **Index date, baseline period and follow-up**
  - **Index date:** For the tarlatamab cohort, the index date will be date of 3L+ tarlatamab initiation. For the comparator therapies cohort, the index date will be date of 3L+ treatment initiation. Included patients will be those who initiated 3L+ therapy between January 1st 2018 to April 30th 2021 to allow for a potential follow-up of at least 6 months for all patients before the end of data availability of the Flatiron data cut (Oct 31st, 2021). Patients in the comparator cohort may meet inclusion/exclusion criteria at multiple lines of therapy; one index treatment line will be selected for each patient to match with the DeLLPhi-301 population as described in Section 8.7.1.1.
  - **Baseline period:** For the tarlatamab cohort, available patient characteristics are assessed at screening or trial baseline. For the comparator therapies cohort, patient characteristics will be assessed either over the baseline period (3-month period prior to the index date), or the pre-index period (the entirety of the period between SCLC diagnosis and the index date).
  - **Follow-up period:** For the tarlatamab cohort, follow-up for outcomes will be from tarlatamab initiation to the earliest of death, loss of follow-up or data cut-off date.

For the comparator therapies cohort, follow-up for outcomes will be from 3L+ treatment initiation to the earliest of death, loss to follow-up, or data cut-off date.

- **Variables**

  - ***Outcome Variables***

Outcome	Definition
OS	Time from index date to death
CCI	
TTD	Time from index date to treatment discontinuation or death
TTNTD	Time from index date to next treatment or death
CCI	

  - ***Exposure Variable:***

Treatment with tarlatamab versus comparator therapies (tentatively: cyclophosphamide/doxorubicin/vincristine (CAV), topotecan, irinotecan, lurbinectedin, platinum-based regimens with or without immunotherapy, immunotherapy only regimens, taxanes (paclitaxel and docetaxel), and others)

  - ***Other Covariates***

Covariate	Level
Age at index	Continuous
Gender	Male, Female
ECOG at index	1 vs. 0
Chemotherapy-free interval (CFI) after 1L therapy	<= 90 days, 90-180 days, >180 days
Number of previous lines of therapy	Categorical (2, 3, 3+)
Brain metastases at index	Yes vs. no
Liver metastases at index	Yes vs. no
Previous use of PD-L1 or PD-1 inhibitor	Yes vs no
SCLC stage at diagnosis	Extensive vs. limited
Time from SCLC diagnosis to index	Continuous
Race	Categorical
Smoking history prior to index	Ever vs. never smoking

- **Study Sample Size**

Assuming a fixed sample size of 97 patients in the tarlatamab group, and death rates of 44% and 65% in the tarlatamab and comparator therapy groups, this study will have >90% power to detect a hazard ratio of 0.5 for OS when the sample size in the Flatiron comparator therapy group is at least 75 patients. We therefore propose an effective sample size after propensity score weighting of 75 patients as a minimal threshold for conduct of adjusted analyses comparing OS between the tarlatamab and comparator therapy groups.

- **Data Analysis**

  Efficacy outcomes will be compared between the tarlatamab and comparator therapy cohorts utilizing a propensity score (PS) weighting approach to adjust for differences in the distributions of key prognostic factors between these two cohorts.

  OS, CCI TTD, and TTNTD will be compared between tarlatamab and comparator therapy groups before and after weighting, using unweighted and weighted Kaplan-Meier analyses and log rank tests. Hazard ratios will be estimated before and after weighting using unweighted and weighted Cox proportional hazards models, respectively.

CCI