Protocol Title

A Non-Interventional Post-Authorization Safety Study (NI-PASS) as an Effectiveness Check of a Patient Card for Padcev™

ISN/Protocol 7465-PV-0002 Version 3.0

10 Oct 2024

EudraCT: Not Applicable EU-PAS: EUPAS104456

Sponsor:

Astellas Pharma Europe B.V.

Sylviusweg 62

2333 BE Leiden, The
Netherlands

Title	A Non-Interventional Post-Authorization Safety Study (NI-PASS) as an Effectiveness Check of a Patient Card for Padcev™
Study identifier / Protocol number	ISN: 7465-PV-0002 EU PAS register number: EUPAS104456
Protocol version & date of last version of protocol	Version: 3.0 Date: 10 Oct 2024
Active substance	Enfortumab vedotin (ATC code: L01FX13)
Medicinal product	Enfortumab vedotin (Padcev™)
Product reference	EMEA/H/C/005392
Procedure number	Not applicable
Marketing authorization holder(s)	Astellas Pharma Europe B.V.
Joint PASS	(Select one below) Yes ☐ No ☒
Research question and objectives	This non-interventional post-authorization safety study (NI-PASS) will assess patients', or their caregivers', awareness and understanding of the content of the Padcev™ Patient Card (PC) related to the risk of skin reactions and reported behaviours to minimise the risk. The PC is an additional risk minimisation measure (aRMM) that is required beyond routine measures such as summary of product characteristics and patient information leaflet.
Countries of study	The study will be conducted in 7 European countries (France, Germany, Italy, Poland, Spain, Sweden, and Switzerland) where Padcev™ is launched (commercial or early access), representing diverse geographic regions across Europe.
Number of patients / Caregivers	A convenience sample of patients (or caregivers) will be recruited from the target population of patients (or caregivers of patients) who received or are currently receiving Padcev™ therapy. A sample of 62 completed surveys is targeted for this study.
Author	Astellas PPD PPD Pharmacovigilance Astellas Pharma Global Development Northbrook, Illinois US ICON PLC PPD ICON Life Sciences Canada Inc. 3455 North Service Road, Unit 400 Burlington, ON Canada L7N 3G2

Marketing Authorization Holder

Marketing authorization holder	Astellas Pharma Europe B.V. Sylviusweg 62 2333 BE Leiden The Netherlands
MAH contact person	PPD PPD Pharmacovigilance Astellas Pharma Global Development, US

ISN 7465-PV-0002
PAS register No: EUPAS104456

Table of Contents

1 RESPONSIBLE PARTIES

ICON PLC South County Business Park Leopardstown Dublin 18 Ireland Registered number: 145835	
Principal Investigator/ Scientific Lead	PPD

Astellas	
Group Lead, Pharmacoepidemiology	PPD Pharmacovigilance Astellas Pharma A.G. PPD
Pharmacoepidemiologist	PPD Pharmacovigilance Astellas Pharma Global Development PPD

2 LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of main abbreviations should be those used specifically in the study protocol

Abbreviations	Description of abbreviations
ADC	Antibody-drug conjugate
AE	Adverse event
aRMM	Additional risk minimisation measure(s)
CA	Competent authorities
CI	Confidence interval
(e)CRF	Electronic case report form
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FMV	Fair market value
GDPR	General Data Protection Regulation
GVP	Good Pharmacovigilance Practice
HCP	Healthcare professional
IEC	Independent ethics committee
ICF	Informed consent form
NCA	National competent authority
MAH	Marketing authorization holder
MMAE	Monoethyl auristatin E
NI-PASS	Non-interventional post-authorisation safety study
PAG	Patient advocacy group
PASS	Post-authorization safety study
PC	Patient card
PD-L1	Programmed death-ligand 1 inhibitor
PRAC	Pharmacovigilance risk assessment committee
RMM	Risk minimisation measure(s)
RMP	Risk management plan
SAP	Statistical analysis plan
SJS	Stevens-Johnson syndrome
SAE	Serious adverse event
SmPC	Summary of product characteristics
SOP	Standard operating procedure(s)
SDRIFE	Symmetrical drug-related intertriginous flexural exanthema
TEN	Toxic epidermal necrolysis
vc	Valine-citrulline

List of main key terms unique in the study protocol.

Terms	Definition of terms
Adverse Event (AE)	An adverse event is any untoward medical occurrence in a subject administered a study drug and which does not necessarily have a causal relationship with this treatment.
Convenience Sample	A convenience sample is one of the main types of non-probability sampling methods. A convenience sample is made up of people who are easy to reach.
Serious Adverse Event (SAE)	An adverse event is considered "serious" if, in the view of either the investigator or sponsor, it: results in death, is life threatening, results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, results in congenital anomaly or birth defect, requires inpatient hospitalization or leads to prolongation of hospitalization, or is a medically important event.

