Cancer Drugs Fund

Managed Access Agreement

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [ID1477]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund – Data Collection Arrangement

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma [ID1477]

Company name: Sanofi

Primary source of data collection: On-going clinical study

Secondary source of data collection: Public Health England routine population-wide cancer data sets, including Systemic Anti-Cancer Therapy data set

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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 isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma (ID1477) (to be updated with TA number after final guidance has been published). 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)	The last patient last visit in the ICARIA-MM trial is planned for [redacted], the final database lock is [redacted].
Data available for development of company submission	The clinical study report (CSR) will be approved on [redacted].
Anticipated company submission to NICE for Cancer Drugs Fund review	A submission to NICE is anticipated in January 2023. This date is based on availability of evidence from ICARIA-MM and SACT.

2.3 Sanofi 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 January 2023. This will allow enough time to incorporate the patient level data into the economic model after the CSR becomes available on [redacted].

2.4 Sanofi acknowledges their responsibility to adhere as closely as possible to the timelines presented in the 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 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 NHS England and NHS Improvement.

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 NHS England and NHS Improvement, 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 Public Health England to provide data over the extended period.

2.12 NICE and NHS England and NHS Improvement 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 isatuximab in the Cancer Drugs Fund include:

- application is being made by and the first cycle of systemic anti-cancer therapy with isatuximab in combination with pomalidomide and dexamethasone will be prescribed by a consultant specialist

specifically trained and accredited in the use of systemic anti-cancer therapy.

- patient has a diagnosis of multiple myeloma.
- patient has received 3 and only 3 prior lines of treatment and that the numbering of a line of treatment is in accordance with the International Myeloma Workshop Consensus recommendations for the uniform reporting of clinical trials (http://doi.org/10.1182/blood-2010-10-299487). A line of therapy is defined as one or more cycles of a planned treatment program. This may consist of one or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner (eg induction chemotherapy/chemotherapies if followed by stem cell transplantation is considered to be 1 line of therapy). A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse or toxicity. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease.
- patient has received prior treatment with at least 2 consecutive cycles of lenalidomide given alone or in combination and has failed treatment with lenalidomide on account of disease progression, refractory disease or intolerance.
- patient has received prior treatment with at least 2 consecutive cycles of a proteasome inhibitor (eg bortezomib or carfilzomib or ixazomib) given alone or in combination and has failed treatment with a proteasome inhibitor on account of disease progression, refractory disease or intolerance.

- patient has responded to at least one previous line of treatment ie the patient does not have primary refractory myeloma.
- patient was refractory to the last line of therapy ie there was progression on or within 60 days of the end of the last line of active anti-myeloma systemic therapy.
- patient either has had no previous therapy with any anti-CD38 antibody (eg daratumumab) or if there has been previous treatment with an anti-CD38 antibody, then the patient has received isatuximab via the EAMS scheme or did not progress whilst still receiving an anti-CD38 therapy other than isatuximab or did not progress within 60 days of the last infusion of an anti-CD38 treatment other than isatuximab.
- patient has not received any prior treatment with pomalidomide either as monotherapy or within combination therapy.
- isatuximab is only to be used in combination with pomalidomide and dexamethasone and not with any other active systemic agents for myeloma.
- isatuximab is to be continued until disease progression or unacceptable toxicity or patient choice to stop treatment.
- patient has an ECOG performance status of 0 or 1 or 2.
- a formal medical review as to how isatuximab in combination with pomalidomide and dexamethasone is being tolerated and whether treatment with isatuximab in combination with pomalidomide and dexamethasone should continue or not will be scheduled to occur at least by the end of the second month of treatment.

- when a treatment break of more than 6 weeks beyond the expected cycle length is needed, a treatment break approval form will be completed to restart treatment, including as appropriate if the patient had an extended break because of COVID 19.

- isatuximab and pomalidomide will otherwise be used as set out in their respective Summary of Product Characteristics (SPCs).

3.2 An Early Access to Medicines Scheme (EAMS) was available for isatuximab. The program opened in December 2019 and closed shortly after marketing authorisation.

