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PASS INFORMATION

Title	Long-term Follow-up of Nivolumab and Ipilimumab (as Monotherapy and as Combination Therapy)-treated Pediatric Patients Enrolled in the Dutch Melanoma Treatment Registry (DMTR)
Protocol version identifier	3.0
Date of last version of protocol	27-May-2020
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EU PAS register number	29722
Active substance	Nivolumab: Active substance: nivolumab Pharmacotherapeutic Group: Melanoma ATC code: L01FF01 Ipilimumab: Active substance: ipilimumab Pharmacotherapeutic Group: Melanoma ATC code: L01FX04
Medicinal product	Nivolumab: OPDIVO® Ipilimumab: YERVOY®
Product reference	Nivolumab: Agency product number: EMEA/H/C/003985 EU number: EU/1/15/1014/001-004 Ipilimumab: Agency product number: EMEA/H/C/002213 EU number: EU/1/11/698/001-002
Procedure number	EMEA/H/C/002213 EMA/H/C/003985
Marketing authorization holder(s)	Bristol-Myers Squibb Pharma EEIG
Joint PASS	No

Research questions and objectives	**Research Questions:** • What are the demographic and clinical characteristics of pediatric melanoma patients who receive treatment with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab? • What are the Grade 3 to 4 treatment-related AEs, including Grade 3 to 4 immune-related AEs in the endocrine system, reported in pediatric melanoma patients treated with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab? How are Grade 3 to 4 treatment-related AEs reported in pediatric melanoma patients managed, and what are the outcomes? What events lead to discontinuation of study drugs? • What are the long-term outcomes for pediatric melanoma patients treated with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab (with emphasis on growth and sexual maturation)? **Objectives:** <u>Primary Objective:</u> • To evaluate the Grade 3 and 4 treatment-related AEs, including Grade 3 and 4 immune-related AEs in the endocrine system, reported in pediatric melanoma patients receiving nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab, their management, and outcome <u>Secondary Objectives:</u> • To evaluate baseline demographic and clinical data (disease characteristics and treatment history) of pediatric melanoma patients receiving nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab to treat advanced (unresectable or metastatic) melanoma • To assess exposure to nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab (dose, frequency, treatment duration or number of infusions administered) • To evaluate changes in nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab treatment following a Grade 3 or Grade 4 AE, including reasons for discontinuation of nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab (including toxicity) and treatment with any subsequent therapies • To evaluate long-term outcomes for pediatric melanoma patients treated with nivolumab monotherapy, ipilimumab

	monotherapy, or nivolumab in combination with ipilimumab (with emphasis on growth and sexual maturation)
Country(ies) of study	The Netherlands
Author	BMS Study Director [redacted] Bristol-Myers Squibb CO [redacted]

MARKETING AUTHORIZATION HOLDER

Marketing Authorization Holder	Bristol-Myers Squibb Pharma EEIG
MAH Contact Person	[redacted] Bristol-Myers Squibb CO [redacted]

This protocol has been reviewed and approved by the marketing authorization holder's Qualified Person for Pharmacovigilance. The electronic signature is available on file.

Bristol-Myers Squibb Research and Development

Replace all previous version(s) of the protocol with this revised protocol, and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

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2 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
AJCC	American Joint Committee on Cancer
BMS	Bristol-Myers Squibb Company
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DMTR	Dutch Melanoma Treatment Registry
eCRF	electronic case report form
EMA	European Medicines Agency
EU	European Union
EU PAS	European Union Post-Authorisation Studies
OS	overall survival
PASS	post-authorization safety study
PFS	progression-free survival
PMC	Princess Maxima Center
PSUR	Periodic Safety Update Report
RECIST	Response Evaluation Criteria in Solid Tumors
RMP	Risk Management Plan
SD	standard deviation
Q	quarter

3 RESPONSIBLE PARTIES

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4 ABSTRACT

4.1 Title

Long-term Follow-up of Nivolumab and Ipilimumab (as Monotherapy and as Combination Therapy)-treated Pediatric Patients Enrolled in the Dutch Melanoma Treatment Registry (DMTR)

Version: 3.0

Date: 29-Sep-2023

Main Author: [redacted], Bristol-Myers Squibb CO

4.2 Rationale and Background

Clinical data regarding the effectiveness and safety of nivolumab (BMS-936558) monotherapy, ipilimumab (BMS-734016) monotherapy, or nivolumab in combination with ipilimumab for the treatment of pediatric patients with advanced (unresectable or metastatic) melanoma, or melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection are limited, due to the rarity of this patient population. Data on long-term outcomes, such as impact on growth and sexual maturation, for nivolumab and ipilimumab-treated pediatric melanoma patients are lacking.

Collection of long-term safety data in adolescent patients ≥ 12 years of age treated with nivolumab monotherapy, ipilimumab monotherapy, and nivolumab in combination with ipilimumab was agreed as a post-authorization safety study (PASS) with the European Medicines Agency during approval of the following variations for OPDIVO (nivolumab) and YERVOY (ipilimumab):

- EMEA/H/C/002213/II/0044 - Extension of indication for YERVOY to include the treatment of advanced (unresectable or metastatic) melanoma in adolescents 12 years of age and older
- EMEA/H/C/002213/II/0100 - Extension of indication for YERVOY to include in combination with nivolumab the treatment of adolescents 12 years of age and older, for advanced (unresectable or metastatic) melanoma
- EMEA/H/C/003985/II/0125/G - Extension of indications for OPDIVO to include adolescents aged 12 years and older in treatment of advanced (unresectable or metastatic) melanoma (nivolumab monotherapy), treatment of advanced (unresectable or metastatic) melanoma (nivolumab in combination with ipilimumab), and adjuvant treatment of melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection (nivolumab monotherapy)