3 AMENDMENTS AND UPDATES

Number	Date	Sections updated	Reason
Version 1.0	18 Jan 2023	N/A	Original protocol
Version 2.0	28 Sep 2023	5, 6, 9, Annex 2	Included the list of countries where the survey will be launched, updated milestone planned dates.
Version 3.0	10 Oct 2024	5, 6, 7, 9, 10	Revised text on patient confidentiality, minor clarifications, updated milestone planned dates.

4 MILESTONES

The survey is planned to launch in each participating country after the launch (commercial or early access) of Padcev™ in each respective country. The milestones listed are planned dates and are not intended to be updated in the protocol if the planned dates change. Communication regarding shifts in the planned dates stated in the protocol will be done outside of an amendment to the protocol (unless other changes to the protocol are made at the same time). The study milestones are as follows:

Milestone	Planned Dates
Study registration in the EU PAS Register	Q4 2023
Start of data collection	Q1 2024
End of data collection	Q1 2025
Data analysis	Q2 2025
Submission of final report to EMA	Q3 2025

5 SYNOPSIS

Date and Version # of Protocol Synopsis: **10 Oct 2024, v3.0**
Sponsor: Astellas Pharma Europe B.V. **Protocol Number ISN: 7465-PV-0002**
EU PAS #: EUPAS104456

Name of Assessed Drug(s):

Enfortumab vedotin (Padcev™)

Type of Study:

Check one below:

☒ Mandated Study - European Medicines Agency (EMA)

☐ Non-mandated Study

Check one below:

☒ Primary data collection

☐ Secondary data collection

☐ Mix of primary and secondary data collection

Check one below:

☒ Post-authorization safety study (PASS)

For PASS studies only, select the appropriate reason to perform the study:

☐ Category 1 – Imposed as a condition of the marketing authorization

☐ Category 2 – Imposed as a specific obligation in the context of a marketingauthorization under exceptional circumstances

☒ Category 3 – Required in the risk management plan to investigate a safety concern or to evaluate the effectiveness of risk minimisation activities

☐ Category 4 – Study conducted voluntarily

☐ Post-authorization efficacy study (PAES)

☐ Post-authorization study (PAS, non-PASS and non-PAES)

☐ Other

Title of Study:

A Non-Interventional Post-Authorization Safety Study (NI-PASS) as an Effectiveness Check of a Patient Card for Padcev™

Study Rationale and Background:

Enfortumab vedotin (Padcev™) was granted marketing authorisation approval by the EMA in April 2022 as monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who have previously received platinum containing chemotherapy and received a programmed death receptor-1 or programmed death-ligand 1 inhibitor (PD-1/PD-L1).

Padcev™ is an antibody-drug conjugate (ADC) comprising a fully human immunoglobulin (Ig) G1Kappa antibody conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable valine-citrulline (vc) maleimidocaproyl linker. Padcev™ induces cytotoxicity in cancer cells by binding the Nectin-4 target on the cell surface and forming an ADC-Nectin-4 complex. This complex is internalised and traffics to lysosomes where MMAE is released by proteolytic cleavage of the vc-linker. Intracellular release of MMAE subsequently disrupts tubulin polymerization resulting in G2/M phase cell cycle arrest and apoptosis.

The recommended dose of Padcev™ is 1.25 mg/kg (up to a maximum dose of 125 mg for patients ≥100 kg) given as an intravenous infusion over 30 minutes on days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity. Padcev™ is supplied as single-dose vials containing sterile, preservative-free, white to off-white lyophilized powder for concentrate for reconstitution for intravenous infusion. Each vial contains either 20 mg or 30 mg Padcev™ active ingredient that is reconstituted to a final concentration of 10 mg/mL.

As part of the EMA approved EU Risk Management Plan (RMP), Astellas is required, upon - launch of Padcev™ in the EU member states, to conduct an effectiveness check of the additional risk minimisation activity implemented as part of the EU RMP. The Padcev™ Patient Card (PC) serves as an additional risk minimisation measure (aRMM) for the important identified risk of skin reactions, that is required beyond the routine risk minimisation measures such as the summary of product characteristics (SmPC) and patient information leaflet. Healthcare professionals (HCPs) who are expected to prescribe Padcev™ will be educated on the PC prior to treating patients and will provide the PC to their patients. HCPs may receive the PC that is included in the Padcev™ package, with the education letter, by downloading a digital copy, or via sales representatives.

The effectiveness check will be carried out as a Non-Interventional Post-Authorisation Safety Study (NI-PASS) (Category 3) which will assess patients', or their caregivers', knowledge of the risk of skin reactions associated with the use of Padcev™, as well as awareness of the PC, knowledge of the content of the PC, and reported behaviours to minimise the risk of skin reactions.

Planned Study Period:

A survey will be carried out in a sample of 7 European countries (France, Germany, Italy, Poland, Spain, Sweden, and Switzerland) beginning at least 3 months following launch (commercial or early access) of Padcev™ in each respective country. Study activities are projected to begin in Q1 2024. A final study report is planned for Q3 2025.

