Managed Access Agreement

Sotorasib for previously treated KRAS G12C mutated, locally advanced or metastatic non-small-cell lung cancer [TA781]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund – Data Collection Arrangement

Sotorasib for previously treated KRAS G12C mutated, locally advanced or metastatic non-small-cell lung cancer (TA781)

Company name: Amgen Limited ("Amgen")

Primary source of data collection: CodeBreaK100 ("CB100"), CodeBreaK200 ("CB200"),

Secondary source of data collection: NHS Digital routine population-wide cancer data sets, including Systemic Anti-Cancer Therapy data set

NICE Agreement Manager	Brad Groves, Associate Director, Managed Access
NHSE&I Agreement Manager	Prof Peter Clark, CDF Clinical Lead
NHS Digital Agreement Manager	Martine Bomb, Head of Data Projects
Amgen Agreement Manager	Julia Sus, Head of HE and HTA for UK&I

1 Purpose of data collection arrangement

1.1 The purpose of the agreement is to describe the arrangements and responsibilities for further data collection for sotorasib for previously treated KRAS G12C mutated, locally advanced or metastatic non-small-cell lung cancer (TA781). A positive recommendation within the context of a managed access agreement (MAA) has been decided by the appraisal committee.

2 Commencement and period of agreement

2.1 This data collection arrangement shall take effect on publication of the managed access agreement.

2.2 Estimated dates for data collection, reporting and submission for CDF guidance review are:

End of data collection (primary source)	**CB100** Commitment to submit CSR to MHRA by 30 June 2023 **CB200** Commitment to submit primary analysis CSR to MHRA will be requested for 31 March 2023
Data available for development of company submission	March 2023
Anticipated company submission to NICE for Cancer Drugs Fund review	March 2024

2.3 Amgen anticipates the results from the additional data collected during the Cancer Drugs Fund period will be incorporated into an evidence submission and the updated economic model by March 2024. More than 2 months will be required between data availability and evidence submission due to requirement of extensive updates to the existing analyses and update to an economic model with the new clinical trial data.

2.4 Amgen acknowledges its responsibility to adhere as closely as possible to the timelines presented in this document.

2.5 NICE will, as far as is practicable, schedule a Cancer Drugs Fund review into the technology appraisal work programme to align with the estimated dates for the end of data collection. The review will use the process and methods in place at the time the invitation to participate in the guidance review is issued, which will be no earlier than 4 weeks prior to the anticipated company submission date. For further details of the expected timelines for the Cancer Drugs Fund guidance review see 6.27 of the technology appraisal process guide.

2.6 As part of the managed access agreement, the technology will continue to be available through the Cancer Drugs Fund after the end of data collection and while the guidance is being reviewed. This assumes that the data collection period ends as planned and the review of guidance follows the Cancer Drugs Fund guidance review timelines described in NICE's guide to the processes of technology appraisal.

2.7 The company is responsible for paying all associated charges for a Cancer Drugs Fund review. Further information is available on the NICE website.

2.8 The company must inform NICE and NHS England and NHS Improvement (NHSE&I) in writing of any anticipated changes to the estimated dates for data collection at the earliest opportunity.

2.9 Any changes to the terms or duration of any part of the data collection arrangement must be approved by NICE and NHSE&I.

2.10 If data collection is anticipated to conclude earlier than the estimated dates for data collection, for example due to earlier than anticipated reporting of an ongoing clinical trial, the company should note:

- Where capacity allows, NICE will explore options to reschedule the Cancer Drugs Fund guidance review date to align with the earlier reporting timelines.
- It may be necessary to amend the content of the final SACT or real-world data report (for example if planned outputs will no longer provide meaningful data).

2.11 If data collection is anticipated to conclude later than the estimated dates for data collection, the company should note:

- The company must submit a written request to NICE and NHSE&I, with details of the extension requested, including an explanation of the factors contributing to the request.
- It may be necessary for the company to mitigate the impact of any delay and reduce any risks of further delays.
- In the event of an extension, it may not be possible to amend the date of the final SACT or real-world data report, although NICE will explore options with NHS Digital to provide data over the extended period.

2.12 Amgen acknowledges its responsibility to provide an evidence submission for this technology to NICE under all circumstances following a period of managed access.

2.13 In the event that Amgen does not make a submission to NICE for the purpose of updating the guidance, NICE and NHSE&I will require the company agree to submit the clinical evidence collected during the managed access period, and to participate in an engagement meeting convened by NICE with attendance from NHSE&I, patient and professional group stakeholders, with the company presenting the clinical evidence collected during the managed access period and an explanation of the decision to proceed with withdrawal of the guidance.

