Real-world use of enfortumab vedotin for the treatment of patients with locally advanced or metastatic urothelial cancer previously treated with chemotherapy and immunotherapy: A multicenter, retrospective, non-interventional study in France.

Real-world use of enfortumab vedotin for the treatment of patients with locally advanced or metastatic urothelial cancer

ISN/Protocol 7465-MA-3480

Version 2.0

08 Nov 2023

Sponsor:

Astellas Pharma Europe Ltd.

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SYNOPSIS

Title	Real-world use of enfortumab vedotin for the treatment of patients with locally advanced or metastatic urothelial cancer previously treated with chemotherapy and immunotherapy: A multicenter, retrospective, non-interventional study in France.
Study identifier / protocol number	ISN: 7465-MA-3480
Protocol version & date of last version of protocol	Version: 2.0 Date: 08 Nov 2023
Active substance	Enfortumab vedotin (ATC code: L01FX13)
Medicinal product	Padcev 20 mg powder for concentrate for solution for infusion Padcev 30 mg powder for concentrate for solution for infusion
Product reference	Not applicable
Type of Study	Non-interventional secondary data-use study
Procedure number	EMEA/H/C/005392
Joint PASS	(Select one below) ☐ Yes ☒ No
Research questions, objectives, and methodology	Research Question: This study will describe real world patients' baseline characteristics, use, and safety of enfortumab vedotin (EV) for the treatment of patients with locally advanced or metastatic urothelial cancer (LA/mUC) previously treated with platinum-based chemotherapy and a programmed death receptor 1 (PD-1) or a programmed death ligand-1 (PD-L1) inhibitor in France. Data will be collected from the medical charts of patients who were treated with at least one dose of EV in the context of the French early access program (EAP) between 8 July 2022 and 31 December 2022. Objectives: Primary Objective: • To describe real-world effectiveness of EV based on overall survival (OS). Secondary Objectives: • To describe real-world effectiveness of EV based on real world progression free survival (PFS). • To describe real-world effectiveness of EV based on time to treatment discontinuation (TTD). • To describe real-world effectiveness of EV based on time to next treatment (TTNT). • To describe real-world effectiveness of EV based on objective response rate (ORR). • To describe real-world effectiveness of EV based on disease control rate (DCR).

	• To describe baseline characteristics of participants who initiated treatment with EV in the real-world clinical practice. • To describe real-world treatment patterns of EV. • To describe subsequent line(s) of treatment administered after EV in real-world clinical practice. • To describe safety data related to the use of EV in the real-world by: o Describing proportions of participants with pre-specified adverse drug reactions (ADR) including ADR that led to dose reduction(s), temporary treatment interruption(s), permanent treatment discontinuation(s), and death. o Describing real-world ADR management when occurrence of Grade 2 or higher skin reaction. <u>Methodology:</u> Retrospective data will be exclusively collected from the medical charts of eligible participants. Collected data will have been generated during routine monitoring clinical visits. No additional visits, assessments, or procedures are required in this study. Eligible participants, alive at study initiation, will be informed of the study, provided with an information and non-opposition note, and given time to decide if they wish to oppose to the collection of their data. Data of participants who died before study initiation will only be collected if the participants had not opposed to the collection of their data for research purpose before their death. All study required data will be collected on site by data abstractors. Data abstractors will be clinical research associates (CRA) from the clinical research organisation (CRO) managing the study or clinical study assistants (CSA) from the site. They will report the required data in the study specific electronic case report form (eCRF) under the supervision of the study physician. The data collected for a given participant will include data that was recorded in the participant's medical charts from the baseline period until the participant's death, loss to follow up, or up to 12 months after treatment initiation, whichever occurred first. The index date will be the date of first administration of EV. The baseline data will be the data recorded at the closest time prior to the index date (i.e., the most recent information available prior EV administration for the considered variable). The baseline period is therefore defined as the period prior to the index date during which the baseline data were recorded in the medical charts. <u>Collected data:</u> Data to collect will include: • Socio-demographic characteristics,

	• Risk factors and comorbidities, • Disease characteristics, • Previous treatment(s), • Laboratory results, • EV treatment and concomitant treatment(s), • Clinical outcomes, • Subsequent line(s) of treatment, • Pre-specified adverse events.
Country of study	France
Description of data sources	Data will be collected from the medical charts of participants treated in centers who took part in the French EV EAP between 8 July 2022 and 31 December 2022.
Description of target population	The target participant population will be adult patients with LA/mUC who received at least one dose of EV within the context of the French EAP between 8 July 2022 and 31 December 2022. At least 50 sites are expected to participate in the study and 206 participants are planned to be enrolled. Inclusion criteria • Male or female participant ≥18 years of age with LA/mUC at the time EV treatment was initiated. • Participant treated with at least one dose of EV between 8 July 2022 and 31 December 2022 as part of the French EAP. Exclusion criteria • Participant alive at study initiation who opposed to data collection for research purpose. • Participant who died before study initiation and who had opposed to data collection for research purpose prior to their death. • Participant who took part in an interventional clinical trial(s) evaluating EV during the study period.
Study Dates	This study is a secondary data use study. Data will be collected from the medical charts of patients who were treated with at least one dose of EV in the context of the French EAP between 8 July 2022 and 31 December 2022.
Study Lead or Contact	PPD Medical Affairs Astellas Pharma Europe, Ltd. PPD

Marketing Authorization Holder(s)

Marketing authorization holder(s)	Astellas Pharma Europe B.V. Sylviusweg 62 2333 BE Leiden The Netherlands
MAH contact person	PPD Medical Affairs Astellas Pharma Europe, Ltd.

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1 RESPONSIBLE PARTIES

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2 LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

Abbreviations	Description of Abbreviations
ADC	Antibody Drug Conjugate
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANSM	French National Security Agency of Medicines and Health Products (*Agence Nationale de Sécurité du Médicament et des Produits de Santé*)
BMI	Body Mass Index
CA	Competent Authority
CAP	Compassionate Access Program
CI	Confidence Interval
CNOM	French Medical Council (*Conseil National de l'Ordre des Médecins*)
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organization
CSA	Clinical Study Assistant
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DMP	Data Management Plan
EAP	Early Access Program
EAU	European Association of Urology
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicine Agency
EV	Enfortumab Vedotin
FDA	Food and Drug Administration
FGF3	Fibroblast Growth Factor 3
HAS	French National Authority for Health *(Haute Autorité de Santé)*
HbA1c	Glycated Haemoglobin
HDH	Health Data Hub
IEC	Independent Ethics Committee
LA/mUC	Locally Advanced or Metastatic Urothelial Cancer
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	Microtubule-disrupting agent Monomethyl Auristatin E
MR-004	Methodology of Reference #004
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-1	Programmed Death receptor-1
PD-L1	Programmed Death Ligand-1
PFS	Progression Free Survival
PR	Partial Response
PT	Preferred Term

Abbreviations	Description of Abbreviations
RNIPH	Research that does Not Involve the Human Person (Recherche N'Impliquant pas la Personne Humaine)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCAR	Serious Cutaneous Adverse Reactions
SD	Stable Disease
SJS	Stevens-Johnson Syndrome
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
TEN	Toxic Epidermal Necrolysis
TTD	Time to Treatment Discontinuation
TTNT	Time to Next Treatment
UC	Urothelial Cancer

Terms	Definition of terms
Adverse Drug Reaction (ADR)	An adverse drug reaction is any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.
Adverse Event (AE)	An adverse event is as any untoward medical occurrence in a participant administered a study drug and which does not necessarily have a causal relationship with this treatment.
Baseline data	Data recorded at the closest time prior to the index date (i.e., the most recent information available prior EV administration for the considered variable).
Baseline period	Period prior to the index date during which all required baseline data were recorded in the medical charts.
Disease Control Rate (DCR)	Proportion of participants who achieve stable disease, partial response, or complete response to therapy (see full definition in section 5.2.2.5).
Follow-up period	Period that includes all standard of care visits that occurred between the initial enfortumab vedotin administration visit and the participant's death, loss to follow-up, or up to 12 months after treatment initiation, whichever occurred first.
Index date	Date of first administration of enfortumab vedotin.
Objective Response Rate (ORR)	Proportion of participants who achieve partial or complete response to therapy (see full definition in section 5.2.2.4).
Overall Survival (OS)	Time (in month) between the first dose of enfortumab vedotin (index date) and the date of death from any cause (see full definition in section 5.2.1).
Progression Free Survival (PFS)	Time (in month) between the first dose of enfortumab vedotin (index date) and the date of progression or death from any cause (see full definition in section 5.2.2.1).
Study period	Period of time from initiation of data collection through to completion of study findings.
Time to Next Treatment (TTNT)	Time (in month) between the first dose of enfortumab vedotin (index date) to the start date of the subsequent line of systemic therapy (see full definition in section 5.2.2.3)
Time to Treatment Discontinuation (TTD)	Time (in month) between the first dose of enfortumab vedotin (index date) and the date of permanent treatment discontinuation for any reason, including disease progression, treatment toxicity, and death (see full definition in section 5.2.2.2).

3 AMENDMENTS AND UPDATES

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	08 Nov 2023
Original Protocol	17 Jul 2023

Amendment 1 [Nonsubstantial] [Date 08 Nov 2023]

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and EU Clinical Trial Regulation because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The primary reason for Amendment 1 was to add the objective: To describe the next line of treatment administered after EV in real-world clinical practice.

Minor errors in the Protocol were also corrected.