3.3 Up until June 2020, [redacted] people with relapsed and refractory multiple myeloma in England had received isatuximab in combination with pomalidomide and dexamethasone under EAMS. Of these [redacted] patients, as of 09 September 2020, [redacted] patients were confirmed as receiving ongoing treatment, [redacted] were off treatment (due to death, progression, did not start treatment or stopped for other reasons) and there are [redacted] patients for whom information on treatment status is pending.

3.4 The key patient eligibility criteria are comparable for those treated within the EAMS scheme and those treated within the Cancer Drugs Fund. Public Health England will explore the feasibility of collecting outcome data for those treated within the EAMS scheme.

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

As estimated by the company	Sanofi accept the estimated number of patients proposed by the NICE resource impact team as shown below.
As estimated by NICE Resource Impact Assessment team	[redacted]

4 Area(s) of clinical uncertainty

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

1. Immaturity of the progression-free and overall survival data,
2. Estimates of time-on-treatment,
3. The proportion of people with disease that progresses on 4th line therapy, and the subsequent treatments used.

4.2 The committee discussed whether further data collection within the Cancer Drugs Fund could resolve these uncertainties. It noted there may not be enough time for meaningful data on subsequent treatments to be collected before ICARIA-MM completes. It also noted that the SACT dataset would collect data on subsequent therapies for people progressing on the technology under appraisal (4th line isatuximab with pomalidomide and dexamethasone), but not for those on other therapies. The committee otherwise concluded that further data collection could resolve these uncertainties. For further details of the committee's discussion see section 3 of the Final Appraisal Document.

5 Sources of data collection

Primary and secondary sources of data collection

Primary source(s)	○ ICARIA-MM trial (NCT02990338)
Secondary sources	○ Systemic Anti-Cancer Therapy (SACT) dataset ○ NHS England and NHS Improvement's Blueteq data

Description of sources

5.1 The ICARIA-MM trial will be the primary source of data collection during the period of managed access. This is a multicenter, multinational, randomized (1:1), open-label, 2-arm, phase III study, which evaluated the efficacy and safety of isatuximab in combination with pomalidomide and low-dose dexamethasone (IsaPd) compared to pomalidomide and low-dose dexamethasone (Pd) in 307 patients with relapsed and refractory multiple myeloma. Treatment was administered in both groups in 28-day cycles until disease progression or unacceptable toxicity.

Table 1 provides a brief description of the trial.

Table 1. Overview of isatuximab pivotal study

Study title	**ICARIA-MM** (NCT02990338)
Study design	Phase III, prospective, open-label, multicentre, multinational, randomised, parallel group, double-arm study
Population	Adult patients (≥18 years old) with RRMM who have received at least two prior lines of therapy, including lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib, or ixazomib) alone or in combination, and have demonstrated disease progression on or within 60 days of completion of the last therapy. Patients with primary refractory disease were excluded.
Intervention(s)	Experimental arm (n=154, ITT), Patients in at 4th line (4L) of treatment (n=52) • Isatuximab, 10 mg/kg IV infusion, on Days 1, 8, 15, and 22 at Cycle 1, and then on Days 1 and 15 for subsequent cycles • Pomalidomide, 4 mg PO, on Days 1 to 21 of each 28-day cycle • Dexamethasone 40 mg (or 20 mg if the patient ≥75 years old) PO or IV, on Days 1, 8, 15 and 22 of each 28-day cycle
Comparator(s)	Active comparator arm (n=153, ITT), Patients at 4L of treatment (n=58)

	• Pomalidomide, 4 mg PO, on Days 1 to 21 of each 28-day cycle • Dexamethasone 40 mg (or 20 mg if the patient ≥75 years old) PO or IV, on Days 1, 8, 15 and 22 of each 28-day cycle
Key study objectives	Primary objective: • To demonstrate the benefit of IsaPd in the prolongation of PFS as compared with Pd in patients with RRMM Secondary objective: • To evaluate the ORR as per IMWG criteria in each study arm • To compare OS between the two study arms

4L – fourth line, IMWG: International Myeloma Working Group, IV, intravenous; MM, multiple myeloma; NA, not applicable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, oral; RRMM, relapsed and/or refractory multiple myeloma; TEAE, treatment-emergent adverse event; TTP, time to progression

5.2 NHS England and NHS Improvement's Blueteq database captures the Cancer Drugs Fund population. NHS England and NHS Improvement shares Blueteq data with Public Health England for the Cancer Drugs Fund evaluation purposes. That sharing is governed by a data sharing agreement between NHS England and NHS Improvement and Public Health England.