Long-term safety data in pediatric patients < 12 years of age treated with nivolumab monotherapy, ipilimumab monotherapy, and nivolumab in combination with ipilimumab, will also be collected as a separate off-label use cohort, to increase study size given the rarity of the population of pediatric patients with melanoma. These data will be collected by the Dutch Melanoma Treatment Registry (DMTR), which consists of a consortium of organizations, including medical specialists, policymakers, healthcare researchers, patient advocates, and pharmaceutical companies. The DMTR was established in Jul-2013 at the request of the Ministry of Health to assure the safety and quality of melanoma care in the Netherlands through clinical auditing, health quality indicators, insight into real-world outcomes on effects and costs, and by serving as a platform for research.

The DMTR is used to provide melanoma treatment centers with benchmarked feedback on the number of patients treated, treatment patterns, toxicity rates and survival data.[1,2]A large majority of patients receiving treatment for melanoma are expected to be enrolled in the DMTR, as participation in the registry guarantees reimbursement via the national health system for any approved melanoma therapy. Moreover, it is anticipated that data capture throughout patient follow-up will be complete, as data completeness and quality are monitored by the data managers within the web-based environment. In addition, patients are followed long-term in order to assess survival. The capture of Grade 3 and 4 immune-related adverse events (AEs) for adult patients (both treatment-naive and previously-treated) receiving ipilimumab in clinical practice who were registered in the DMTR between Jul-2012 and Jul-2015 appears to be complete and comprehensive.[2]

With the extension of the indications for nivolumab and ipilimumab (as monotherapy or in combination therapy), as cited above, the DMTR will extend enrollment to this adolescent patient population (and patients younger than 12 years old, if available), thus collecting long-term data on the safety of nivolumab and ipilimumab to treat melanoma in pediatric patients.

4.3 Research Questions and Objectives

Research Questions:

- What are the demographic and clinical characteristics of pediatric melanoma patients that receive treatment with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab?
- What are the Grade 3 to 4 treatment-related AEs, including Grade 3 to 4 immune-related AEs in the endocrine system, reported in pediatric melanoma patients treated with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab? How are Grade 3 to 4 treatment-related AEs reported in pediatric melanoma patients managed, and what are the outcomes? What events lead to discontinuation of study drugs?
- What are the long-term outcomes for pediatric melanoma patients treated with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab (with emphasis on growth and sexual maturation)?

Objectives:

Primary Objective:

- To evaluate the Grade 3 and 4 treatment-related AEs, including Grade 3 and 4 immune-related AEs in the endocrine system, reported in pediatric melanoma patients receiving nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab, their management, and outcome

Secondary Objectives:

- To evaluate baseline demographic and clinical data (disease characteristics and treatment history) of pediatric melanoma patients receiving nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab to treat advanced (unresectable or metastatic) melanoma
- To assess exposure to nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab (dose, frequency, treatment duration or number of infusions administered)
- To evaluate changes in nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab treatment following a Grade 3 or Grade 4 AE, including reasons for discontinuation of nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab (including toxicity) and treatment with any subsequent therapies
- To evaluate long-term outcomes for pediatric melanoma patients treated with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab (with emphasis on growth and sexual maturation)

4.4 Study Design

This is an observational, national, retrospective cohort study based on secondary use of data from a registry in pediatric patients (12 to < 18 and < 12 years of age) with advanced (unresectable or metastatic) melanoma and with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection, treated with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab. The patients will be identified in the DMTR in the Netherlands. The DMTR collects real-world clinical effectiveness, safety data and healthcare utilization data.[1,2]To date, the DMTR includes 14 participating adult centers in the Netherlands, selected by the Netherlands Association of Medical Oncology based on their expertise in the systemic treatment of melanoma, their infrastructure, and to ensure geographic distribution. With the extension of melanoma treatments to pediatric patients, an additional center, the Princess Maxima Center (PMC), a pediatric oncology hospital, will participate in the DMTR.

Because the treatment of all pediatric cancer patients is to be based at the PMC, the data for the current study will be primarily derived from this center. In the event a patient is seen at a participating DMTR center during adulthood, linked data will be provided when possible.

4.5 Population

The study population will consist of pediatric patients with:

- newly diagnosed or previously treated, advanced (unresectable or metastatic) melanoma who are treated with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab and enrolled in the DMTR
- melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection and who are treated with adjuvant nivolumab monotherapy and enrolled in the DMTR

The patients will be divided into 2 cohorts (Cohort 1: 12 to < 18 years old; Cohort 2: < 12 years old), for each treatment (nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab) to make a total of 6 sub-cohorts.

4.6 Variables

The DMTR provides detailed information on patient and tumor characteristics, diagnostics, treatment strategies, AEs, time to progression, and survival.