Summary of Changes

Nonsubstantial Changes

Section Number	Description of Change	Brief Rationale
Synopsis, section 5 Objectives and endpoints, section 6.4.9 Clinical outcomes.	New study objective: To describe subsequent line(s) of treatment administered after EV in real-world clinical practice. Addition of the study endpoints and corresponding variables to collect.	Objective added to describe treatment choice after EV administration.
Section 5 Objectives and endpoints, section 6.4 variables.	Minor corrections to definitions and calculations.	Alignment with definitions and calculations described in the statistical analysis plan.
Section 6.6.2.2.1 General Considerations.	Addition that subgroup analysis of interest may be performed.	Alignment with planned statistical analyses.
Section 7.2 Ethical Conduct of the Study.	Addition of the adherence to Good Pharmacoepidemiology Practices.	Minor clarification with no effect on the study.

4 RATIONALE, BACKGROUND, AND RESEARCH QUESTION

4.1 Rationale (why and how)

A compassionate access program (CAP) for enfortumab vedotin (EV) was opened in France in July 2021 for patients suffering from locally advanced or metastatic urothelial cancer (LA/mUC), who previously received a programmed death receptor-1 (PD-1) or a programmed death ligand-1 (PD-L1) inhibitor and a platinum-based chemotherapy. The CAP was opened because of the existing unmet need in this population and the decision was based on the results of the EV-301 trial (1). A total of 220 patients were registered in the program between July and 24 December 2021.

A pause to new enrollment in the CAP was enacted on 24 December 2021 at a request from the National Agency for the Safety of Medicines and Health Products (ANSM, L'Agence Nationale de Sécurité du Médicament et des Produits de Santé) pending the necessary investigations, following the occurrence of six serious cases of cutaneous toxicity, three of which were fatal. The CAP in France remained closed for new patient registration until the opening of the EV early access program (EAP) on 8 July 2022.

Astellas Pharma Europe B.V. was granted European Medicines Agency (EMA) marketing authorization approval for EV via the centralized procedure on 13 April 2022. As monotherapy, EV is indicated for the treatment of adult patients with LA/mUC who previously received a platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor. The EMA required the addition of risk minimization measures to ensure appropriate use of EV, including guidance for the management of patients, to minimize the risk of skin reactions. Therefore, all patients treated with EV systematically receive a patient card providing all information regarding Serious Cutaneous Adverse Reactions (SCAR), including a description of the signs and symptoms of skin reactions and instructions on how and when to seek medical care.

The French national authority for health (HAS, Haute Autorité de Santé) granted authorization of the EV EAP on 16 June 2022. It was initiated on 8 July 2022 (2). Patients eligible for the EAP are adult patients with LA/mUC who previously received platinum-based chemotherapy and a PD-1 or PD-L1 inhibitor. Patients are however not eligible if they have a hypersensitivity to the active substance or to any of the excipients of EV. All patients registered in the program receive a patient kit that is to say: a patient card and a patient leaflet. By 31 December 2022, 638 patients were approved in over 170 hospitals and cancer centers across France. This EAP offers Astellas an opportunity to conduct a real-world study, to complement clinical trial results by generating real-world evidence regarding the effectiveness, patients' baseline characteristics, use, and safety of EV in a wider patient population. The study results would help to have a better understanding of EV.

4.2 Background

Urothelial cancer is a neoplastic growth affecting the lining of the urinary tract, and is most commonly found in the bladder. Urothelial cancers account for 90% of bladder cancers (3). Based on the latest GLOBOCAN data, bladder cancer is the 10th most commonly diagnosed cancer worldwide, with approximately 573,000 new cases and 213,000 deaths in 2020 (4).

Incidence and mortality rates vary across countries due to differences in diagnostic practices, treatment availability, and risk factors (e.g., tobacco smoking, chronic urinary tract infection, occupational exposures, genetic predisposition, etc.) (3, 5). Globally, urothelial cancer occurs approximately 4 times more frequently in men than women and incidence rates, in both sexes, are highest in Europe and North America (5). In 80% of cases, bladder cancer is diagnosed in adults aged over 60, a population likely to have comorbidities impacting survival (5, 6).

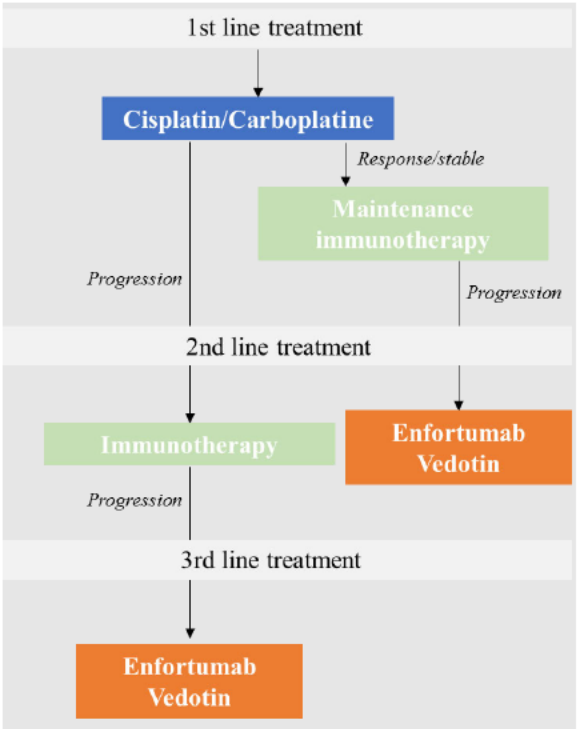
In France, according to the French National Institute of Cancer, in 2018, bladder cancer was the 5th most common cancer (13,074 new cases) and the 7th most common cause of cancer death (5,333 deaths) (7, 8). Its incidence is steadily rising by approximately 1% a year (8). Between 2015 and 2020, over 50,000 people were being treated for bladder cancer in France (9).

At diagnosis, 70%-75% of bladder cancer are detected in early stages (i.e., non-muscle invasive bladder cancer) allowing for complete resection and improved survival (96% five-year survival rate) (10, 11). Patients with locally advanced (i.e., muscle invasive cancer) or metastatic urothelial cancer, however, have a poor prognosis with a 5-year survival rate of approximately 36% and 6%, respectively (10, 11).

For the treatment of LA/mUC, the European Association of Urology (EAU) recommends platinum-based chemotherapy (e.g., cisplatin or carboplatin) as first line treatment (12). As an alternative, for cis-ineligible and carboplatin eligible patients but positive for PD-L1, immunotherapy can be administered instead (e.g., atezolizumab, pembrolizumab). When response or stable disease is observed with platinum-based therapy, a switch to maintenance immunotherapy (e.g., avelumab) is recommended. Otherwise, in case of progression, patients can receive a second-line regimen with immunotherapy (e.g., pembrolizumab, atezolizumab). If progression is observed in either pathway, later-line therapy can include: taxane-based chemotherapy (e.g., paclitaxel, docetaxel) with limited response (13), erdafitinib for the minority of patients with Fibroblast Growth Factor 3 (FGFR3) alteration (14), or EV.

EV is an antibody drug conjugate (ADC) directed against Nectin-4, an adhesion protein, highly expressed in urothelial carcinoma. EV is comprised of a fully human IgG1-kappa antibody conjugated to the microtubule-disrupting agent Monomethyl auristatin E (MMAE) via a protease-cleavable maleimidocaproyl valine-citrulline linker. The binding of the ADC to Nectin-4-expressing cells, followed by internalisation of the ADC-Nectin-4 complex and the release of MMAE via proteolytic cleavage, results in cell-cycle arrest and apoptosis. In France, EV is indicated for the treatment of adults with LA/mUC who previously received a PD-1 or PD-L1 inhibitor and a platinum-based chemotherapy (Figure 1).

Figure 1: Enfortumab vedotin in locally advanced or metastatic urothelial cancer



Regulatory approval of EV by the Food and Drug Administration (FDA) and the EMA was based on the results of the global, multicenter, open-label, randomized, phase 3 trial EV-301, which evaluated the efficacy of EV versus physician's choice of chemotherapy in 608 patients with LA/mUC, who were previously treated with a PD-1 or PD-L1 inhibitor and platinum-based therapy (NCT03474107) (1). The primary endpoint was overall survival (OS) and secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and the assessment of safety. Significant benefits were observed with EV compared to the chemotherapy arm (median OS, 12.88 vs 8.97 months; median PFS, 5.55 vs 3.71 months; confirmed ORR, 40.6% vs 17.9%). The most common adverse reactions were alopecia, peripheral neuropathy, skin reaction, and fatigue. Treatment-related hyperglycaemia was also more common with EV compared to chemotherapy (6.4% vs 0.3%).

Since its approval, EV is being investigated in combination strategies and in earlier disease settings (15). A retrospective chart review (the UNITE study) was also carried out in the United States (US) to assess the effectiveness of EV in the real world; it included 304 patients across 16 institutions (16). Results were consistent with clinical trial data (median OS, 14.4 months, median PFS, 6.8 months), and encouraging, when compared to real-world patient outcomes previously investigated in the US, prior EV approval, when patients were treated with taxanes or immunotherapies after failure of standard first- and second-line therapies (median OS, 7.6 months, median PFS, 2.9 months) (13). The UNITE study also reported that all populations of interest benefited from EV, including patients previously excluded from clinical trials due to comorbidities such as renal insufficiency, uncontrolled diabetes, or significant neuropathy.

Patients with pure urothelial histology had a higher ORR compared to patients whose tumors had a component of variant histology (58% vs 42%), and urothelial cancer originating in the upper urinary tract responded better than tumors located in the bladder (ORR, 61% vs 50%).

In France, no data analyses on EV are yet available outside of clinical trials.