Study Objective(s):

The objectives of this NI-PASS are to assess patients' (or caregivers') knowledge of the risk of skin reactions associated with the use of Padcev™, as well as awareness of the Padcev™ Patient Card (PC), knowledge of the content of the PC, and reported behaviours to minimise the risk of skin reactions.

Data Sources(s):

A web-based survey will be developed using a market research software platform that complies with the European Privacy Data Act including General Data Protection Regulation (GDPR). The survey will consist of a full survey questionnaire, addressing all endpoints. The survey will have a data collection module as well as a reporting module for raw data export to data analysis software. Prior to the launch of the survey, cognitive pre-testing of the full survey questionnaire will occur, including at least one pre-testing interview for each of the participating countries in the native language. The full survey, including all administrative portions, should take no more than 15 minutes to complete. Participants will be encouraged to finish in one sitting, although if they are disconnected or need to return to the survey at a later time, they will be able to resume where they left off.

The goal is to obtain 62 completed survey questionnaires (see below for justification). Achieving the target sample size is a known challenge for these types of surveys. A recent systematic review found that only 3 of 8 such surveys (37.5%) targeting patients and/or caregivers reached the target [Artime E et al, 2019]. Therefore, a realistic convenience sample of patients/caregivers from the European countries where Padcev™ is launched will be actively recruited via several recruitment channels listed below in order of priority or importance:

- HCP referrals
- Patient advocacy groups (PAGs), patient associations, and support groups (different level of PAG involvement in recruitment will be based on preferences of PAGs)
  - PAG asks interested leads to contact recruiters
  - PAGs get consent to share contact details of interested leads with recruiters

- Recruiter databases (members consenting to participate in future studies)
  - Pre-profiled cancer patients
  - Referrals from members
  - Snowballing, or participant to participant referrals
- Recruiter website and social media posts
- Other social media channels (i.e., Facebook, Instagram)

The survey is anticipated to be open for up to 6 months from the time of survey launch in each European country.

Study Population:

The study population will be patients in European countries with locally advanced or metastatic urothelial carcinoma who previously received platinum and PD-1/L1 inhibitor therapy and

have received or are currently receiving Padcev™ therapy. If a patient is unable to participate in the survey, their caregiver will be asked to participate.

Study Size:

A sample of 62 completed patient or caregiver surveys is targeted for this study (see below).

Study Design Overview:

This is a multi-national, non-interventional, cross-sectional survey study with primary data collection to evaluate the effectiveness of the patient card (PC) for Padcev™. The study will be conducted in 7 European countries (France, Germany, Italy, Poland, Spain, Sweden, and Switzerland) in which Padcev™ is launched.

A sample of patients (or caregivers) will be invited to participate in the study via:

- HCP referrals
- Patient advocacy groups (PAGs), patient associations, and support groups (different level of PAG involvement in recruitment will be based on preferences of PAGs)
  - PAG asks interested leads to contact recruiters
  - PAGs get consent to share contact details of interested leads with recruiters
- Recruiter databases (members consenting to participate in future studies)
  - Pre-profiled cancer patients
  - Referrals from members
  - Snowballing, or participant to participant referrals
- Recruiter website and social media posts
- Other social media channels (i.e., Facebook, Instagram)

Up to 2 follow-up reminders will be sent per participant to complete the survey. Participants completing the survey will be provided fair market value compensation for their time.

Data will be collected by online, web-based data capture. Prior to launching the survey, cognitive pre-testing interviews of the survey questionnaire will be conducted for the survey. The survey questionnaire will collect information on the receipt of the Padcev™ PC (aRMM), knowledge of the core messages related to risk conveyed in the PC, reported behaviours to minimise risk, and respondent demographic characteristics. Survey completion and information needed for processing compensation payments will also be tracked and captured.

Inclusion/Exclusion Criteria:
Inclusion:

Respondents will be eligible to participate in the survey if they:

- Are patients (or caregivers of patients) who have received or are currently receiving
- Padcev™ therapy,
- Are residing in a participating European country,
- Are 18 years of age or older, and
- Agree to participate in the survey.

Exclusion:

Patients or caregivers will not be eligible to participate in the study if they:

- Participated in the cognitive pre-testing of the survey,
- Are a caregiver of a deceased patient that received Padcev™, or
- Have themselves (or have immediate family members who have) worked for Astellas, ICON (coordinating investigator), EMA, or the National Competent Authorities (NCAs) of the participating countries within the past 5 years.

Participant Selection:

All patients that meet the eligibility criteria will be selected.