Variables include the following:

- Baseline patient, tumor, and treatment characteristics
- Exposure to nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab (dose, frequency, treatment duration or number of infusions administered)

Grade 3 to 4 treatment-related AEs (collected according to the current Common Terminology Criteria for Adverse Events (CTCAE) version at the time of AE collection), including:

  - blood disorders, such as leukopenia, thrombocytopenia, anemia
  - neuropathy
  - gastrointestinal, such as colitis, perforation
  - skin toxicity
  - uveitis
  - endocrinopathy, such as adrenal insufficiency, pituitary insufficiency, thyroid insufficiency, diabetes mellitus
  - hepatitis
  - hypersensitivity
  - nephritis and renal dysfunction
  - pneumonitis
  - myocarditis
  - other
- Treatment/action taken for any Grade 3 to 4 treatment-related AEs, as well as AE outcomes
- Parameters related to growth and sexual maturation (eg, height, weight, Tanner stage)
- Efficacy outcomes: time to progression, progression free survival (PFS), and overall survival (OS)
- Subsequent therapy post-nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab

Other variables, similar to those provided for the adult registry and/or as applicable for pediatric patients may be provided for further descriptive analysis.

4.7 Data Sources

Data will be abstracted annually and retrospectively from medical charts (secondary use of data) from all pediatric melanoma patients enrolled in the DMTR. Trained data managers will coordinate and perform data collection in the melanoma centers. The Dutch Institute for Clinical Auditing will supervise data collection and management; oncologists will supervise the registration process and confirm all results at the patient level.[1,2]

Data are entered into the DMTR electronic case report form (eCRF) for all patients receiving treatment at PMC. The evaluation of nivolumab- and ipilimumab-treated pediatric melanoma patients for this PASS will be carried out using data from the DMTR. Given the comprehensive list of information that is already collected in the current DMTR eCRF, the likelihood that important data will be missed is small.

Additional data concerning outcomes related to growth and sexual maturation (eg, height, weight, Tanner stage) among nivolumab- or ipilimumab-treated pediatric patients that are not specified in the current DMTR data specifications will be abstracted via a pediatric-specific case report form (CRF) annex to the current eCRF. The special pediatric-specific CRF annex (Annex 4), was designed in collaboration with the participating pediatric oncologists and the DMTR scientific board.

The DMTR collects and analyzes Grade 3 and Grade 4 treatment-related AEs (according to the current CTCAE version at the time of AE collection), data associated with the treatment of melanoma and clinical outcomes of all Dutch patients diagnosed with advanced (unresectable or metastatic) melanoma, or melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection. Grade 1 and 2 events are not captured by the DMTR. Death is recorded as a consequence of a Grade 3 or 4 toxicity, or as a reason for treatment discontinuation, rather than reporting as a Grade 5 event. Furthermore, the DMTR CRF includes queries for AE terms specific to the immune-mediated nature of the toxicity associated with immune-modulating therapies such as nivolumab and ipilimumab.

The DMTR uses a web-based environment for data entry and data management and employs a secure website to provide participating healthcare professionals. The Registry receives continuous benchmarked feedback with respect to the number of patients treated, treatment patterns, toxicity rates, and survival data on a weekly basis in relation to the national average and in relation to the results of other anonymized melanoma centers. All results are discussed at the quarterly meetings of the Medical Committee, in which all centers participate.[1,2]

As described earlier, the data collected in the extension of the DMTR to pediatric patients will be primarily derived from the PMC. The PMC is currently the sole treatment center in the Netherlands for pediatric oncology. This centralized treatment center was created specifically for pediatric oncology patients in order to provide specialized care with expertise concentrated at this site. This hospital sees all pediatric oncology patients from the Netherlands and some from neighboring countries.

4.8 Study Size

Given the rarity of the population of pediatric patients with advanced (unresectable and metastatic) melanoma, and the difficulty that has been encountered recruiting pediatric patients into a clinical trial with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab treatment, enrollment of pediatric patients into the Dutch registry is expected to be relatively low. Furthermore, with the introduction and expanded use of new classes of medications, such as the programmed death-1/programmed death-ligand 1 inhibitors, the treatment of advanced (unresectable and metastatic) melanoma is anticipated to evolve and perhaps lead to even less use of ipilimumab monotherapy for this indication.

Based on the annual incidence of all pediatric cancer in the Netherlands, the DMTR estimated 10 new cases of pediatric melanoma are expected annually in the Netherlands. However, not all melanoma cases will present with the disease histology or severity to warrant treatment, nor will nivolumab or ipilimumab be the treatment of choice for all treatment-eligible pediatric patients. Therefore, it is estimated that there will be fewer than 10 nivolumab- or ipilimumab-exposed pediatric patients enrolled in the DMTR annually.

Data collection for pediatric patients is planned for at least 10 years to obtain long-term follow-up on enrolled pediatric patients treated with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab. The follow-up period for an individual patient may vary depending on the index date.

4.9 Study Analysis

The data provided for pediatric patients will be divided into 2 cohorts, based on age at time of first dose of nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab treatment (index date). Cohort 1 will include patients 12 to under 18 years old at time of enrollment, and Cohort 2 will include patients < 12 years of age at the time of enrollment. Patients treated before the nivolumab or ipilimumab marketing approval date will be included and assigned to the appropriate age-based cohort, regardless of timing with respect to date of approval. Interim data on pediatric patients treated with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab will be reported by Bristol-Myers Squibb Company to the Pharmacovigilance Risk Assessment Committee in the Periodic Safety Update Report, in the interim study report, and in the final study report.

Descriptive statistics will be used to assess baseline patient characteristics, disease and other clinical characteristics, and treatment patterns. Descriptive statistics will also be used to assess safety outcomes (Grade 3 and 4 events) and observations related to parameters for growth and sexual maturation. Additionally, premature or delayed puberty will be analyzed based on gender and normal sexual maturation scales.

A description of patient and tumor characteristics for all pediatric patients receiving alternative therapies will be provided for the overall treatment landscape for this patient population.

Kaplan-Meier methodology will be used for the assessment of OS and progression-free survival.