4.3 Research Question

This study will describe real world effectiveness, patients' baseline characteristics, use, and safety of EV in patients treated in the context of EV EAP in France. Data will be collected from the medical charts of patients of the EV EAP who were treated with at least one dose of EV between 8 July 2022 and 31 December 2022.

5 OBJECTIVES AND ENDPOINTS

5.1 Study Objectives

5.1.1 Primary Objective

The primary objective of the study is to describe real-world effectiveness of EV based on OS.

5.1.2 Secondary Objectives

The secondary objectives of the study are:

- To describe real-world effectiveness of EV based on:
    - Progression free survival (PFS),
    - Time to treatment discontinuation (TTD),
    - Time to next treatment (TTNT),
    - Objective response rate (ORR),
    - Disease control rate (DCR).
- To describe baseline characteristics of participants who initiated treatment with EV in the real-world clinical practice.
- To describe real-world treatment patterns of EV.
- To describe the subsequent line(s) of treatment administered after EV in real-world clinical practice.
- To describe safety data related to the use of EV in the real-world by:
    - Describing proportions of participants with pre-specified adverse drug reactions (ADR) including ADR that led to dose reduction(s), temporary treatment interruption(s), permanent treatment discontinuation(s), and death.
    - Describing real-world ADR management when occurrence of Grade 2 or higher skin reaction.

5.2 Study Endpoints

5.2.1 Primary Endpoint – Overall Survival (OS)

The primary endpoint of this study is to describe real-world effectiveness of EV based on OS.

OS is defined as the time (in month) between the first dose of EV (index date) and the reported date of death from any cause.

Participants alive at the time of their last recorded follow-up visit will be censored at the date of their last follow-up visit (e.g., date of last contact when participant was lost to follow-up, or last date participant known to be alive at the end of study data collection period).

A sensitivity analysis will be performed to describe participant survival when cancer is the cause of death.

5.2.2 Secondary Endpoints

5.2.2.1 Progression Free Survival (PFS)

PFS is defined as the time (in month) between the first dose of EV (index date) and the date of progression or death from any cause.

Date of progression will be determined by the physician as per clinical judgment (based on clinical, laboratory, or radiological findings) as the date where tumor growth or worsening of the disease is observed. The date of the earliest source document reporting a progression event will be collected as date of progression.

Participants alive without disease progression at the time of their last recorded follow-up will be censored at the date of last follow-up (e.g., date of last contact when participant was lost to follow-up, or last date participant known to be alive at the end of study data collection period).

5.2.2.2 Time to Treatment Discontinuation (TTD)

TTD is defined as the time (in month) between the first dose of EV (index date) and the date of permanent treatment discontinuation for any reason, including disease progression, treatment toxicity, and death.

Participants alive who had not experienced treatment discontinuation during the study observation period will be censored at the date of last follow-up (e.g., date of last contact when participant was lost to follow-up, or last date participant known to be alive at the end of study data collection period).

5.2.2.3 Time to Next Treatment (TTNT)

TTNT is defined as the time (in month) between the first dose of EV (index data) and the start date of the subsequent line of systemic therapy.

Participants who did not initiate a next treatment during the study observation period will be censored at the date of last follow-up (e.g., date of last contact when participant was lost to follow-up, or last date participant known to be alive at the end of study data collection period) or at death.

5.2.2.4 Objective Response Rate (ORR)

ORR is defined as the proportion of participants who achieved a partial response (PR) or complete response (CR).

Responses will be determined by the physician as per clinical judgment (based on clinical, laboratory, or radiological findings). Responses will be based on the physician’s general impression of tumor reduction and not on predefined tumor size thresholds. No specific tumor measurements will be collected, and no central review will be performed.

5.2.2.5 Disease Control Rate (DCR)

DCR is defined as the proportion of participants who achieved stable disease (SD), PR, or CR.

Responses will be determined by the physician as per clinical judgment (based on clinical, laboratory, or radiological findings). Responses will be based on the physician's general impression of tumor reduction and not on predefined tumor size thresholds. No specific tumor measurements will be collected, and no central review will be performed.

5.2.2.6 Distribution of Participants' Baseline Characteristics

Socio-demographic characteristics:

- Age
    - Mean (SD) age (years) at start of EV treatment with age calculated as: (Year of initial EV dose) – (Year of birth).
    - Number and percentage of participants per age category (<65 years, 65 to <75 years, ≥ 75 years).
- Gender
    - Number and percentage of participants per gender.
- Body Mass Index (BMI)
    - Mean (SD) weight (kg) at study inclusion.
    - Mean (SD) height (m) at study inclusion.
    - Mean (SD) BMI at study inclusion with BMI calculated as: (weight)/(height)^2.
    - Number and percentage of participants per BMI category (<18.5 kg/m^2, 18.5 to <25 kg/m^2, 25 to < 30 kg/m^2, ≥30 kg/m^2).
- Treatment center
    - Number and percentage of participants per site.
    - Number and percentage of participants per treatment center type (e.g., university hospital, general hospital, private hospital, cancer center, clinic, other)
    - Number and percentage of participants treated per geographical location.
    - Number and percentage of participants per specialty of treating physician.

Risk factors and comorbidities:

- Risk factors
    - Number and percentage of participants per type of tobacco use (former user, current user, never used).

- Comorbidities
    - Number and percentage of participants with a history of diabetes.
    - Number and percentage of participants per type of diabetes (e.g., Type 1, Type 2).
    - Number and percentage of participants with a history of peripheral neuropathy.
    - Number and percentage of participants with at least one comorbidity. A comorbidity is defined as a distinct additional medical condition to LA/mUC.
    - Number and percentage of participants per comorbidity.

Disease characteristics:

- Eastern Cooperative Oncology Group Performance Status (ECOG-PS)
    - Number and percentage of participants per ECOG-PS category (0, 1, ≥2).
- Primary site of tumor
    - Number and percentage of participants per primary site of tumor (bladder, upper urinary tract, urethra, other).
- Histological type
    - Number and percentage of participants per histological type (pure urothelial type, variant type (micropapillary, nested, plasmacytoid), mixed type (urothelial with sarcomatoid /carcinosarcoma, neuroendocrine, adenocarcinoma), other).
- Tumor stage
    - Number and percentage of participants per tumor stage at initial urothelial cancer (UC) diagnosis (e.g., non-muscle-invasive, muscle invasive, locally advanced, metastatic).
    - Number and percentage of participants per tumor stage at LA/mUC diagnosis (locally advanced, metastatic).
    - Number and percentage of participants per tumor stage at EV treatment start (locally advanced, metastatic).
    - Mean (SD) time (month) between initial UC diagnosis and LA/mUC diagnosis calculated as: ((Date of initial UC diagnosis) – (Date of LA/mUC diagnosis) + 1)/30.4375
- Metastases
    - Number and percentage of participants at LA/mUC diagnosis per number of metastatic site (0, 1, 2, >2).
    - Number and percentage of participants with metastases per metastatic site location at LA/mUC diagnosis (lymph nodes, liver, lung, bone, other).

- Number and percentage of participants at EV treatment start per number of metastatic site (0, 1, 2, >2).
- Number and percentage of participants with metastases per metastatic site location at EV treatment start (lymph nodes, liver, lung, bone, other).

Previous treatments:

- Systemic therapy
  - Number and percentage of participants per number of prior lines of treatment (1, 2, ≥3 lines).
  - Number and percentage of participants per previous type of platinum-based chemotherapy (e.g., cisplatin, carboplatin, both).
  - Number and percentage of participants per stage of administration of each platinum-based chemotherapy administered (neoadjuvant, adjuvant, locally advanced, metastatic).
  - Number and percentage of participants per previous type of immunotherapy (e.g., atezolizumab, avelumab, durvalumab, nivolumab, pembrolizumab, other).
  - Number and percentage of participants per stage of administration of each immunotherapy administered (neoadjuvant, adjuvant, locally advanced, metastatic)
  - Number and percentage of participants per previous type of other therapies administered at the LA/mUC stage.
  - Mean (SD) duration of each previous lines of systemic treatment calculated as: ((End date of prior line) – (Start date of prior line) + 1)/30.4375.
  - Number and percentage of participants per best response among participants treated with checkpoint inhibitor (CPI) (CR, PR, SD, PD).

Laboratory results prior first EV treatment:

- Mean (SD) for each of the following laboratory parameter:
  - Glucose
  - Glycated haemoglobin (HbA1c)
  - Haemoglobin
  - Platelet count
  - Neutrophil count
  - Serum Creatinine
  - Creatinine clearance

- Lactate dehydrogenase (LDH)
- Albumin

5.2.2.7 Distribution of EV Treatment Patterns

Treatment initiation:

- Mean (SD) time (month) since initial LA/mUC cancer diagnosis calculated as: ((Date of initial EV administration) – (Date of initial LA/mUC diagnosis) + 1)/30.4375.
- Mean (SD) time (month) since previous systemic treatment calculated as: ((Date of initial EV administration) – (End date of previous systemic treatment) + 1)/ 30.4375.
- Number and percentage of participants who received EV according to the line of treatment in which EV was administered (2^{nd} line, 3^{rd} line, $>3^{rd}$ line).

Treatment received:

- Mean (SD) initial dose received.
- Mean cumulative dose received (i.e., total dose received) with cumulative dose received defined as the sum of all EV doses administered to the participant. and calculated as: ∑(dose administered (mg/kg) * number of doses administered at this dose * weight (kg))
- Mean overall EV treatment duration with treatment duration calculated as: ((Last date of exposure) – (First dose date) + 1)/30.4375.