Endpoints for Evaluation:
Primary:

The primary endpoint is:

- Knowledge level of patients, or their caregivers, of the risk of skin reactions
- associated with the use of Padcev™

Secondary:

The secondary endpoints are:

- Awareness and use of the Padcev™ PC among patients or caregivers
- Knowledge levels of patients, or their caregivers, of the symptoms and recommended
- care for skin reactions associated with the use of Padcev™
- Reported behaviours of patients, or their caregivers, to minimise the risk associated
- with the use of Padcev™

Exploratory:

Not applicable

Key Variables:

The questions will be designed to evaluate participants' awareness of the Padcev™ PC, understanding of the key messages of the PC related to risk of skin reactions, and behaviours to minimise the risk including:

- Knowledge of risk of severe skin reactions such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) or other severe rashes,
- Knowledge of symptoms of skin reactions,
- Knowledge to immediately seek medical care if the patient experiences signs of a severe skin reaction,
- Awareness and receipt of the PC, and
- Carrying the Padcev™ PC at all times and to present it to any healthcare professional providing treatment.

Statistical Methods:
Sample Size Justification:

The study will endeavor to achieve a minimum of 62 completed surveys. A planned sample size of 62 or more patients or caregivers (overall) will provide adequate precision around estimates of knowledge levels. Using a normal approximation to the binomial distribution, assuming a proportion of correct responses to individual questions of 80%, we have 95% confidence that the true response rate is between 70% and 90% when the sample size is 62. This sample size takes into account the limited size of the target population at the time of the survey administration as well as typical response rates for surveys among patient populations [Ferlay et al, 2013].

Data Analysis:

A statistical analysis plan (SAP) will be developed to describe all planned analyses in detail, along with shells for variable lists, tables and figures to be produced. All analyses will be performed using SAS® Version 9.0 or later. A final report summarizing the results of the survey will be developed.

The study population included in the data analysis will include patients/caregivers who completed the question in the survey associated with the primary endpoint. A threshold of success for the primary endpoints is to have 80% or more patients/caregivers providing a correct response to this question.

Descriptive data analyses will be conducted. Levels of awareness and knowledge, self-reported behaviours as well as patient characteristics will be calculated with 95% two-sided CIs. These descriptive results will be reported for the overall population of respondents and by country and, if the data permit, for sub-groups such as patients versus caregivers or length of time receiving Padcev™ treatment.

Safety:

All cognitive interviews and returned survey responses will be monitored for potential adverse event (AE) reports or product complaints. Any potential AE reports, special situations or product complaints will be forwarded according to requirements to Astellas Pharmacovigilance for evaluation and reporting, if required. Survey respondents may be contacted in order to obtain the information required for collecting and reporting potential AE reports, special situations, or product complaints to relevant health authorities, as per the applicable law.

Interim Analyses:

Not applicable

Dissemination Plan:

The results of this study will be summarised in a final study report that, after review and approval by Astellas, will be communicated to the applicable health authorities (including PRAC). A scientific publication may be considered.

ISN 7465-PV-0002
PAS register No: EUPAS104456

6 RATIONALE, BACKGROUND, AND RESEARCH QUESTION

Bladder cancer is the fifth most common cancer in the EU, with approximately 150 000 new cases annually, of which urothelial carcinoma cases account for more than 90% [Ferlay et al, 2013] [Miyazaki & Nishiyama, 2017]. Treatment for advanced urothelial carcinoma has been limited and prognosis poor, with more than 38,200 deaths per year in the EU [Burger et al, 2013].

Enfortumab vedotin (Padcev™) was granted marketing authorization approval by the EMA in April 2022 as monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who have previously received platinum containing chemotherapy and received a programmed death receptor-1 or programmed death-ligand 1 inhibitor (PD-1/PD-L1) [EMA Padcev, 2022]. Compared to chemotherapy, trials indicate that patients who received Padcev™ lived approximately 3.9 months longer, with a similar incidence of adverse events between the two study arms [Powles et al, 2021].

Padcev™ is an antibody-drug conjugate (ADC) comprising a fully human immunoglobulin (Ig) G1Kappa antibody conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable valine-citrulline (vc) maleimidocaproyl linker. Padcev™ induces cytotoxicity in cancer cells by binding the Nectin-4 target on the cell surface and forming an ADC-Nectin-4 complex. This complex is internalised and traffics to lysosomes where MMAE is released by proteolytic cleavage of the vc-linker. Intracellular release of MMAE subsequently disrupts tubulin polymerization resulting in G2/M phase cell cycle arrest and apoptosis [Rosenberg et al, 2020].

The recommended dose of Padcev™ is 1.25 mg/kg (up to a maximum dose of 125 mg for patients ≥100 kg) given as an intravenous infusion over 30 minutes on days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity. Padcev™ is supplied as single-dose vials containing sterile, preservative-free, white to off-white lyophilized powder concentrate for reconstitution for intravenous infusion. Each vial contains either 20 mg or 30 mg Padcev™ active ingredient that is reconstituted to a final concentration of 10 mg/mL [Astellas, 2022].

As part of the EMA approved EU Risk Management Plan (RMP), Astellas is required, upon - launch (commercial or early access) of Padcev™ in the EU member states, to conduct an effectiveness check of the additional risk minimisation measure (aRMM) implemented as part of the EU RMP. The Padcev™ Patient Card (PC) serves as an aRMM for the important identified risk of skin reactions, that is required beyond the routine risk minimisation measures such as the summary of product characteristics and patient information leaflet. Healthcare professionals (HCPs) who may prescribe Padcev™ will be educated on the PC prior to treating patients and will provide to their patients the PC. HCPs may receive the PC that is included in the Padcev™ package, with the education letter, by downloading a digital copy, or via sales representatives.