2.14 NICE and NHSE&I may consider the data collection agreement no longer valid, and withdraw the technology from the Cancer Drugs Fund for the following, non-exhaustive, grounds:

- The primary sources of data are delayed, without reasonable justification.
- The primary sources of data are unlikely to report outcome data that could resolve the uncertainties identified by the technology appraisal committee.
- Amendments are made to the marketing authorisation.

3 Patient eligibility

3.1 Key patient eligibility criteria for the use of sotorasib in the Cancer Drugs Fund include:

- the application for sotorasib is being made by and the first cycle of systemic anti-cancer therapy with sotorasib will be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy

- the patient has locally advanced or metastatic non-small cell lung cancer

- the patient has a histologically or cytologically confirmed diagnosis of non-small cell lung cancer that has been shown to exhibit a KRAS G12C mutation using a validated assay and determined on a tumour tissue biopsy or a plasma specimen (liquid biopsy) or both

- completion of the checklist regarding the status of the patient's lung cancer with respect to other actionable mutations in NSCLC and if present that all commissioned targeted therapies have been fully explored

- the patient has been treated with platinum doublet chemotherapy and/or PD-1/PD-L1 targeted immunotherapy
- the patient has not been previously treated with a drug specifically targeting the KRAS G12C mutation unless the patient has received sotorasib via a company early access scheme and the patient meets all the other treatment criteria on this form
- the patient has an ECOG performance status (PS) score of 0 or 1
- the patient either has no known brain metastases or if the patient does have brain metastases then the patient is symptomatically stable before staring sotorasib
- sotorasib will be used as monotherapy
- the clinician is aware of the side-effects of sotorasib including the risks of developing interstitial lung disease and hepatotoxicity
- the clinician is aware that proton pump inhibitors and H2 receptor antagonists reduce absorption of sotorasib and should not be co-administered with sotorasib but if an acid-reducing agent cannot be avoided, sotorasib should be administered >4hrs before and >10hrs after a local antacid
- the patient will be treated until loss of clinical benefit or excessive toxicity or patient choice to discontinue treatment whichever is the sooner
- a formal medical review as to how sotorasib is being tolerated will be done before the start of the second month of treatment and the next review to determine whether treatment with sotorasib should continue

or not will be scheduled to occur at least by the end of the second month of therapy

- when a treatment break of more than 6 weeks beyond the expected 4-weekly cycle length is needed, I will complete a treatment break approval form to restart treatment, including as appropriate if the patient has had an extended break on account of Covid-19

- sotorasib will be otherwise used as set out in its Summary of Product Characteristics (SPC).

3.2 A company-sponsored Early Access Program was available for sotorasib for 6 months from March 2021 until October 2021. [redacted] patients in total had sotorasib across England, Scotland, Wales and the Channel Islands. Patients that meet the eligibility criteria will transfer over to the managed access agreement, but analyses will not be presented from this population as there are expected to be differences between this population and those who start treatment during managed access. Patients receiving sotorasib who are not eligible to receive CDF-funded treatment may continue without change to the funding arrangements in place for them, until they and their NHS clinician consider it appropriate to stop.

3.3 Sotorasib has been available since September 2021 on a budget-neutral basis to the NHS while NICE completes its ongoing appraisal. These patients will continue into the managed access agreement, and data collected from this population will be included in analyses.

3.4 The estimated patient numbers per year for this technology within the Cancer Drugs Fund are:

As estimated by the company	2022 (year 1) [redacted]

	2023 (year 2) [redacted] 2024 (year 3) [redacted]
As estimated by NICE Resource Impact Assessment team	2022 (year 1) – 523 patients 2023 (year 2) – 669 patients 2024 (year 3) – 695 patients

4 Patient safety

4.1 The company and NHSE&I have the responsibility to monitor the safety profile of the technology and must provide an overview of any new or updated safety concerns to NICE. If any new safety concerns are confirmed, NICE and NHSE&I will take steps, as appropriate, to mitigate the risk including but not limited to updating the eligibility criteria or recommending that the managed access agreement be suspended.

5 Area(s) of clinical uncertainty

5.1 The appraisal committee identified the following key areas of uncertainty during the course of the appraisal process:

1. The use of an unanchored indirect treatment comparison
2. The utility and disutility values used in the economic model
3. The magnitude of any treatment waning
4. Whether the technology meets the end of life (EoL) 3-month extension criterion.

5.2 The committee concluded that further data collection within the Cancer Drugs Fund could resolve these uncertainties. For further details of the committee's discussion see section 3 of the Final Appraisal Document.