Dose reduction:

Dose reduction is defined as a decrease in the quantity of EV administered as recommended in the summary of product characteristics (SmPC) of EV (Table 1 and Table 2) (17).

Table 1: Recommended dose reductions for adverse reactions

	Dose Level
Starting dose	1.25 mg/kg up to 125 mg
First dose reduction	1.0 mg/kg up to 100 mg
Second dose reduction	0.75 mg/kg up to 75 mg
Third dose reduction	0.5 mg/kg up to 50 mg

Source: Summary of Product Characteristics – Enfortumab Vedotin

Table 2: Dose interruption, reduction and discontinuation

Adverse reaction	Severity*	Dose modification
Skin reactions	Suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) or bullous lesions	Immediately withhold and refer to specialized care
	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3	Permanently discontinue.
	Grade 2 worsening Grade 2 with fever Grade 3	• Withhold until Grade ≤1 • Referral to specialized care should be considered • Resume at the same dose level or consider dose reduction by one dose level (see Table 1)
Hyperglycaemia	Blood glucose >13.9 mmol/L (>250 mg/dL)	• Withhold until elevated blood glucose has improved to ≤13.9 mmol/L (≤250 mg/dL) • Resume treatment at the same dose level
Peripheral neuropathy	Grade 2	• Withhold until Grade ≤1 • For first occurrence, resume treatment at the same dose level • For a recurrence, withhold until Grade ≤1 then, resume treatment reduced by one dose level (see Table 1)
	Grade ≥3	Permanently discontinue.

Source: Summary of Product Characteristics – Enfortumab Vedotin
*Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0) where Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe and Grade 4 is life-threatening

Dose reduction related endpoints are:

- Number and percentage of participants who had at least one dose reduction.
- Mean (SD) number of dose reduction per participant.

- Number and percentage of participants who had a dose reduction per number of dose reduction (1, 2, >2).
- Mean (SD) dose following dose reduction.
- Mean (SD) difference in dose between the initial and final dose administered during the follow-up period, if dose reduction occurred, calculated as (Initial dose administered) – (Final dose administered).
- Number and percentage of participants per reason for dose reduction (skin reaction, hyperglycaemia, peripheral neuropathy, other).

Temporary treatment interruption:

Temporary treatment interruption is defined as a discontinuation of the study treatment for any period of time, after which the treatment was resumed.

- Number and percentage of participants who had at least one temporary treatment interruption.
- Mean (SD) number of temporary treatment interruption(s) per participant.
- Number and percentage of participants who had a temporary treatment interruption per number of temporary treatment interruption (1, 2, >2).
- Mean (SD) duration of temporary treatment interruption with duration calculated as: sum of each temporary interruption period calculated as: ((End date of treatment interruption) – (Start date of treatment interruption) + 1)/30.4375.
- Number and percentage of participants per dose received (same dose, dose reduction) following temporary treatment interruption(s).
- Number and percentage of participants per reason for temporary treatment interruption (skin reaction, hyperglycaemia, peripheral neuropathy, other).

Permanent treatment discontinuation:

Permanent treatment discontinuation is defined as a definitive discontinuation of the study treatment.

- Number and percentage of participants who had a permanent treatment discontinuation.
- Number and percentage of participants per reason for permanent treatment discontinuation (withdrawal, lost to follow-up, death, tumor progression, skin reaction, hyperglycaemia, peripheral neuropathy, other).

Concomitant treatments:

Concomitant treatments are defined as medication, taken for the treatment of a comorbidity or adverse event, for which at least one dose was taken between the date of first and last EV dose (inclusive).

- Number and percentage of participants with at least one concomitant treatment.

5.2.2.8 Subsequent line(s) of treatment after EV

- Number and percentage of participants who had at least one subsequent line of treatment post EV.
- Number and percentage of participants per number of lines of subsequent treatment post EV.
- Number and percentage of participants per type of line of treatment post EV.

5.2.2.9 Safety data related to the use of EV in the real-world

Pre-specified ADR:

Table 3: List of pre-specified ADR

Grade ≥ 2	• Skin reaction • Peripheral neuropathy • Pneumonitis
Grade ≥ 3	• Fatigue • Decreased appetitive • Acute kidney injury • Pneumonia • Urinary tract infection • Cellulitis • Thrombocytopenia • Neutropenia
Any grade	• Hyperglycaemia • Neutropenic fever • ADR that led to dose reduction • ADR that led to temporary treatment interruption • ADR that led to permanent treatment discontinuation • ADR that led to death

Safety endpoints are:

- Number and percentage of participants with pre-specified ADR.
- Mean (SD) duration between start of EV treatment and onset of pre-specified ADR.
- In case of skin reactions:
    - Number and percentage of participants per type of skin reaction (e.g., alopecia, pruritus, rash, rash maculo-papular, dry skin, other).
    - Number and percentage of participant per grade of skin reaction.
    - Number and percentage of participants with a skin biopsy.
    - Number and percentage of participants with necrosis seen in skin biopsy.

- Mean (SD) duration between the onset of pre-specified ADR and the date of the first visit with dermatologist to whom the participant was referred to (if applicable).

5.3 Study Objectives and Endpoints

Study objectives are described in section 5.1 and study endpoints are described in section 5.2. Both are summarized in Table 4.

Table 4: Study objectives and endpoints

Objectives	***Endpoints***
Primary	
To describe real-world effectiveness of EV based on overall survival (OS).	OS, defined as the time (in month) between the first dose of EV (index date) and the date of death from any cause. A sensitivity analysis will be performed to describe participant survival when cancer is reported as the cause of death.
Secondary	
To describe real-world effectiveness of EV based on real world progression free survival (PFS).	PFS, defined as the time (in month) between the first dose of EV (index date) and the date of progression or death from any cause. Progression will be determined by the physician as per clinical judgment.
To describe real-world effectiveness of EV based on time to treatment discontinuation (TTD)	TTD, defined as the time (in month) between the first dose of EV (index date) and the date of permanent treatment discontinuation for any reason, including disease progression, treatment toxicity, and death.
To describe real-world effectiveness of EV based on time to next treatment (TTNT)	TTNT, defined as the time (in month) between the first dose of EV (index date) and the start date of the subsequent line of systemic therapy.
To describe real-world effectiveness of EV based on objective response rate (ORR).	ORR, defined as the proportion of participants who achieved a partial or complete response to therapy. Response will be determined by the physician as per clinical judgment.
To describe real-world effectiveness of EV based on disease control rate (DCR).	DCR, defined as the proportion of participants who achieved stable disease, partial response, or complete response to therapy. Response will be determined by the physician as per clinical judgment.
To describe baseline characteristics of participants who initiated treatment with EV in the real-world clinical practice.	Distribution of participants' baseline characteristics including: • Socio-demographic characteristics: o Age, o Gender, o Body Mass Index (BMI), o Treatment center type and location and treating physician specialty. • Risk factors and comorbidities: o Tobacco use, o History of diabetes, o History of peripheral neuropathy, o Comorbidities.

	• Disease characteristics:
	  ○ Eastern Cooperative Oncology Group Performance Status (ECOG-PS),
	  ○ Primary site of tumor,
	  ○ Histological type,
	  ○ Tumor stage at diagnosis and at start of EV treatment,
	  ○ Metastatic site(s) at diagnosis and start of EV treatment.
	• Previous treatment(s):
	  ○ Number of prior treatments, their type and duration,
	  ○ Best response on previous checkpoint inhibitor treatment.
	• Laboratory results prior first EV treatment.

To describe real-world treatment patterns of EV.	Distribution of treatment patterns of EV including:
	• Treatment initiation:
	  ○ Time since diagnosis,
	  ○ Time since previous systemic treatment,
	  ○ Line of treatment.
	• Treatment received:
	  ○ Initial dose received,
	  ○ Cumulative dose received,
	  ○ Treatment duration.
	• Dose reduction(s):
	  ○ Number of dose reduction(s),
	  ○ New dose received when dose reduction(s),
	  ○ Reason for dose reduction(s).
	• Temporary treatment interruption(s):
	  ○ Number and duration of temporary interruption(s),
	  ○ Dose received following temporary interruption(s) (same dose vs dose reduction),
	  ○ Reason for temporary treatment interruption(s).
	• Reason for permanent treatment discontinuation.
	• Concomitant treatments.

To describe the subsequent line(s) of treatment administered after EV in real-world clinical practice.	• Number and type of subsequent line(s) of treatment administered post EV.
To describe safety data related to the use of EV in the real-world by:	• Proportion of participants with pre-specified ADR (Table 3). • Time of onset of pre-specified ADR. • Management of Grade 2 or higher skin reaction:

• Describing proportions of participants with pre-specified ADR including ADR that led to dose reduction(s), temporary treatment reduction(s), permanent treatment discontinuation(s), and death. • Describing real-world ADR management when occurrence of Grade 2 or higher skin reaction.	○ Type and grade, ○ Biopsy and presence of necrosis, ○ Time to dermatologist visit (if applicable). If a pre-specified ADR recurs, information related to all instances of this ADR will be captured.

5.4 Estimands

Estimands are described for:

- <u>The key primary objective:</u>

  To describe real-world effectiveness of EV based on OS.

The estimand is described by the following attributes:

- <u>Target population:</u>

  The target participant population will be adult patients with LA/mUC who received at least one dose of EV within the context of the French EAP between 8 July 2022 and 31 December 2022.

- <u>Outcome measurement:</u>

  OS defined as the time (in month) between the first dose of EV (index date) and the reported date of death from any cause.