This effectiveness check will be carried out as a Non-Interventional Post-Authorisation Safety Study (NI-PASS) (Category 3) which will assess patients', or their caregivers', knowledge of

the risk of skin reactions associated with the use of Padcev™, as well as awareness of the Padcev™ PC, knowledge of the content of the PC, and reported behaviours to minimise the risk of skin reactions.

7 OBJECTIVES, ENDPOINTS AND ESTIMANDS

7.1 Study Objectives and Endpoints

7.1.1 Objectives

This NI-PASS will assess the awareness and knowledge of the safety concerns associated with Padcev™ use among patients or their caregivers.

- Primary objective:
  - To assess knowledge levels of patients, or their caregivers, of the risk of skin reactions associated with the use of Padcev™
- Secondary objectives:
  - To assess the awareness and use of the Padcev™ PC among patients or caregivers
  - To describe knowledge levels of patients, or their caregivers, of the symptoms and recommended care for skin reactions associated with the use of Padcev™
  - To describe reported behaviours of patients, or their caregivers, to minimise
  - the risk associated with the use of Padcev™

No a priori hypothesis is defined for this study.

7.1.2 Endpoints

7.1.2.1 Primary

The primary endpoint is:

- Knowledge level of patients, or their caregivers, of the risk of skin reactions associated with the use of Padcev™

The relevant question (8), shown in the Survey Questionnaire in [Annex 4], is defined as follows:

8. Which one of the following is a potential complication that may occur while being treated with Padcev™?

   □ Urinary tract infections

   ✓ Severe skin reactions

   □ Abnormal heart rhythms

   □ Stroke

   □ I don’t know/am not sure

The success criteria for the primary endpoint percentage is that at least 80% of patients, or caregivers, provide a correct response to this question.

7.1.2.2 Secondary

The secondary endpoints are:

- Awareness and use of the Padcev™ PC among patients or caregivers
- Knowledge levels of patients, or their caregivers, of the symptoms and recommended
- care for skin reactions associated with the use of Padcev™
- Reported behaviours of patients, or their caregivers, to minimise the risk associated
- with the use of Padcev™

The relevant questions (1-7, 9-12), shown in the Survey Questionnaire in [Annex 4], are defined as follows:

1. Are you aware of the Padcev™ Patient Card?
   - □ Yes
   - □ No ➔ **PROCEED TO Q8**
   - □ I don't know/am not sure
2. How did you access the Padcev™ Patient Card?
   - □ The doctor who prescribed Padcev™ gave me the card
   - □ I found it online
   - □ I have not accessed the Patient Card ➔ PROCEED TO Q8
   - □ I don't know/am not sure
3. Did you review information in the Padcev™ Patient Card?
   - □ Yes
   - □ No ➔ **PROCEED TO Q5**
   - □ I don't know/am not sure
4. How much of the Padcev™ Patient Card did you review?
   - □ All of it
   - □ Some of it
   - □ I don't know/am not sure
5. How often do you, or the patient you care for, carry the Padcev™ Patient Card?
   - □ All of the time
   - □ Some of the time / Only when interacting with healthcare professionals
   - □ None of the time
   - □ I don't know/am not sure
6. Have you, or the patient you care for, had a doctor's appointment, interacted with a pharmacist, gone to a walk-in clinic, or had a hospital visit since starting Padcev™?
   - □ Yes ➔ **PROCEED TO Q7**

□ No ➔ **PROCEED TO Q8**

□ I don't know/am not sure ➔ **PROCEED TO Q9**

7. How often did you show the Padcev™ Patient Card when interacting with healthcare professionals?

□ At each visit to a healthcare professional

□ At each visit, apart from with the prescribing physician

□ At some visits. I forgot the Patient Card on at least one occasion

□ None of the time

□ I don't know/am not sure

Q9-Q12 only appear if Q1 is answered "YES" and Q2 is answered "The doctor who prescribed Padcev™ gave me the card" or "I found it online."

9. Which of the following are severe skin reactions listed on the Padcev™ Patient Card?

□ Stevens-Johnson Syndrome (SJS)

□ Toxic Epidermal Necrolysis (TEN)

□ Symmetrical drug-related intertriginous flexural exanthema (SDRIFE)

□ All the above

□ I don't know/am not sure

10. According to the Padcev™ Patient Card, which symptoms below may indicate severe complications associated with Padcev™? For each item, please select "Yes" (symptom may indicate severe complication), "No" (symptom does not indicate severe complication), or "I don't know/am not sure".