6 Sources of data collection

Primary and secondary sources of data collection

Primary source(s)	○ CB100 and CB200
Secondary sources	○ Systemic Anti-Cancer Therapy (SACT) dataset ○ NHSE&I's Blueteq data

Description of sources

6.1 CB100: A Phase 1/2, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 510 Monotherapy in Subjects With Advanced Solid Tumors With *KRAS p.G12C* Mutation and AMG 510 Combination Therapy in Subjects With Advanced NSCLC With *KRAS p.G12C* Mutation

6.2 CB200: A Phase 3 Multicenter, Randomised, Open Label, Active-controlled, Study of AMG 510 Versus Docetaxel for the Treatment of Previously Treated Locally Advanced and Unresectable or Metastatic NSCLC Subjects With Mutated KRAS p.G12C. Study of AMG 510 Versus Docetaxel for the Treatment of Previously Treated Locally Advanced and Unresectable or Metastatic NSCLC Subjects With Mutated KRAS p.G12C

6.3 NHSE&I's Blueteq database captures the Cancer Drugs Fund population. NHSE&I shares Blueteq data with NHS Digital for the Cancer Drugs Fund evaluation purposes. The lawfulness of this processing is covered under article 6(1)e of the United Kingdom General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). NHS Digital, through the National Disease Registration Service, does have statutory authority to process confidential patient information (without prior patient consent)

afforded through the National Disease Registries (NDRS) Directions 2021 issued to it by the Secretary of State for Health and Social Care, and has issued the NDRS Data Provision Notice under section 259 of the Health and Social Care Act 2012 regarding collection of the Blueteq data from NHSE&I.

6.4 The Systemic Anti-Cancer Therapy (SACT) dataset, is a mandated dataset as part of the Health and Social Care Information Standards. NHS Digital is responsible for the collection, collation, quality-assurance and analysis of this dataset.

6.5 NHS Digital will collect data, including via the SACT dataset, alongside the primary source of data collection.

7 Outcome data

Clinical trial

7.1 CodeBreaK100 is an ongoing phase 1/2 study of sotorasib. The phase 2 portion is a multi-centre, nonrandomised, open-label study designed to evaluate efficacy and safety/tolerability of sotorasib as monotherapy in subjects with KRAS p.G12C-mutated advanced solid tumours (NSCLC, colorectal cancer, and other tumours)

7.2 CodeBreak 200 is a Phase 3 Study to Compare AMG 510 With Docetaxel in NSCLC Subjects With KRAS p.G12C Mutation

- To compare the efficacy of AMG 510 versus docetaxel as assessed by progression-free survival (PFS) in previously treated subjects with KRAS p.G12C mutated non-small cell lung cancer (NSCLC)
- To compare the efficacy of AMG 510 versus docetaxel as assessed by: Overall Survival (OS), Objective response rate (ORR)

- To compare patient-reported outcomes (PRO) as assessed by: European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 13 (EORTC QLQ-LC13) and European Organisation for Research and Treatment of Cancer Quality-of-life

- To compare efficacy of AMG 510 versus docetaxel as assessed by: duration of response (DOR), time to response (TTR), and disease control rate (DCR)

The randomised controlled trial will reduce uncertainty in the expected OS and confirm if the end-of-life criteria are met. Data from the phase 3 trial will reduce uncertainty in the indirect treatment comparison by providing head-to-head trial data with the key comparator docetaxel. Quality of Life data from the phase 3 trial will also provide more certainty in the utility values used in the economic model. CB200 will provide additional information about time on treatment which will help to establish treatment waning effect.

Other data, including SACT

7.3 NHS Digital will collect the following outcomes through SACT unless it is determined by the SACT Operational Group that no meaningful data will be captured during the period of data collection:

- Number of patients starting treatment

- Baseline patient characteristics, including gender, age and performance status

- Treatment duration

- Overall survival

7.4 NHSE&I's Blueteq system will collect the following outcomes:

- Number of applications to start treatment
- Baseline patient characteristics, including presence of brain metastases
- Previous treatment with chemotherapy/immunotherapy

8 Data analysis plan

Clinical trials

8.1 CB100 Analysis of efficacy and safety data for regulatory purposes was conducted 01 December 2020, with a further updated analysis conducted 15 March 2021 and published 04 June 2021 and formed the basis of the company submission.

CB200: The primary analysis of PFS will occur when approximately 230 PFS events have been observed. The OS primary analysis will occur when at least 198 OS events (~60% maturity) have been observed, which is expected to be at approximately 3 months after PFS primary analysis. The analysis of ORR will be done at the time when PFS is claimed statistically significant and the last randomised subject has had the opportunity to have at least 12 weeks of follow up. The final analysis will be performed when the last subject has completed long-term follow-up (LTFU).