- <u>Intercurrent events:</u>
  - Patients may have switched treatment during follow-up. As the study uses retrospective data from routine clinical practice, this may occur at any point during follow-up. In this study, switching will be considered as a random ignorable event.
  - Loss to follow-up, end of study period and the 365th day of follow-up are considered censoring events. Participants alive at the time of their last recorded follow-up visit will be censored at the date of their last follow-up visit (e.g., date of last contact when participant was lost to follow-up, or last date participant known to be alive at the end of study data collection period).
- <u>Population-based summary:</u>

  Cumulative incidence of deaths expressed as a probability of death at 365 days.

6 RESEARCH METHODS

6.1 Study Design

This study is multicenter, retrospective, non-interventional study conducted in France that does not involve the human person as defined in the French legislation (RNIPH, recherche n'impliquant pas la personne humaine). Study data will be collected from the medical charts of participants who received at least one dose of EV in the context of the French EV EAP between 8 July 2022 and 31 December 2022.

Only participants meeting the eligibility criteria will be considered for inclusion. Participants still alive at study initiation will be informed of the study and provided with a patient information and non-opposition note during a visit scheduled as part of patient usual care, if possible. They will be given time (2 weeks) to decide if they wish to oppose the collection of their data. Data of participants who died before study initiation will only be collected if the participants had not opposed to the collection of their data for research purposes before their death.

Collected data will exclusively be data found in medical charts and previously recorded during routine clinical visits. No extra visit, exam, or intervention are required for the study.

Data collection will be performed on site by clinical research associates (CRA) from the clinical research organization (CRO) managing the study or by clinical study assistants (CSA) from the site. The CRA/CSAs will report the required data in the study specific electronic case report form (eCRF) under the supervision of the physician, who will electronically sign the eCRF.

The study will be considered to have started on the first day of data collection and to have ended on the last day of data collection.

6.1.1 Study Schematic

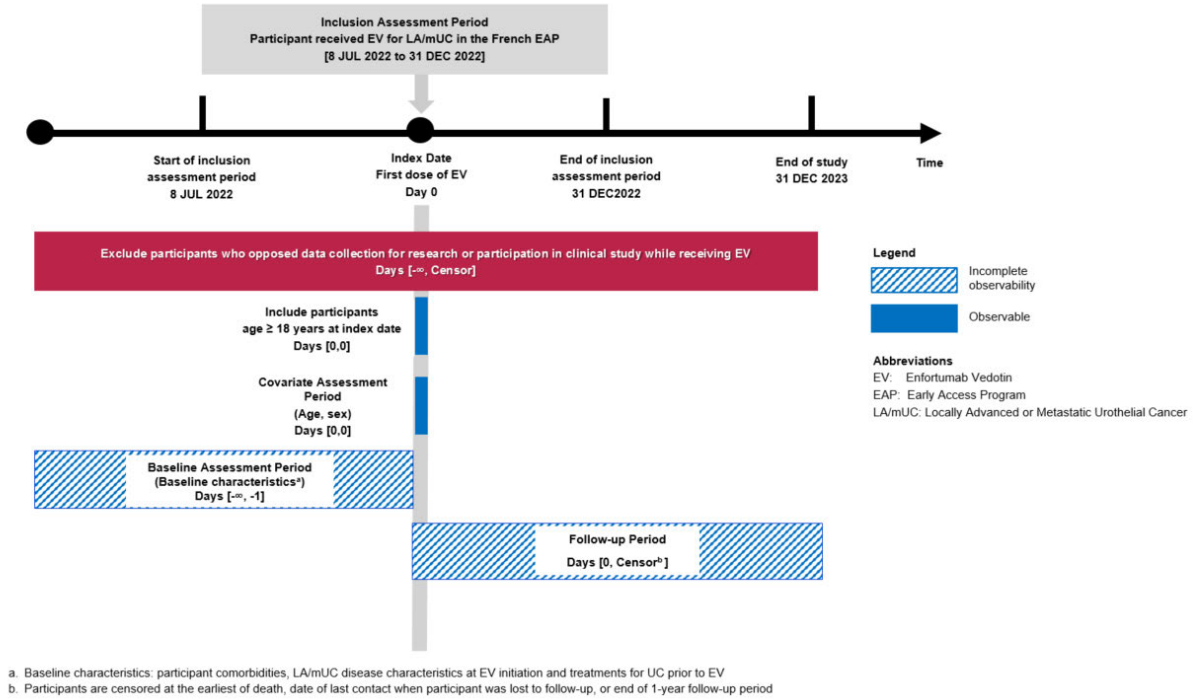
For a given participant, the data to collect will include data from the baseline period until the participant's death, loss to follow up, or up to 12 months after treatment initiation, whichever occurred first (Figure 2).

The following definitions will be used:

- The index date is the date of first administration of EV.
- Baseline data are the data recorded at the closest time prior to the index date (i.e., at the most recent information available prior EV administration for the considered variable).
- The baseline period is the period prior to the index date, during which all required baseline data were recorded in the medical charts.
- The follow-up period includes all standard of care visits that occurred between the initial EV administration visit and the participant's death, loss to follow up, or up to 12 months after treatment initiation, whichever occurred first.

As this is a retrospective study that does not involve human person, no specific withdrawal criteria are specified.

Figure 2: Study design



6.2 Data Sources

Participant data will be collected from their medical charts (e.g., original files, hospital reports, laboratory tests reports, various correspondence, etc.). Data will be entered into the eCRF using an electronic data capture (EDC) system via an internet browser interface.

Participants will be identified by a unique number (pseudonymized).

Sites will be trained to the use of the EDC system. Data will be recorded by CRAs from the CRO or the sites' CSA under the responsibility of participating physicians.

All original source documents, from which the information reported in the eCRF will be obtained, must be kept up-to-date and readily available. By signing the eCRF, the participating physician will confirm the accuracy, completeness, legibility, and timeliness of the data reported.

The quality control of the collected data is described in section 6.7.

6.3 Study Population

Only participants who meet all the inclusion criteria and none of the exclusion criteria can be included in the study.

6.3.1 Inclusion Criteria

1. Male or female participant ≥18 years of age with LA/mUC at the time EV treatment was initiated.
2. Participant treated with at least one dose of EV between 8 July 2022 and 31 December 2022 as part of the French EAP.

6.3.2 Exclusion Criteria

1. Participant alive at study initiation who opposed to data collection for research purpose.
2. Participant who died before study initiation and who had opposed to data collection for research purpose prior to their death.
3. Participant who took part in an interventional clinical trial(s) evaluating EV during the study period.

6.3.3 Participant Selection

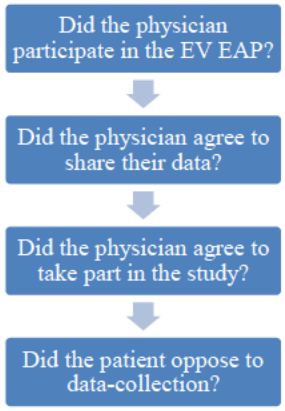
Participants will be selected from centers who treated patients with EV between 8 July 2022 and 31 December 2022 in the context of the French EAP (Figure 3).

All physicians who took part in the French EV EAP during the period of interest and who agreed to share their information will be invited to take part in the study. As there is a low number of patients treated by physicians at each site within the required dates of EV treatment for eligibility into the study, it is estimated that physicians from at least 50 sites will need to participate in the study to reach the required population sample size (see sample size calculation in section 6.6.1), within the given timelines. Entering patients from a wider number of sites will however reduce selection bias.

The CRO will contact considered physicians by email, mail and/or phone call and will invite them to participate in the study. Physicians who agree to participate (voluntary participation) can then be contracted and initiated by the CRO.

As the participation of physicians is voluntary, an *a posteriori* assessment of the location and type of sites where the physicians are based (e.g., private or public) will be performed and put in perspective with data collected from sites where are based the physicians who refused to participate. Its potential impact will be discussed in the study results.

Figure 3: Participant selection process



Abbreviations: EAP=early access program; EV= enfortumab vedotin.

6.4 Variables

6.4.1 Study Flowchart for Data Collection

Table 5: Study Flowchart for retrospective data collection in the eCRF

	First data collection	Standard of care visit(s)[d]
Inclusion/Exclusion criteria	X	
Information and non-opposition note [a]	X	
Site characteristics		
• Type	X	
• Location	X	
• Treating physician specialty	X	
Socio-demographic characteristics		
• Year of birth	X	
• Gender	X	
• Height/Weight	X	
Risk factors and comorbidities		
• Tobacco use	X	
• History of diabetes, or peripheral neuropathy	X	
• Comorbidities	X	
Disease characteristics at diagnosis		
• Date of initial UC and LA/mUC diagnosis	X	
• Primary site of tumor	X	
• Histological type at initial LA/mUC diagnosis	X	
• Tumor stage at initial UC and LA/mUC diagnosis	X	

	First data collection	Standard of care visit(s)[d]
• Number and site(s) of metastases at LA/mUC diagnosis (if applicable)	X	
Disease characteristics at study inclusion		
• ECOG-PS	X	
• Tumor stage at start of EV treatment (locally advanced vs metastatic)	X	
• Number and site(s) of metastases (if applicable)	X	
Previous treatment		
• Type, start, and end dates of prior lines of treatment	X	
• Best response among patients who previously received CPI therapy	X	
Laboratory data		
• Laboratory results prior EV treatment [b]	X	
Enfortumab vedotin treatment		
• Dates and doses of EV administrations (initial and final)	X	X
• Number of dose(s) administered		X
• Dose reduction (number, date, reason, new dose)		X
• Temporary treatment interruption (number, start and end date, reason, subsequent dose)		X
• Permanent treatment discontinuation (date and reason)		X
• Concomitant treatment(s)	X	X
Clinical outcomes		
• Patient vital status		X
• Tumor response		X
• Subsequent line(s) of treatment		X
Pre-specified adverse drug reactions[c]		
• Pre-specified ADRs occurring during EV treatment (type, grade, date of onset)		X
• Specific data when skin reaction (type, biopsy, presence of necrosis, visit by dermatologist)		X

CPI = Checkpoint Inhibitor; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; EV = Enfortumab Vedotin; LA/mUC = Locally Advanced or Metastatic Urothelial Cancer.
[a] Only for patients still alive at the time of study initiation.