		Yes	**No**	**I don't know/am not sure**
A	Chest pain	☐	✓	☐
B	Skin blistering or peeling	✓	☐	☐
C	Painful sores or ulcers in the mouth or nose, throat, or genital area	✓	☐	☐
D	Bloody nose	☐	✓	☐
E	Painful urination	☐	✓	☐
F	Fever or flu like symptoms	✓	☐	☐

11. The severe skin complications listed on the Padcev™ Patient Card can only occur during the first few weeks of treatment.

    □ True
    ✓ False
    □ I don't know/am not sure

12. If you or the person you care for has one of the symptoms listed on the Padcev™ Patient Card, when should you seek medical treatment?

    □ When it's convenient
    □ Within a week
    □ In the next day or two
    ✓ Immediately
    □ I don't know/am not sure

Success criteria for secondary endpoints, such as reported behaviours to reduce risk, are not applied. Success criteria will be based on the primary endpoint.

7.2 Estimands

Not applicable.

8 RESEARCH METHODS

8.1 Study Design

This is a multi-national, non-interventional, cross-sectional survey study with primary data collection to evaluate the effectiveness of patient education materials for Padcev™ (the Padcev™ PC). The study is planned to be conducted in 7 European countries (including at least 1 country per geographic region, see [Table 1]), beginning at least 3 months following launch (commercial or early access) of Padcev™ in each respective country. The country list may be expanded if a limited number of patients agree to participate in the survey in the selected countries. Study activities are projected to begin in Q1 2024. A final study report is planned for Q3 2025. The survey is anticipated to be open for up to 6 months from the time of survey launch in each European country.

A sample of patients (or caregivers) will be invited to participate in the study via:

- HCP referrals
- Patient advocacy groups (PAGs), patient associations, and support groups (different level of PAG involvement in recruitment based on PAGs preferences)
  - PAG asks interested leads to contact recruiters
  - PAGs get consent to share contact details of interested leads with recruiters
- Recruiter databases (members consenting to participate in future studies)
  - Pre-profiled cancer patients
  - Referrals from members

  - Snowballing, or participant to participant referrals
- Recruiter website and social media posts
- Other social media channels (i.e., Facebook, Instagram)

All participants recruited via social media will participate in a screening call to validate their eligibility. During the screening call, recruiters will go through an approved screener. The screener will be designed in a non-leading way, and answers that will lead to qualification will not be obvious to the participant. All screening questions will be asked during the call regardless of participant responses, so answers needed for eligibility will not be obvious.

If eligible, up to 2 follow-up reminders will be sent per potential participant to complete the survey. Participants completing the survey will be provided fair market value compensation for their time, according to local regulations.

Data will be collected by online, web-based data capture. Prior to launching the survey, cognitive pre-testing interviews of the survey questionnaire will be conducted for the survey. The survey questionnaire will collect information on the receipt of the PC (aRMM), awareness and knowledge of the core messages conveyed in the PC, reported behaviours to minimise risk, and respondent demographic characteristics. Survey completion and information needed for processing compensation payments will also be tracked and captured by the recruiter.

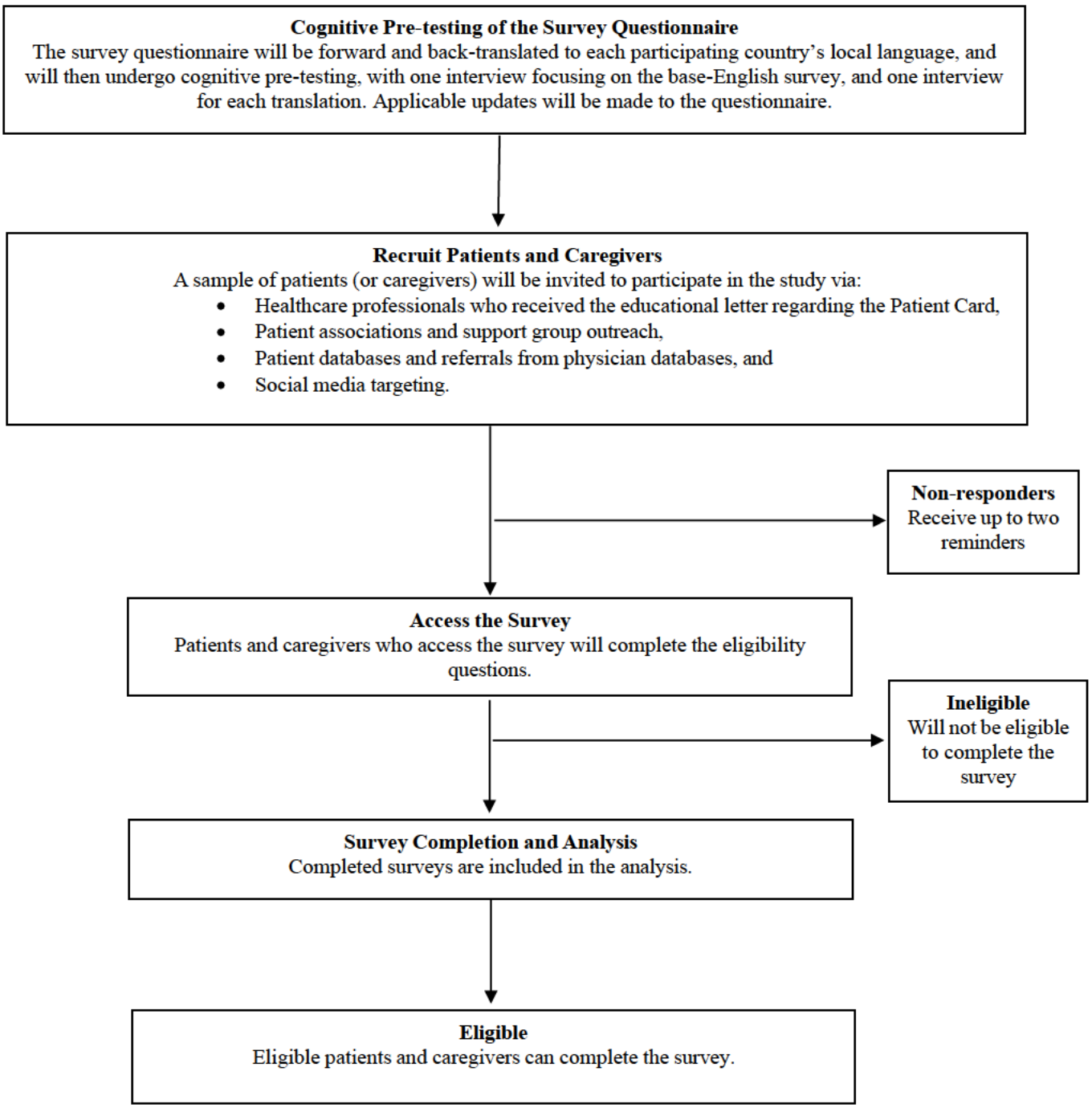
Table 1 Padcev™ European Market Launch Dates