4.10 Milestones

- Start of data collection:
  - End of Quarter (Q)2 2019 for ipilimumab monotherapy cohort;
  - End of Q1 2024 for nivolumab monotherapy and nivolumab in combination with ipilimumab cohorts
- Data will be collected retrospectively, and all pediatric patients entered in the DMTR who received nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab will be included, even if the treatment started prior to the data collection start date.
- Progress report:
  - End of Q2 2022 for ipilimumab monotherapy cohort
- Interim report:
  - Q4 2026 for nivolumab monotherapy, ipilimumab monotherapy, and nivolumab in combination with ipilimumab therapy cohorts
- End of data collection
  - End of Q1 2029 for ipilimumab monotherapy cohort (as required per ipilimumab European Union Risk Management Plan [EU RMP])
  - End of Q1 2033 for nivolumab monotherapy and nivolumab in combination with ipilimumab cohorts
- Final reports of study results (as required per nivolumab and ipilimumab EU RMPs):
  - End of Q3 2029 for ipilimumab monotherapy cohort;
  - Q4 2033 for nivolumab monotherapy and nivolumab in combination with ipilimumab cohorts

5 AMENDMENTS AND UPDATES

Table 5-1: Information of Protocol Amendments

Number	Date	Section of Study Protocol	Amendment or Update	Reason
2.0		Section 6, Table 6-1, Study Milestones	Planned dates for the recruitment period, progress report, and interim study report	
2.0		Section 9.3.3	Concomitant medications to the list of other covariates/control variables collected	
3.0		All sections	Addition of nivolumab monotherapy-treated and nivolumab in combination with ipilimumab treated pediatric patients to the study	
3.0		Section 6, Table 6-1, Study Milestones	Revision of milestone dates per nivolumab EU RMP v30.1.	
3.0		Section 9.7	Definitions and analysis of long-term outcomes for survival, time to progression and progression free survival (PFS)	
3.0		Section 9.3.1	Immune mediated AE categories as per nivolumab Summary of Product characteristics	

Table 5-1: Information of Protocol Amendments

Number	Date	Section of Study Protocol	Amendment or Update	Reason
3.0		Section 11.1	Updated per new BMS protocol template	

6 MILESTONES

Table 6-1: Study Milestones

Milestone	Treatment Group(s)[a]	Planned Date
Start of data collection[b]	Ipilimumab monotherapy	End of Q2 2019
Start of data collection[b]	Nivolumab monotherapy Nivolumab in combination with ipilimumab	End of Q1 2024
Progress report	Ipilimumab monotherapy	End of Q2 2022
Interim study report[c]	Nivolumab monotherapy Ipilimumab monotherapy Nivolumab in combination with ipilimumab	Q4 2026
End of data collection	Ipilimumab monotherapy	End of Q1 2029
Final report of study results	Ipilimumab monotherapy	End of Q3 2029
End of data collection	Nivolumab monotherapy Nivolumab in combination with ipilimumab	End of Q1 2033
Final report of study results	Nivolumab monotherapy Nivolumab in combination with ipilimumab	Q4 2033

[a] Study Milestones are planned as per nivolumab and ipilimumab commitments documented in nivolumab and ipilimumab EU RMPs.

[b] The start of data collection began in Q2 2019, when the Princess Maxima Center (PMC) officially confirmed its collaboration with the pediatric extension of the Dutch Melanoma Treatment Registry (DMTR) for patients treated with ipilimumab monotherapy. The start of data collection for patients treated with nivolumab monotherapy and nivolumab in combination with ipilimumab will be at the end of Q1 2024. However, because data will be collected retrospectively, all pediatric patients entered in the DMTR who received nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab will be included, even if the treatment started prior to the data collection start date.

[c] Interim study report is planned in Q4 2026 aligning with nivolumab EU RMP v30.1 and will include the nivolumab monotherapy, ipilimumab monotherapy and nivolumab with ipilimumab combination therapy cohorts in the interim analysis.

Abbreviations: Q, quarter.

7 RATIONALE AND BACKGROUND

Clinical data regarding the effectiveness and safety of nivolumab (BMS-936558) monotherapy, ipilimumab (BMS-734016) monotherapy, or nivolumab in combination with ipilimumab for the treatment of pediatric patients with advanced (unresectable or metastatic) melanoma, or melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection are limited, due to the rarity of this patient population. Data on long-term outcomes, such as impact on growth and sexual maturation, for nivolumab and ipilimumab-treated pediatric melanoma patients are lacking.

Collection of long-term safety data in adolescent patients ≥ 12 years of age treated with nivolumab monotherapy, ipilimumab monotherapy, and nivolumab in combination with ipilimumab was agreed as a post-authorization safety study (PASS) with the European Medicines Agency during approval of the following variations for OPDIVO (nivolumab) and YERVOY (ipilimumab):

- EMEA/H/C/002213/II/0044 - Extension of indication for YERVOY to include the treatment of advanced (unresectable or metastatic) melanoma in adolescents 12 years of age and older
- EMEA/H/C/002213/II/0100 - Extension of indication for YERVOYto include in combination with nivolumab the treatment of adolescents 12 years of age and older, for advanced (unresectable or metastatic) melanoma
- EMEA/H/C/003985/II/0125/G - Extension of indications for OPDIVO to include adolescents aged 12 years and older in treatment of advanced (unresectable or metastatic) melanoma (nivolumab monotherapy), treatment of advanced (unresectable or metastatic) melanoma (nivolumab in combination with ipilimumab), and adjuvant treatment of melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection (nivolumab monotherapy)