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

5.4 Public Health England will collect data, including via the SACT dataset, alongside the primary source of data collection.

6 Outcome data

Clinical trial

6.1 Evidence presented during the NICE appraisal for isatuximab was based on a data cut-off of October 2018 (median follow-up of 11.6 months). At this timepoint, the median overall survival (OS) had not been reached in the ICARIA-MM trial; 69% of the 4L patients were still alive and were, consequently, censored. In terms of time-on-treatment, 45.1% were still receiving IsaPd combination treatment and were censored.

The final overall survival (OS) analysis data cut (at which point [redacted] of OS events are anticipated in the 4L population) will provide almost [redacted] years of follow-up data including OS, PFS, subsequent therapies and time-on-treatment. These will be used to inform the economic model for IsaPd on resubmission.

Other data, including SACT

6.2 Public Health England 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
- The proportion of people who have subsequent treatments following progression on 4th line isatuximab with pomalidomide and dexamethasone, and the specific treatments used.

6.3 NHS England and NHS Improvement's Blueteq system will collect the following outcomes:

- Number of applications to start treatment

7 Data analysis plan

Clinical trials

7.1 At the end of the data collection period, long term data on OS, PFS, subsequent therapies and time-on-treatment for IsaPd will become available from ICARIA-MM. At the final database lock, it is anticipated

there will be an additional [redacted] years follow-up data compared to the data cut (~ 2 years) provided to NICE as part of the technical engagement process. The analysis follows the analysis plan outlined in the phase III trial protocol for OS. The time frame for the data collection was defined such that it will provide sufficient length of follow up to alleviate key uncertainties particularly around the continued treatment benefit associated with isatuximab.

7.2 A second interim analysis is expected to be available in [redacted]. At the interim analysis for OS, it is expected that there will be [redacted] completed survival events in the 4L population.

7.3 The date of the last patient last visit (LPLV) is planned for [redacted], database lock is [redacted] and the clinical study report will be approved on [redacted].

Other data

7.4 At the end of the data collection period Public Health England will provide a final report for NHS England and NHS Improvement which provide analyses based on NHS England and NHS Improvement'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.

8 Ownership of the data

8.1 For all clinical trial data listed above, Sanofi will be the owner

8.2 Governance arrangements for the ongoing clinical trial are in place in line with the standard approvals and ethical procedures followed as per the defined study protocols.

8.3 The data analysed by Public Health England is derived from patient-level information collected by the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Cancer Registration and Analysis Service, which is part of Public Health England. Access to the data is facilitated by the Public Health England Office for Data Release. The company will not have access to the Public Health England patient data, but will receive de-personalised summary data, with appropriate governance controls in place.

8.4 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 Public Health England, have been established with NHS Trusts and NHS England and NHS Improvement.

8.5 Blueteq's Cancer Drugs Fund system data is owned by NHS England and NHS Improvement. NHS England and NHS Improvement is responsible for implementing Blueteq data collection and generally for the analysis of these data. NHS England and NHS Improvement, however, shares Blueteq data with Public Health England for Cancer Drugs Fund evaluation purposes. That sharing is governed by a data sharing agreement between NHS England and NHS Improvement and Public Health England.

9 Publication

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

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

9.3 Public Health England will produce interim reports, which will be shared with NHS England and NHS Improvement, 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.

9.4 Publications of any data from the Public Health England 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.

9.5 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.

10 Data protection

10.1 The terms of clause 7 (data protection) of the managed access agreement, that apply between NHS England and NHS Improvement and Sanofi, shall also apply between the parties to this data collection arrangement in relation to the performance of their obligations under this data collection arrangement

11 Equality considerations

11.1 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.