Country & Region	Padcev™ Launch Date†
Southern Europe	
Italy	June 2023
Spain	December 2023
Western Europe	
Switzerland‡	December 2021
Germany	June 2022
France	July 2023
Northern Europe	
Sweden	July 2022
Eastern Europe	
Poland	September 2022

† Projected launch dates

‡ The distribution of the PC in Switzerland mimics the distribution of the PC in EU countries.

8.1.1 Study Schematic



8.2 Data Sources

8.2.1 Main Survey

The web-based survey will be developed using a market research software platform that complies with the European Privacy Data Act including General Data Protection Regulation (GDPR). The survey will consist of a full survey questionnaire, addressing all endpoints. The survey will have a data collection module as well as a reporting module for raw data export to data analysis software. Prior to the launch of the survey, cognitive pre-testing and qualitative inquiry of the full survey questionnaire will occur, see [Section 8.2.2]. The full survey, including all administrative portions, will take no more than 15 minutes to complete. Participants will be encouraged to finish in one sitting, although if they are disconnected or need to return to the survey later, they will be able to resume where they left off.

The goal is to obtain 62 completed survey questionnaires (see below for justification). Achieving the target sample size is a known challenge for these types of surveys. A recent systematic review found that only 3 of 8 such surveys (37.5%) targeting patients and/or caregivers reached the target [Artime et al, 2019]. Therefore, a convenience sample of patients/caregivers from the European countries where Padcev™ is launched will be actively recruited via several recruitment channels, listed below in order of priority or importance:

- HCP referrals
- Patient advocacy groups (PAGs), patient associations, and support groups (different level of PAG involvement in recruitment will be based on preferences of PAGs)
  - PAG asks interested leads to contact recruiters
  - PAGs get consent to share contact details of interested leads with recruiters
- Recruiter databases (members consenting to participate in future studies)
  - Pre-profiled cancer patients
  - Referrals from members
  - Snowballing, or participant to participant referrals
- Recruiter website and social media posts
- Other social media channels (i.e., Facebook, Instagram)

To encourage involvement, participants will complete the survey online. A customised invite with a link to the survey will be sent directly by recruiters to all interested participants via email address, text message, or direct message through a social media platform (i.e., Facebook). This link is unique to each participant and will be used to directly access and complete the survey on whatever platform the participant is using (e.g., computer, phone, tablet, etc.).

8.2.2 Cognitive Pre-testing and Qualitative Interviews

Prior to launching the survey, the data collection instrument will undergo cognitive pre-testing and qualitative inquiry. A first round of 4 to 6 interviews will be conducted in Germany, consisting of i) qualitative interview questions to capture patient feedback on the Padcev™ PC; as well as ii) cognitive pre-testing to validate the translated questionnaire. The questionnaire may be adapted based on feedback from these interviews. The final

questionnaire will then be translated for the remaining countries and will undergo one pre-test interview in each participating country.