Long-term safety data in pediatric patients < 12 years of age treated with nivolumab monotherapy, ipilimumab monotherapy, and nivolumab in combination with ipilimumab, will also be collected as a separate off-label use cohort, to increase study size given the rarity of the population of pediatric patients with melanoma. These data will be collected by the Dutch Melanoma Treatment Registry (DMTR), which consists of a consortium of organizations, including medical specialists, policymakers, healthcare researchers, patient advocates, and pharmaceutical companies. The DMTR was established in Jul-2013 at the request of the Ministry of Health to assure the safety and quality of melanoma care in the Netherlands through clinical auditing, health quality indicators, insight into real-world outcomes on effects and costs, and by serving as a platform for research. The DMTR is used to provide melanoma treatment centers with benchmarked feedback on the number of patients treated, treatment patterns, toxicity rates, and survival data.[1,2]A large majority of patients receiving treatment for melanoma are expected to be enrolled in the DMTR, as participation in the registry guarantees reimbursement via the national health system for any approved melanoma therapy. Moreover, it is anticipated that data capture throughout patient follow-up will be complete, as data completeness and quality are monitored by the data managers within the web-based environment. In addition, patients are followed long-term in order to assess survival. The capture of Grade 3 and 4 immune-related AEs for adult patients (both treatment-

naive and previously-treated) receiving ipilimumab in clinical practice who were registered in the DMTR between Jul-2012 and Jul-2015 appeared to be complete and comprehensive.[2]

With the extension of the indications for nivolumab and ipilimumab (as monotherapy or in combination therapy), as cited above, the DMTR will extend enrollment to this adolescent patient population (and patients younger than 12 years old, if available), thus collecting long-term data on the safety of nivolumab and ipilimumab to treat melanoma in pediatric patients.

8 RESEARCH QUESTION AND OBJECTIVES

8.1 Research Questions

- What are the demographic and clinical characteristics of pediatric melanoma patients that receive treatment with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab?
- What are the Grade 3 to 4 treatment-related AEs, including Grade 3 to 4 immune-related AEs in the endocrine system, reported in pediatric melanoma patients treated with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab? How are Grade 3 to 4 treatment-related AEs reported in pediatric melanoma patients managed, and what are the outcomes? What events lead to discontinuation of study drugs?
- What are the long-term outcomes for pediatric melanoma patients treated with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab (with emphasis on growth and sexual maturation)?

8.2 Objectives

8.2.1 Primary Objective

The primary objective of this study is:

- To evaluate the Grade 3 and 4 treatment-related AEs, including Grade 3 and 4 immune-related AEs in the endocrine system, reported in pediatric melanoma patients receiving nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab, their management, and outcome

8.2.2 Secondary Objectives

The secondary objectives are:

- To evaluate baseline demographic and clinical data (disease characteristics and treatment history) of pediatric melanoma patients receiving nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab to treat advanced (unresectable or metastatic) melanoma
- To assess exposure to nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab (dose, frequency, treatment duration or number of infusions administered)
- To evaluate changes in nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab treatment following a Grade 3 or 4 AE, including reasons for discontinuation of nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab (including toxicity) and treatment with any subsequent therapies

- To evaluate long-term outcomes for pediatric melanoma patients treated with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab (with emphasis on growth and sexual maturation)

9 RESEARCH METHODS

9.1 Study Design

This is an observational, national, retrospective cohort study based on secondary use of data from a registry in pediatric patients (12 to < 18 and < 12 years of age) with advanced (unresectable or metastatic) melanoma and with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection, treated with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab. The patients will be identified in the DMTR in the Netherlands. The DMTR collects real-world clinical effectiveness, safety data and healthcare utilization data.[1,2]To date, the DMTR includes 14 participating adult centers in the Netherlands, selected by the Netherlands Association of Medical Oncology based on their expertise in the systemic treatment of melanoma, their infrastructure, and to ensure geographic distribution. With the extension of melanoma treatments to pediatric patients, an additional center, the Princess Maxima Center (PMC), a pediatric oncology hospital, will participate in the DMTR.

Because the treatment of all pediatric cancer patients is to be based at the PMC, the data for the current study will be primarily derived from this center. In the event a patient is seen at a participating DMTR center during adulthood, linked data will be provided when possible.

9.1.1 Primary Endpoint

The primary endpoints will be the frequency of Grade 3 and 4 treatment-related AEs and their management and outcomes.

9.1.2 Secondary Endpoints

The secondary endpoints will be:

- Baseline demographic, comorbidities, disease characteristics, and treatment history
- Exposure to nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab (dose, frequency, treatment duration, number of infusions)
- Changes in ipilimumab or nivolumab treatment: dose interruptions/discontinuations (with reason) and subsequent therapies
- Long-term outcomes: overall survival (OS), time to progression, assessment of growth and sexual maturation, and progression free survival (PFS)

9.2 Setting

In the Netherlands, all pediatric patients are treated at 1 hospital, PMC. Therefore, the data for this study will be collected from this institution. Data collection is planned for approximately 10 years to obtain long-term follow-up on all enrolled pediatric melanoma patients treated with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab.

9.2.1 Study Population

The study population will consist of pediatric patients with:

- newly diagnosed or previously treated, advanced (unresectable or metastatic) melanoma who are treated with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab and enrolled in the DMTR
- melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection and who are treated with adjuvant nivolumab monotherapy and enrolled in the DMTR

The patients will be divided into 2 cohorts (Cohort 1: 12 to < 18 years old; Cohort 2: < 12 years old), for each treatment (nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab) to make a total of 6 sub-cohorts.