[b] Results of the following laboratory tests performed prior the first dose of EV will be collected if available: glucose, glycated haemoglobin, haemoglobin, platelets, neutrophils, creatinine, lactate dehydrogenase (LDH), and albumin
[c] Pre-specified ADR are: Grade ≥ 2 skin reactions, peripheral neuropathy and pneumonitis ; Grade≥ 3 fatigue, decreased appetite, acute kidney injury, pneumonia, urinary tract infection, cellulitis, thrombocytopenia, neutropenia ; hyperglycaemia, neutropenia of any grade ; any ADRs that led to dose reduction, temporary treatment interruption, permanent treatment discontinuation, or death.
[d] All follow-up visits performed as per standard of care, when required data was recorded in the medical charts, from the baseline period until the patient's death, loss to follow up, or up to 12 months after treatment initiation, whichever occurred first.

6.4.2 Participant Disposition

Data to collect prior study inclusion:

- Inclusion and exclusion criteria check
- Information and non-opposition note check

6.4.3 Socio-demographic Characteristics

Data to collect from baseline period:

- Year of birth
- Gender (female/male)
- Height (in meter)
- Weight (in kilogram)

6.4.4 Risk Factors and Comorbidities

Data to collect from baseline period:

- Tobacco use (e.g., former user, current user, never used)
- History of diabetes (yes/no)
    - If yes, type of diabetes (e.g., Type 1, Type 2)
- History of peripheral neuropathy (yes/no)
- Other comorbidities:
    - Myocardial infarction (yes/no)
    - Congestive heart failure (yes/no)
    - Peripheral vascular disease (yes/no)
    - Cerebrovascular disease (yes/no)
    - Dementia (yes/no)
    - Chronic pulmonary disease (yes/no)

- Rheumatic disease (yes/no)
- Peptic ulcer disease (yes/no)
- Mild liver disease (yes/no)
- Moderate or severe liver disease (yes/no)
- Hemiplegia or paraplegia (yes/no)
- Renal disease (yes/no)
- Other malignancies, solid tumor (yes/no)
    - If yes:
        - Type of solid tumor
        - Presence of metastases (yes/no)
- Other malignancies, leukemia (yes/no)
- Other malignancies, lymphoma (yes/no)
- AIDS (yes/no)

6.4.5 Disease Characteristics

Data to collect from baseline period:

- ECOG-PS (0/1/2/3/4)
- Date of initial UC diagnosis (month/year)
- Date of initial LA/mUC diagnosis (month/year)
- Primary site of tumor (e.g., bladder, upper urinary tract, urethra, other)
- Histological type at initial LA/mUC diagnosis (e.g., pure urothelial, micropapillary, nested, plasmacytoid, urothelial + sarcomatoid/carcinosarcoma, urothelial + neuroendocrine, urothelial + adenocarcinoma, other)
- Tumor stage at initial UC diagnosis (e.g., non-muscle invasive/muscle invasive/locally advanced/metastatic)
- Tumor stage at initial LA/mUC diagnosis (locally advanced/metastatic)
- Tumor stage at start of EV treatment (locally advanced/metastatic)
- Metastases at initial LA/mUC diagnosis (if applicable):
    - Number of metastatic sites (1/2/>2)
    - Sites (e.g., lymph nodes, liver, lung, bone, other)
- Metastases at start of EV treatment (if applicable):

- Number of metastatic sites (1/2/>2)
- Sites (e.g., lymph nodes, liver, lung, bone, other)

6.4.6 Previous Systemic Treatment

Data to collect from baseline period:

- Type of prior systemic treatment (e.g., platinum-based chemotherapy, immunotherapy, other)
- Type of prior platinum-based chemotherapy administered in neoadjuvant, adjuvant, locally advanced or metastatic setting (e.g., cisplatin, carboplatin, both)
- Stage of administration of the last platinum-based chemotherapy administered (e.g., neoadjuvant, adjuvant, locally advanced, metastatic)
- Type of prior immunotherapy administered in neoadjuvant, adjuvant, locally advanced or metastatic setting (e.g., atezolizumab, avelumab, durvalumab, nivolumab, pembrolizumab, other).
- Stage of administration of the last immunotherapy administered (e.g., neoadjuvant, adjuvant, locally advanced, metastatic)
- For each prior treatment, start date(s) and end date(s) (month/year)
- Best response among participants who previously received CPI therapy (CR/PR/SD/PD/Unknown)

6.4.7 Laboratory Results

Data to collect from baseline period:

- Glucose
- HbA1c
- Haemoglobin
- Platelet count
- Neutrophil count
- Serum Creatinine
- Creatinine clearance
- LDH
- Albumin

6.4.8 EV Treatment and Concomitant Treatment(s)

Data to collect from baseline period:

- Initial EV administration:
    - Initial dose
    - Date of initial dose (day/month/year)

Data to collect from follow-up period:

- Number of doses administered at initial dose (n)
- Dose reduction (yes/no)
    - For each dose reduction:
        - Reason for dose reduction (s) (e.g., skin reaction, hyperglycaemia, peripheral neuropathy, other)
        - Start date of new dose (day/month/year)
        - New dose
        - Number of doses administered at new dose (n)
- Temporary treatment interruption (yes/no)
    - For each treatment interruption,
        - Reason for temporary treatment interruption(s) (e.g., skin reaction, hyperglycaemia, peripheral neuropathy, other)
        - Start date of treatment interruption (day/month/year)
        - End date of treatment interruption (day/month/year)
        - Dose following treatment interruption (same dose/dose reduction)
- Final EV administration recorded:
    - Final dose administered
    - Date of final dose recorded (day/month/year)
    - Permanent treatment discontinuation (yes/no)
    - If yes,
        - Reason for permanent treatment discontinuation (withdrawal, lost to follow-up, death, tumor progression, skin reaction, hyperglycaemia, peripheral neuropathy, other)

Data to collect from baseline and follow-up period:

- Concomitant treatment(s) (yes/no)
    - If yes, name(s) (international nonproprietary name), indication, start date(s), end date(s) (day/month/year)

6.4.9 Clinical Outcomes

Data to collect from follow-up period:

- Participant vital status at end of data collection period (e.g., alive, dead, lost to follow-up)
    - If dead:
        - Date of death (day/month/year)
        - Cause of death (tumor related/treatment related/other)
    - If alive or lost to follow-up:
        - Date of last contact (day/month/year)
- Tumor response during data collection period:
    - Best overall response (CR/PR/SD/PD/Unknown)
        - Date of best overall response (day/month/year)
    - Tumor progression (yes/no)
        - If yes, date of first progression (day/month/year)
- New line(s) of systemic treatment initiated after EV (yes/no)
    - If yes:
        - Number of new lines of systemic treatment initiated after EV
        - Type and line number of each new line of systemic treatment initiated after EV
        - Date of treatment initiation of the first new treatment initiated after EV (day/month/year)

6.4.10 Pre-specified Adverse Drug Reactions

Data to collect from follow-up period:

- Pre-specified ADR(s) occurring during EV treatment for LA/mUC (yes/no)
    - If yes:
        - Type of ADR from the list of pre-specified ADR

        - Grade
        - Date of onset (day/month/year)
        - End date (day/month/year)
        - Previous occurrence of ADR prior to initiation of EV treatment
- Additional data to collected for each case of skin reaction:
    - Type (e.g., alopecia, pruritus, rash, rash maculo-papular, dry skin)
    - Biopsy (yes/no)
        - If yes, presence of necrosis (yes/no)
    - Referral made to dermatologist (yes/no)
        - If yes, date of the first visit made by dermatologist

6.4.11 Site Characteristics

To assess *a posteriori* a potential selection bias of the participating physicians, the following data will be collected from all physicians contacted during the selection process.

- Institution type (e.g., private, public)
- Geographical location (according to the 13 French regions)
- Medical specialty of treating physician

In addition, for active sites only, the following information will also be collected:

- Type of center (e.g., university hospital, general hospital, private hospital, cancer center, clinic, other)

6.5 Data Management

Data management will be performed in accordance with the standard operating procedures (SOPs) of the CRO and will adhere to the minimum standards of Astellas.

At study initiation, the data manager will transpose all data management steps to be carried out and the applicable procedures into a Data Management Plan (DMP). The DMP will detail the data management system, stakeholders, applicable procedures, data flow, organisation of data collection, and coding methods.

An electronic database specific to the study will be developed. Its characteristics will be described in an annotated case report form (CRF) and dictionary of variables. These documents will be validated prior to the development of the data entry tool.

Input masks will be developed and validated before they are put into production.

Procedures for checking the reliability and validity of the entered data will also be defined (e.g., training, creation of input guide, double entry, reconciliation, quality control).

Medical history will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medications will be coded using World Health Organization drug dictionary (latest version available).