8.2 In addition to the stratification factors for randomisation, number of prior lines of therapy **in advanced disease** (1 versus 2 versus > 2), race (Asian versus non-Asian), history of CNS involvement (yes versus no), primary and selected secondary endpoints will be examined in the following subgroups to investigate the consistency of treatment effects:

- region (North America and Europe vs rest of world)

- best response on prior therapy primary refractory (progression on first scan), suboptimal response (stable disease), recurrent (initial response with subsequent growth)
- age (< 65 vs 65)
- sex (male or female)
- race (white, black, Asian, other)
- ECOG status (0 vs 1)
- Liver metastasis at baseline (yes or no)
- stage (locally advanced and unresectable versus metastatic)
- smoking history (yes or no)
- histology (squamous or non-squamous)
- presence of specific co-mutation at baseline (yes or no). Specific co-mutations to be specified in SAP.
- brain metastasis at baseline (yes or no)
- bone metastasis at baseline (yes or no)
- PD-L1 protein expression (< 1%, ≥ 1%, and < 50%; ≥ 50%)
- STK11 mutation
- KEAP1 mutation

The final analysis will follow the analysis plan outlined in the trial protocol.

[redacted]

An interim analysis (IA) of PFS for superiority is planned when approximately 70% (160 events) of the total PFS events have been observed from both arms, or when the enrollment is finished and the last randomised subject have had the opportunity to have 6 weeks of follow up, whichever occurs later.

Early efficacy at the proposed PFS interim analysis will be claimed if the observed PFS difference meets the pre-specified statistical significance as well as being considered clinically meaningful.

In December 2021, the data monitoring committee (DMC) reviewed the results from the PFS interim analysis. Based on its review, the DMC recommended that the study continue.

[redacted]

Other data

8.3 At the end of the data collection period NHS Digital will provide a final report for NHSE&I which provide analyses based on NHSE&I's Blueteq data and routinely collected population-wide data, including that

collected via SACT. The necessary controls will be put in place to ensure that patient confidentiality is not put at risk. The report will be shared with the company in advance of the planned review of guidance. Where SACT is a secondary source of data, availability of the final SACT report will be aligned to the availability of data from the primary source. The end of SACT data collection will be 8 months prior to the availability of the final SACT report to allow for NHS trusts to upload SACT data, data cleaning, and report production.

9 Ownership of the data

9.1 For all primary sources of data listed above, Amgen Inc will be the data owner.

9.2 This work uses data that has been provided by patients and collected by the NHS as part of their care and support. The data are collated, maintained and quality assured by the National Disease Registration Service, which is part of NHS Digital. The company will not have access to the NHS Digital patient data, but will receive de-personalised summary data, with appropriate governance controls in place.

9.3 The SACT dataset is a mandated dataset as part of the Health and Social Care Information Standards. All necessary governance arrangements through SACT, and other datasets brought together by NHS Digital, have been established with NHS Trusts and NHSE&I.

9.4 Blueteq's Cancer Drugs Fund system data is owned by NHSE&I. NHSE&I is responsible for implementing Blueteq data collection and generally for the analysis of these data. NHSE&I, however, shares Blueteq data with NHS Digital for Cancer Drugs Fund evaluation purposes. The lawfulness of this processing is covered under article 6(1)e of the United Kingdom General Data Protection Regulations (UK

GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). NHS Digital, through the National Disease Registration Service, does have statutory authority to process confidential patient information (without prior patient consent) afforded through the National Disease Registries (NDRS) Directions 2021 issued to it by the Secretary of State for Health and Social Care. The lawfulness of NHS Digital's processing is covered under article 6(1)(c) of the UK GDPR – processing is necessary for compliance with a legal obligation to which the controller is subject (the NDRS Directions).

10 Publication

10.1 The details/authorship of any proposed publications arising from these studies will be planned with the publication of the final study results.

10.2 NHS Digital will produce a final report which includes analysis of data collected through SACT and from NHSE&I's Blueteq system. This report will be provided to NHSE&I and the company at the end of the managed access period. The final report will form part of NHSE&I's submission to the Cancer Drugs Fund guidance review, and will therefore be publicly available at the conclusion of the guidance review.

10.3 NHS Digital will produce interim reports, which will be shared with NHSE&I, NICE and the company at regular intervals during the data collection period. These reports will be used to determine whether real-world data collection is proceeding as anticipated, and will not form part of the guidance review.

10.4 Publications of any data from the NHS Digital reports is not permitted until after the date of publication of the NICE committee papers (on the

NICE website) following the first NICE guidance review committee meeting.

10.5 The contribution of all relevant individuals must be acknowledged in any publications regarding the data collection or analyses generated from the data collection arrangement. Authors will need to contact the NICE Managed Access Team for the full list of relevant individuals.

11 Data protection

11.1 The terms of clause 7 (data protection) of the managed access agreement, that apply between NHSE&I and Amgen, shall also apply between the parties to this data collection arrangement in relation to the performance of their obligations under this data collection arrangement.

12 Equality considerations

12.1 Do you think there are any equality issues raised in data collection?

☐ Yes ☒ No

Commercial Access Agreement

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The contents of this document have been redacted as they are confidential

- A glossary of terms relating to managed access agreements in the Cancer Drugs Fund is available here.