9.2.2 Inclusion Criteria

- < 18 years of age at first dose of nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab (index date) used for the treatment of advanced (unresectable or metastatic) melanoma
- Histologically or cytological confirmation of advanced (unresectable or metastatic) melanoma diagnosis or melanoma (with involvement of lymph nodes or metastatic disease) who have undergone complete resection or patients treated with nivolumab monotherapy in adjuvant treatment

9.2.3 Exclusion Criteria

- Participation in a clinical trial within the past 4 weeks prior to first dose with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab or concurrently

9.3 Variables

9.3.1 Outcomes/Endpoint Variables

Grade 3 and 4 treatment-related AEs will be collected according to the current Common Terminology Criteria for Adverse Events (CTCAE) version at the time of AE collection.

The DMTR provides detailed information on patient and tumor characteristics, diagnostics, treatment strategies, AEs, time to progression, and survival.

Variables include the following:

- Grade 3 and 4 treatment-related AEs, including:
  - blood disorders, such as leukopenia, thrombocytopenia, anemia
  - neuropathy
  - gastrointestinal, such as colitis, perforation
  - skin toxicity
  - uveitis

  - endocrinopathy, such as adrenal insufficiency, pituitary insufficiency, thyroid insufficiency, diabetes mellitus
  - hepatitis
  - hypersensitivity
  - nephritis and renal dysfunction
  - pneumonitis
  - myocarditis
  - other
- Grade 3 to 4 treatment-related AEs onset date
- Grade 3 to 4 treatment-related AEs resolution date
- Grade 3 to 4 treatment-related AEs action taken with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab treatment: dose interruption, discontinuation
- Grade 3 to 4 treatment-related AEs management: concomitant (interventional) medication or procedure
- Grade 3 to 4 treatment-related AEs outcome: resolved, resolved with sequelae, unresolved, death, unknown
- Parameters related to growth and sexual maturation (eg, height, weight, Tanner stage)
- Efficacy outcomes: time to progression, PFS, OS

9.3.2 Exposure/Independent Variables of Interest

- Exposure to nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab used for advanced (unresectable or metastatic) melanoma or exposure to nivolumab monotherapy in adjuvant therapy for melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection
  - Dose
  - Frequency
  - Treatment duration
  - Number of infusions administered
- Subsequent therapy post- nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab (time to next treatment, type, duration)

9.3.3 Other Covariates/Control Variables

The following baseline demographic, tumor, and treatment characteristics will be collected:

- Demographics such as:
  - Age
  - Gender
- Disease Characteristics:
  - Date of initial diagnosis and American Joint Committee on Cancer (AJCC) Stage

  - Date of diagnosis and AJCC Stage, prior to first dose with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab
  - Breslow depth (mm)
  - Melanoma type
  - Tumor location
  - Mutation type(s) (eg, *BRAF* and/or other mutation types)
  - Serum lactate dehydrogenase level(s)
  - Serum protein S100 level(s)
  - Presence of brain metastases
  - Presence of liver metastases
  - Prior melanoma therapy(ies)
- Clinical Characteristics
  - Comorbid conditions/prognostic indicators
  - Karnofsky/Lansky
- Concomitant Medications (given 30 days prior to first dose and up to 100 days post last dose of nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab):
  - Medication name
  - Medication category
  - Start date
  - Stop date
  - Reason for Use a) comorbidity, b) nivolumab- and/or ipilimumab-treatment related AEs c) management for melanoma disease-related event, d) other

Baseline characteristics are defined as characteristics assessed before the date and time of the first dose of nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab treatment (index date).

Additional variables, similar to those provided for the adult registry and/or as applicable for pediatric patients may be provided for further descriptive analysis.

9.4 Data Sources

Data will be abstracted annually and retrospectively from medical charts (secondary use of data) from all pediatric melanoma patients enrolled in the DMTR. Trained data managers will coordinate and perform data collection in the melanoma centers. The Dutch Institute for Clinical Auditing will supervise data collection and management; oncologists will supervise the registration process and confirm all results at the patient level.[1,2]

Data are entered into the DMTR electronic case report form (eCRF) for all patients receiving treatment at PMC. The evaluation of nivolumab- and ipilimumab-treated pediatric melanoma patients for this PASS will be carried out using data from the DMTR. Given the comprehensive

list of information that is already collected in the current DMTR eCRF, the likelihood that important data will be missed is small.

Additional data concerning outcomes related to growth and sexual maturation (eg, height, weight, Tanner stage) among nivolumab- or ipilimumab-treated pediatric patients that are not specified in the current DMTR data specifications will be abstracted via a pediatric-specific case report form (CRF) annex to the current eCRF. The special pediatric-specific CRF annex (Annex 4), was designed in collaboration with the participating pediatric oncologists and the DMTR scientific board.

The DMTR collects and analyzes Grade 3 and 4 treatment-related AEs (according to the current CTCAE version at the time of AE collection), data associated with the treatment of melanoma and clinical outcomes of all Dutch patients diagnosed with advanced (unresectable or metastatic) melanoma, or melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection. Grade 1 and 2 events are not captured by the DMTR. Death is recorded as a consequence of a Grade 3 or 4 toxicity, or as a reason for treatment discontinuation, rather than reporting as a Grade 5 event. Furthermore, the DMTR CRF includes queries for AE terms specific to the immune-mediated nature of the toxicity associated with immune-modulating therapies such as nivolumab and ipilimumab.