Data review meetings will be held to discuss tables, listings, and graphs representing the content of the database. The strategy of how to take into account missing data, outliers, etc. will be decided in agreement with Astellas. The set of deviations from the protocol will also be described, particularly the list of participants wrongly included. If it becomes necessary to define different participant populations for analysis, these populations will be described. All the decisions taken during this data review, prior to the analysis, will be recorded in a specific report kept in the study file.

Once this report is approved, the study database will be locked and sent to the statistician for analysis.

6.6 Statistical Methods

No hypothesis will be tested in this study as it is a descriptive, non-interventional, retrospective study.

6.6.1 Sample Size Justification

As the primary objective of this study is to describe OS, sample size has been computed to provide adequate precision for the survival rates (S(t)), the Kaplan Meier estimators and especially the survival medians.

The two-sided 95% confidence interval (95%CI) for S(t) is as followed:

$$\text{IC (1-}\alpha\text{)} = \hat{S}(t) \pm z_{\alpha/2} \times \sqrt{Var\,(\hat{S}(t))}$$

Where:

- $z_{\alpha/2}$, is the 97.5% percentile of the normal distribution for α=5%
- $Var\,(\hat{S}(t))$ is the variance of S(t)

An estimate of $Var\,(\hat{S}(t)$ is provided by the Greenwood formula as follows:

$$\widehat{Var}\,[\hat{S}(t)] = [\hat{S}(t)]^2 \sum_{j:t_j \le t} \frac{d_j}{n_j(n_j - d_j)}$$

With tj the event time points, dj the number of events at these time points and nj the number of participants still at risk at these time points.

Assuming the absence of right-censored data before the median time and only one event

occurrence by event time points, the Greenwood formula can be simplified for the survival median as follows:

$$\widehat{Var}\,[\hat{S}(t)] = \frac{0.5^2}{n}$$

The number of required assessable participants to estimate the survival median according to the desired precision using a two-sided 95%CI can be calculated as follows:

$$n = \frac{0{,}5^2}{e^2} \times \left(z_{\alpha/2}\right)^2$$

Where e is the desired absolute accuracy, i.e. the half-length of the 95%CI.

Table 6 shows that 196 assessable participants are required to allow the survival median to be estimated with a precision of 7.0 %. Assuming that up to 5 % of included participants will not be evaluable for the primary analysis, 206 participants will have to be recruited.

Table 6: Sample size required to estimate the survival medians with a desired precision

Precision (e)	0.1	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02
Number of assessable participants required	96	119	150	196	267	385	601	1068	2401

6.6.2 Statistical Analysis

Data analysis will be performed by the CRO in accordance with their SOPs for statistics and clinical programming.

6.6.2.1 Analysis Set

The analysis population will be made up of all the participants included in the study and meeting the inclusion and exclusion criteria. The final composition of the analysis population will be determined after the data review meeting.

6.6.2.2 Statistical Methodology

A Statistical Analysis Plan (SAP) will be drafted by the CRO's statistician and will be finalized before the database lock.

Statistical analyses will be performed using SAS® software (version 9.4 or later – SAS Institute, North Carolina, USA).

6.6.2.2.1 General Considerations

All analyses will be descriptive. No comparison will be performed.

Depending on the nature of the analyzed variables, the descriptive statistics will be:

- Continuous: the variables will be described by the following summary statistics: sample size (number of available answers and missing values), mean, standard deviation, median, 1st and 3rd quartiles (Q1 and Q3), minimum and maximum observed values. If relevant, Wald 95% CI will be presented.
- Categorical: the variables will be described by the sample size (number of available answers and missing values), the frequency and percentage per modality. The number of missing values will not be taken into account into percentage calculation. If relevant, Agresti-Coull 95%CI of the proportion will be presented.

The proportion of missing values is expected to be low and randomly distributed. Hence no imputation procedure of missing data will be applied.

All time-to-event variables (e.g., OS, PFS) will be analysed using Kaplan Meier product-limit survival curve. The median time to event with 2-sided 95% CI will be estimated and graphics will be provided.

Sub-group analysis of interest, described in the SAP will be performed if permitted by number of participants.

6.6.2.2.2 Endpoint Analysis

All analyses will be descriptive (i.e., all the endpoints listed in section 5.2 will be analyzed as described in section 6.6.2.2.1)

6.6.2.2.3 Safety Analysis

Safety analysis will be performed on all treated subjects (i.e. analysis population).

The verbatim terms used in the eCRF by participating physicians to identify ADR will be coded using MedDRA and will be classified by MedDRA Preferred Term (PT) and System Organ Class (SOC).

Descriptive statistics for the number and percentage of participants with dose reductions, temporary treatment interruptions, and treatment discontinuation(s) following the occurrence of a pre-specified ADR during treatment with EV will be reported as part of the descriptive analysis. Confidence intervals (95% CI) will be provided as appropriate, using the Clopper-Pearson method.

6.6.2.2.4 Sites Characteristics

Actives sites will be those who included at least one subject in the study.

The characteristics of sites (location, type, treating physician specialty) and the number of participants included per site will be described. The representativeness of the active sites will be verified a posteriori by comparing the data of the sites involved in the study with data from non-participating sites.

6.6.2.2.5 Interim Analysis

No interim analysis is planned in this study.

6.7 Quality Control

Data quality, integrity, accuracy, and legibility will be ensured at different steps during the study:

- The protocol and study related procedures will be introduced and explained to the participating physician during an initiation phone call.
- Data will be recorded by CRAs from the CRO or the sites CSAs under the responsibility of participating physicians.
- During the study, site visits for quality control will be performed.
- The quality of collected data will also be ensured via coherence controls and the sending of potential queries to participating physicians. There will also be regular phone calls with the sites to follow up on pending activities such as query answers.

In any case, the participating physician and his/her collaborators commit to cooperating with Astellas or the CRO personnel to resolve any problems, corrections, or possible misunderstandings concerning the findings detected in the course of the study.

6.8 Strengths and Limitations of the Research Methods

The design of this study was carried out in order to limit the major usual biases for this type of study. However, as any observational research this study is subject to risks of bias.

6.8.1 Limitations

Generalizability of results:

As data are collected from a large selection of sites among those who treated patients with EV in the context of the French EAP between 8 July 2022 and 31 December 2022, this will limit selection bias. Results will therefore provide a good insight on real-world data and outcomes related to EV users during the study period outside the context of an interventional study. The representativeness of the active sites will be verified by the description of site characteristics. The description of this subset of participants followed in France will be of scientific value due to the novelty of the results.

Information bias:

Participants included in the study were followed by different physicians; effectiveness and safety assessments may have not been uniform. In addition, study data will be collected retrospectively, and it is expected that information issued from various source documents (i.e., medical file, including laboratory and imaging results) will be recorded differently by the physicians. This may possibly lead to an information bias. This bias is inherent to the usual

physician practice and such study design and cannot be avoided. Nonetheless every effort will be made to collect high quality data.

Missing data and attrition bias:

Due to the observational and retrospective nature of the study, missing data and attrition/loss-to follow-up are expected. Indeed, not all required data may be recorded in the charts and a limited number of patients may be followed by other centers. This limitation should be considered when interpreting results. The DMP and the overall study follow-up will aim to limit missing data.

6.8.2 Strengths

Despite the limitations described in section 6.8.1, a retrospective observational chart review provides the following strengths:

- Chart review studies provide access to the purest and most complete real-life data on patient care, disease management, and treatment pathway, and can also identify unmet needs. Expected data gaps are likely to be small in key data fields required for the main endpoints.
- Chart reviews detail past and recent clinical practice and can outline latest standard of care in a real-life setting, unlike randomized clinical trials, which reflect only a narrow proportion of a study population.
- Participant personal data can be anonymised/coded at source for capture to reduce the risk of directly identifiable information exposure. After completion of all data verification activities, participant data can be fully anonymised for analysis and storage purposes. This ensures compliance with regulatory requirements and makes data access faster and safer.

The impact of the study limitations are expected to be small. While data gaps inevitably occur when sourcing real-life data, the key data required for the primary and secondary outcome measures will be routinely recorded in clinical practice. Although there may be some discrepancy between sites in relation to recording information, the CRO teams entering the data under the sites' responsibility will apply similar assumptions to the data and will be trained to question and validate any inconsistencies on a case-by-case basis.

7 PROTECTION OF PARTICIPANTS

This study will be conducted in compliance with national and European Union requirements to ensure the participants rights in non-interventional studies.

7.1 Independent Ethics Committee (IEC)/Competent Authorities (CA)

This study is a retrospective observational study that does not involve the human person as defined in the French legislation. Therefore, no submission to the opinion of an Ethic Committee (IEC) or authorisation from the French Competent Authority (CA), the French National Security Agency of Medicines and Health Products (ANSM), is required.

For this type of study, only a registration on the Health Data Hub (HDH) is required. This protocol is also subject to a compliance commitment to the Reference Methodology MR-004.

7.2 Ethical Conduct of the Study

This study will be conducted in compliance with all applicable requirements in France for ensuring the rights of participants in non-interventional studies (article L1122-1-1 of the French Public Health code). The study will also be conducted in compliance with national and European Union requirements for ensuring the rights of participants in non-interventional studies.

This study will be conducted in adherence with the ethical principles stated in the Declaration of Helsinki amended version, Fortaleza, Brazil, October 2013, according to the ethics recommendations and Good Epidemiologic Practices French version 2007 as well as the Good Pharmacoepidemiology Practices version 2015 and subsequent versions, as required, and applicable regulations. Each personal member involved in the study will have the necessary qualifications (education, training, and experience) to perform the task(s) entrusted to him/her.

In accordance with the French legislation regarding studies not falling into the scope of interventional researches involving human persons, insurance is not required for this study.