The DMTR uses a web-based environment for data entry and data management and employs a secure website to provide participating healthcare professionals. The Registry receives continuous benchmarked feedback with respect to the number of patients treated, treatment patterns, toxicity rates, and survival data on a weekly basis in relation to the national average and in relation to the results of other anonymized melanoma centers. All results are discussed at the quarterly meetings of the Medical Committee, in which all centers participate.[1,2]

As described earlier, the data collected in the extension of the DMTR to pediatric patients will be primarily derived from the PMC. The PMC is currently the sole treatment center in the Netherlands for pediatric oncology. This centralized treatment center was created specifically for pediatric oncology patients in order to provide specialized care with expertise concentrated at this site. This hospital sees all pediatric oncology patients from the Netherlands and some from neighboring countries.

9.5 Study Size

Given the rarity of the population of pediatric patients with advanced (unresectable and metastatic) melanoma, and the difficulty that has been encountered recruiting pediatric patients into a clinical trial with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab treatment, enrollment of pediatric patients into the Dutch registry is expected to be relatively low. Furthermore, with the introduction and expanded use of new classes of medications, such as the programmed death-1 /programmed death-ligand 1 inhibitors, the treatment of advanced (unresectable and metastatic) melanoma is anticipated to evolve and perhaps lead to even less use of ipilimumab monotherapy for this indication.

Based on the annual incidence of all pediatric cancer in the Netherlands, the DMTR estimated 10 new cases of pediatric melanoma are expected annually in the Netherlands. However, not all

melanoma cases will present with the disease histology or severity to warrant treatment, nor will nivolumab or ipilimumab be the treatment of choice for all treatment-eligible pediatric patients. Therefore, it is estimated that there will be fewer than 10 nivolumab- or ipilimumab-exposed pediatric patients enrolled in the DMTR annually.

Data collection is planned for approximately 10 years to obtain long-term follow-up on enrolled pediatric patients treated with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab. The follow-up period for an individual patient may vary depending on the index date.

9.6 Data Management

The DMTR provides pharmaceutical companies, such as Bristol-Myers Squibb Company (BMS), with aggregate information regarding the use and performance of their drugs in clinical practice. As the data received for this study are secondary and abstracted retrospectively from medical charts, data management activities will be the responsibility of the DMTR. The sponsor will obtain annual reports, and clarify any additional analysis needed.

9.7 Data Analysis

The data provided for pediatric patients will be divided into 2 cohorts, based on age at time of first dose of nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab treatment (index date). Cohort 1 will include patients 12 to under 18 years old at time of enrollment, and Cohort 2 will include patients < 12 years of age at the time of enrollment. Patients that were treated before the nivolumab or ipilimumab marketing approval date will be included and assigned to the appropriate age-based cohort, regardless of timing with respect to date of approval. Interim data on pediatric patients treated with nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab will be reported by BMS to the Pharmacovigilance Risk Assessment Committee in the Periodic Safety Update Report (PSUR), in the interim study report, and in the final study report.

A description of patient and tumor characteristics for all pediatric patients receiving alternative therapies will be provided, for the overall treatment landscape for this patient population.

9.7.1 Primary Objective

Descriptive statistics (frequency, count, and percentage) will be provided to assess safety outcomes (Grade 3 and 4 events) and their management and outcomes. Time to onset and time to resolution will be summarized with mean, median, minimum, maximum, and standard deviation (SD).

9.7.2 Secondary Objectives

Descriptive statistics will be used to assess:

- Baseline characteristics, disease, and other clinical characteristics
- Treatment patterns, such as exposure to nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab (dose, frequency, treatment duration or number of infusions administered), and changes in nivolumab monotherapy, ipilimumab monotherapy, or nivolumab in combination with ipilimumab treatment following a Grade 3 to 4 AE, including

reasons for discontinuation of nivolumab or ipilimumab (including toxicity) and treatment with any subsequent therapies

- Observations related to parameters for growth and sexual maturation (height, weight, and Tanner stage)

Additionally, premature or delayed puberty will be analyzed based on gender and normal sexual maturation scales.

General descriptive statistics will include mean, median, minimum, maximum, and SD for continuous variables; count and percentages will be used to examine categorical variables.

Long-term outcomes for survival, time to progression, and PFS will be defined and analyzed as follows:

OS is defined as the time between the date of first treatment with study drug and the date of death. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive. OS medians and rates at several points of time (eg, at year 1 year, year 5), will be estimated using the Kaplan-Meier methodology for each treatment group.

Time to progression is defined as time from the first treatment with study drug to the date of the first documented progression, as assessed by investigator per the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

The PFS is defined as the time between the date of the first treatment with study drug and the date of first documented tumor progression, based on investigator assessments (per RECIST v1.1), or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last (most recent) date of visit to the treating physician in the hospital.

Median PFS in each treatment group will be derived from the Kaplan Meier estimate.

9.8 Quality Control

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

Standard processes of the DMTR will be followed to ensure the quality of the data in the registry. Data quality is verified at several key time points along the registration process. Missing or potentially incorrect data are fed back directly to the data managers within the web-based environment. Furthermore, the PMC data managers verify 10% of the registered data annually. Oncologists supervise the registration process and control all results at the patient level.[1]

9.8.1 Database Retention and Archiving of Study Documents

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact BMS prior to

destroying any records associated with the study. Location of database and supporting documentation will be outlined in the final observational study report.

9.8.2 Registration of Study on Public Website

This study has been registered on clinicaltrials.gov and the European Union Post-authorisation Studies (EU PAS) register, at the time of the initial protocol.

9.9 Limitations of the Research Methods

Because of the low incidence of advanced (unresectable or metastatic) melanoma or melanoma with involvement of lymph nodes or metastatic disease in pediatric patients in the Netherlands who have undergone complete resection and the availability of other treatments, it is expected that less than 10 patients will be enrolled per year. This low sample size does not provide statistical power and may not fully reflect the safety profile of pediatric patients receiving these therapies.

The measurement of Tanner stage as a variable is not part of standard practice in PMC; therefore, this variable may be missing in patients' records.

9.10 Other Aspects

9.10.1 Strengths of Research Methods

As discussed in Section 7, a large majority of patients receiving treatment for melanoma in the Netherlands are expected to be enrolled in the DMTR, as participation in the registry guarantees reimbursement via the national health system for any approved melanoma therapy patients receive. Data capture throughout patient follow-up is expected to be complete, as data completeness and quality are monitored by the data managers within the web-based environment.

The capture of Grade 3 and 4 immune-related AEs for adult patients (both treatment-naive and previously-treated) receiving ipilimumab in clinical practice who were registered in the DMTR between Jul-2012 and Jul-2015 appeared to be complete and comprehensive.[1,2] In addition, patients are followed long term in order to assess long-term outcomes.

10 PROTECTION OF HUMAN SUBJECTS

10.1 Ethics Committee Review and Informed Consent

This study does not require review and approval by ethics committees or informed consent. The DMTR will consent patients for their participation in the registry outside of the scope of this study.

10.2 Confidentiality of Study Data

The confidentiality of records that could identify patients within the database must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse Event Definitions

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The intent of this study is to capture those AEs referenced in Section 9.3.1. No other AEs will be reported as this PASS is an observational study using secondary data from an established disease registry.

11.1 Adverse Event Collection and Reporting

11.1.1 Adverse Event Collection

All AEs collected will be reported in aggregate in the interim report and in the final study report. No individual or expedited reporting is required.

11.1.1.1 Fatal Outcomes

Treatment-related AEs with fatal outcome are reportable to BMS (or designee) unless the fatal outcome is associated with a study endpoint. Endpoint events with fatal outcome will be summarized in the interim report and in the final study report.

As per Section 9.4, the DMTR only collects treatment-related AEs as the objective of the Registry is focused on high-level toxicity rates at DMTR centers, national averages in the Netherlands, and other non-DMTR centers.[1] Furthermore, the DMTR only provides information with the pharmaceutical companies that is specific to their respective treatments. Therefore, this study is restricted to collecting Grade 3 and 4 AEs related to nivolumab and/or ipilimumab, and death is reported as a consequence of toxicity.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

As per this Category 3 post-approval measure captured in the nivolumab and ipilimumab EU Risk Management Plans (RMPs), BMS is committed to submit progress updates via the PSUR, an interim study report and a final study report as described in Section 0.

Progress updates via the PSUR will include counts of patients and AEs reported in each treatment cohort. Interim and final study reports will include descriptive analyses for primary and secondary endpoints as described in Section 9.7.

13 REFERENCES

1 Jochems A, Schouwenburg MG, Leeneman B, et al. Dutch Melanoma Treatment Registry: Quality assurance in the care of patients with metastatic melanoma in the Netherlands. Eur J Cancer 2017;72:156-65.

2 Jochems A, Leeneman B, Franken MG, et al. Real-world use, safety, and survival of ipilimumab in metastatic cutaneous melanoma in The Netherlands. Anticancer Drugs 2018;29(6):572-8.

ANNEX 1 LIST OF STAND-ALONE DOCUMENTS

Not applicable.

ANNEX 2 ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: Long-term Follow-up of Ipilimumab-treated Pediatric Patients Enrolled in the Dutch Melanoma Treatment Registry (DMTR)

EU PAS Register® number: 29723
Study reference number (if applicable): CA184-557

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6, 9.8.2
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7, 8.2, 9.7
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.6
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	☐	9.7.1, 9.7.2
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	9.3.1, 9.4

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2
4.2.2 Age and sex	☒	☐	☐	
4.2.3 Country of origin	☒	☐	☐	
4.2.4 Disease/indication	☒	☐	☐	
4.2.5 Duration of follow-up	☒	☐	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.2
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.7
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.2, 9.7.2
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Descriptive Statistics. See 9.9-Limitation of small sample size

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.1.1, 9.1.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.7.1, 9.7.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Descriptive Statistics. See 9.9-Limitation of small sample size

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.4

Comments:

Descriptive Statistics. See 9.9-Limitation of Small sample size

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7

Comments:

2 cohorts -age

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☐	9.3.2
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☐	9.3.1
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☐	9.3.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.1
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7-9.9

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5, 9.9
10.3 Are descriptive analyses included?	☒	☐	☐	9.7, 9.7.1, 9.7.2
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments

Descriptive Statistics. See 9.9-Limitation of small sample size

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8.1
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	9.10.1
12.1.2 Information bias?	☒	☐	☐	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5 and 9.9

Comments:

Descriptive Statistics. See 9.9-Limitation of small sample size

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.2

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	9.7 and 12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: [redacted]

Date: 29/APR/2019

Signature: _____

ANNEX 3 ADDITIONAL INFORMATION

None.

ANNEX 4 PEDIATRIC CRF

PROTOCOL CA184XXX SITE NUMBER SUBJECT NUMBER

☐☐☐☐☐☐ ☐☐☐☐ ☐☐☐☐☐

Visit Date	Height (cm)	Weight (kg)	Tanner Stage