7.3 Participant Information and Consent

The data collection in this study is based on pre-existing registers and/or pre-existing data sources from representative patient populations and involves the secondary use of existing data, routinely collected in standard treatment and other processes. The Sponsor and/or any service provider working with the Sponsor for this study will receive only pseudonymized data and as a result the Sponsor does not receive access to directly identifying patient-level data at any time of the study. As described in section 7.4, CRAs will however have access to source data for data collection and monitoring purposes.

An information and non-opposition note will be given to each patient by the participating physician in order to inform them of the purpose of the processing, the collected data, the nature of data transmitted, the recipients of data and of their right of access, rectification, limitation, restriction of processing or to object to processing as well as their right to refuse the

transmission of their data. Once informed, time shall be given (2 weeks) to each patient to think about their participation as to whether s/he agrees to participate in the study or not.

If a patient died prior study start, the patient will be included in the study only if there is no written opposition from the patient known by the physician who treated them.

7.4 Participant Confidentiality

During this secondary use study, all applicable data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing participant's data.

The Sponsor maintains confidentiality standards by ensuring that the Sponsor does not receive from those pre-existing registers and/or pre-existing data sources names or other directly identifying personal information of participants in any CRF or other documents submitted to the Sponsor (unless this is required by law for reporting of adverse events). This is achieved by using at inclusion codes or other random identification numbers to serve as the participant's identifiers in the study, as well in the study database retained by the Sponsor.

In some cases, a service provider may get access to study participants' data but only within the controlled environment of the data source and/or the register concerned and always in conformity with all security and standard operating procedures of the data owner. However, the Sponsor will not receive access to patient-level data. Only aggregated results will be presented to the Sponsor.

The Sponsor will use the data collected in order to run the study and to use and publish the results of the study. However, all study reports will contain aggregate data only and will not identify any individual participants.

The participating physician should ensure that personal data of participants, including their identity and medical information are kept confidential at all times. Participants' names will not be transmitted. Only the site number and the participant number will appear on CRFs. Participants' data will be collected in accordance with European Regulation 2016-679 of 27 April 2016 (General Data Protection Regulation) and the French Law 78-17 of 6 January 1978 on information technology, data files and civil liberties amended.

Personal medical information may be reviewed for the purpose of verifying data recorded on the CRF. The patient information note includes explicit agreement and non-opposition for the processing of his/her personal data and for the direct access to his/her original medical records for study-related monitoring, audit, and regulatory inspection by properly authorised persons on behalf of the Sponsor or regulatory authorities as appropriate, in accordance with local regulations and ethical considerations, in the strict respect of confidentiality and professional secrecy.

No information enabling the identification of participants will be given to third parties other than those authorised by regulations to hold this information (and who are subject to professional secrecy). All personal data of participants collected and treated in the study, will

be collected by CRO's CRAs or the sites CSAs with the appropriate precautions to ensure the confidentiality of such data.

Only the participating physician will retain the file with the link between participant identity and the participant number in the study file.

As part of the data confidentiality, the computerised file used for data entry and data treatment will be compliant with the Reference Methodology MR-004 "Research not involving the human person, study or evaluation in the field of public health".

7.5 French Medical Council

The financial agreement template signed between Astellas, and the participating physician will be sent to the French medical Council (CNOM) according to Article L1453-3 and following the French Health Public Code (CSP).

According to article L4113-9 of the CSP, the participating physician must fulfil his own obligations towards the Medical Council on which he depends. The participating physician undertakes to send a copy of this Agreement, insofar as it constitutes a contract for the practice of his profession, to the Departmental Medical Council to which he belongs, within one month of its conclusion, under penalty of criminal sanctions.

In accordance with article L1453-1 of the CSP, Astellas will publish remuneration and benefits of €10 or more on the "Transparence Santé" website.

8 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study is a non-interventional retrospective study with a design based on secondary use of data (i.e., where adverse events have already occurred and have been collected for another purpose); therefore, expedited reporting of adverse events (AEs) to the authorities is not required according to GVP Module VI.C.1.2.1. AEs (Annex 2) will not be prospectively collected and submission of ADRs in the form of individual case safety reports to authorities is not required for this study.

Pre-specified ADRs will be listed in the final CSR.

In accordance with the PTU of the early access, the healthcare professionals notify ADRs directly to the patient's Regional Pharmaco Vigilance Center (CRPV), preferably via the reporting portal: https://signalement.social-sante.gouv.fr/, specifying that the treatment is given as part of an EAP.

9 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The data and research results are the exclusive property of the Astellas. No information or publication may be made without prior authorization of Astellas.

The completed study will be summarised in a final report that will accurately and fully present the study objectives, the methods used, the results, the study limits, and the interpretation of results.

The results of the study may be reported through publication in a peer reviewed journal or submitted to conferences.

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11 ANNEXES

ANNEX 1 LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2 DEFINITIONS

DEFINITION OF ADVERSE EVENTS

An AE is defined as any untoward medical occurrence in a participant administered a study drug, 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), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product whether or not considered related to the medicinal (investigational) product.

An abnormality identified during a medical assessment is defined as an AE per the following criteria:

- Any abnormal laboratory test result (e.g., hematology, clinical chemistry, or urinalysis) or other safety assessment (e.g., ECGs, radiographic scans, vital signs measurements, physical examination), including those that worsen from baseline, that is considered to be clinically significant in the medical and scientific judgment of the investigator and not related to underlying disease, is to be reported as an AE/SAE.
- Any clinically significant abnormal laboratory finding or other abnormal safety assessment which is associated with the underlying disease does not require reporting as an AE/SAE, unless judged by the investigator to be more severe than expected for the participant's condition.
- Repeating an abnormal laboratory test or other safety assessment, in the absence of any of the above criteria, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event is considered "serious" if, in the view of either the investigator or Sponsor, it:

- Results in death.
- Is life threatening (an adverse event is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the participant at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death).
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly or birth defect of a child conceived during the exposure of one of the parents to the drug studied.
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious).
- Is a medically important event or reaction.

DEFINITION OF SPECIAL SITUATIONS

Special Situations are:

- Off-label use: situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information.
- Overdose: administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied.
- Misuse of a medicinal product: situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information.
- Abuse of a medicinal product: persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.
- Drug exposure during pregnancy and/or breast-feeding.
- Lack of efficacy/effectiveness
    - Some countries may have additional local requirements for events that are required to be reported as AEs or in an expedited manner similar to an SAE. In these cases, it is the investigator's responsibility to ensure these AEs or other reporting requirements are followed and the information is appropriately recorded in the eCRF accordingly. For example, unusual failure in efficacy is required to be reported as an AE in Canada when the study involves a marketed product. A review of local requirements for additional reporting requirements must be done before initiating the study to ensure appropriate communication on the additional requirements for reporting.
- Medication error: an inadvertent, unintentional, or unsupervised action by either healthcare provider, patient, or consumer. This may involve the drug treatment process including the prescription, dispensing, storage or administration of a medicinal product or dosage regimen that is not consistent with that intended in the authorized Product Information. Medication Errors are collected even when they are not associated with any AE/SAE. Medication errors can include the following:
    - Intercepted medication error: an intervention caused a break in the chain of events in the treatment process before reaching the patient, which would have resulted in a 'potential' harm/AE.
    - Potential medication error: the recognition of circumstances that could realistically lead to a medication error while the medication is in the control of a healthcare provider, patient, or consumer, and may or may not involve a patient.
- Occupational exposure: this refers to the exposure to a medicinal product, as a result of one's professional or non-professional occupation.
- Suspected Drug-drug interaction.

12 SIGNATURES

INVESTIGATOR'S SIGNATURE

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I will also ensure that any sub-investigator(s) and other relevant members of my staff have access to copies of this protocol and applicable non-interventional guidelines (European Medicines Agency, Guideline on good pharmacovigilance practices, good pharmacoepidemiology practices) to enable them to work in accordance with the provisions of these documents.

I understand that information that identifies me will be used and disclosed as described in the protocol and the Use and Disclosure of Personal Data notice provided to me, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

Principal Investigator:

Signature: .....

<Insert name and qualifications of the Investigator> Date (DD Mmm YYYY)

Printed Name: .....

Address: .....

.....

PROTOCOL APPROVED BY:

Protocol Approval Committee **Signature:** PPD **Date (DD Mmm YYYY)** **Medical Affairs Protocol Approval Committee**

Medical Lead EST-M **Signature:** PPD **Date (DD Mmm YYYY)** PPD **Oncology-Hematology** **Astellas Pharma Europe, Ltd.**
Signature: PPD **Date (DD Mmm YYYY)** PPD **TA Oncology** **Astellas Pharma France**

Medical Lead Astellas Pharma France **Signature:** PPD **Date (DD Mmm YYYY)** PPD **Oncology** **Astellas Pharma France**

Biostatistician **Signature:** PPD **Date (DD Mmm YYYY)** **Astellas Pharma Europe, Ltd.**

Pharmacovigilance **Signature:** PPD **Date (DD Mmm YYYY)** PPD **Medical Safety** **Astellas Pharma Global Development**

PV Epidemiology Lead

Signature:

PPD

Date (DD Mmm YYYY)

PPD

Pharmacoepidemiology
Astellas Pharma Global Development

HEOR Lead

Signature:

PPD

Date (DD Mmm YYYY)

PPD **HEOR Oncology**
Astellas Pharma Europe, Ltd.

Evidence Generation Operations

Signature:

PPD

Date (DD Mmm YYYY)

PPD **Medical & Clinical Operations**
Astellas Pharma Europe Ltd