The sample size is based on both qualitative research standards and feasibility considerations. In qualitative research, a sample of 12 interviews for homogeneous groups is considered sufficient to achieve saturation [Guest & Johnson, 2006]. Given the limited population of patients eligible to receive Padcev™, it would be impractical to conduct pre-testing with 12 participants for each language. Based on experience working with European-based patients on similar surveys, one interview per language has routinely enabled adequate coverage from pre-testing performed in similar surveys.

The goals of the cognitive pre-testing are to identify any survey questions that require clarification or revision based on areas of confusion or miscomprehension revealed by patients or caregivers in the cognitive pre-test interviews, and to ensure that questionnaire translations are conceptually and cross-culturally equivalent in each of the country local languages.

Qualitative interview questions will be included in the first round of 4 to 6 German interviews to more thoroughly explore the participants' knowledge of the risk of skin reactions associated with the use of Padcev™, as well as awareness of the Padcev™ PC, knowledge of the content of the PC, and reported behaviours to minimise the risk of skin reactions. The collection of additional qualitative data provides the opportunity to capture variations in the individual participant's level of awareness and understanding beyond simple self-assessment using probing questions and can help to alleviate risk of biased self-reported responses by allowing for open-ended data collection.

Interviews will be completed through 1-on-1 remote interviews. Patients (or caregivers of patients) who have received or are currently receiving Padcev™ therapy, are more than 18 years of age, reside in a participating European country, and agree to participate will be eligible to participate in interviews. Due to an anticipated time commitment of 45 to 60 minutes to participate in the interview, participants will receive FMV compensation in all participating countries for their time according to local regulation.

During the conduct of the interviews, the survey questionnaire will be presented item by item, and feedback will be obtained for each question using an interview guide designed to solicit feedback. The interviewer will also record information regarding any questions received by participants, or other observations indicating difficulty with any particular question or wording. Based on interview results, the survey questionnaire will undergo additional revision if necessary.

8.3 Study Population

The study population will be patients in 7 European countries (France, Germany, Italy, Poland, Spain, Sweden, and Switzerland) with locally advanced or metastatic urothelial carcinoma who previously received platinum and PD-1/L1 inhibitor therapy and have received or are currently receiving Padcev™ therapy. If a patient is unable to participate in the survey, their caregiver will be asked to participate.

8.3.1 Inclusion Criteria

Respondents will be eligible to participate in the survey if they:

1. Are patients (or caregivers of patients) who have received or are currently receiving
2. Padcev™ therapy,
3. Are residing in a participating European country,
4. Are 18 years of age or older, and
5. Agree to participate in the survey.

8.3.2 Exclusion Criteria

Patients or caregivers will not be eligible to participate in the study if they:

1. Participated in the cognitive pre-testing of the survey,
2. Are a caregiver of a deceased patient that received Padcev™, or
3. Have themselves (or have immediate family members who have) worked for Astellas, ICON (coordinating investigator), EMA, or the NCAs of the participating countries within the past 5 years.

8.3.3 Participant Selection

To determine patient and caregiver eligibility based on criteria in [Section 8.3.1] followed by [Section 8.3.2], screening questions will be presented in the online survey.

8.3.4 Treatments and Evaluation

No tests or reference treatments are evaluated in this cross-sectional survey study.

8.3.5 Discontinuation Criteria

Participation in this survey is voluntary. Participants may withdraw from the study for any reason, at any time, without penalty or prejudice. If requested by a participant, their survey responses will be removed from the analysis database and not used in the final study report.

8.4 Variables

The questions will be designed to evaluate participants' knowledge of the risk of skin reactions associated with the use of Padcev™, as well as awareness of the Padcev™ PC, knowledge of the content of the PC, and reported behaviours to minimise the risk of skin reactions including:

- Knowledge of risk of severe skin reactions such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) or other severe rashes,
- Knowledge of symptoms of skin reactions,
- Knowledge to immediately seek medical care if the patient experiences signs of a severe skin reaction,
- Awareness and receipt of the PC, and
- Carrying the PC at all times and to present it to any healthcare professional providing any treatment.

8.5 Data Management

Survey data collection will be completed online in Forsta Plus (formerly Confirmit), a software platform specifically designed for the creation and delivery of multi-lingual surveys. Data collected will be stored at secure servers and will be maintained to ensure compliance with applicable local and national regulations.

Response sets for multiple-choice questions will be randomised to minimise bias. Respondents will be asked to complete the survey in 1 sitting and will not be allowed to revise their answers after they have advanced to the next question.

Survey database lock is anticipated to occur shortly after the survey is closed in all countries. To reduce opportunity for bias, survey respondents will not be contacted to clarify or revise their responses to knowledge assessment-related questions.

Data management will be in accordance with ICON's standard operating procedures (SOPs). Study data and documents will be retained for the lifetime of Astellas (and not less than 5 years). Additional details regarding data collection, management of missing data, data storage, and validation procedures will be detailed in the survey manual and SAP.

8.6 Statistical Methods

8.6.1 Sample Size Justification

Based on the rates of bladder cancer (150 000 new cases per year in EU) and the requirement for treatment with Padcev™ (patients with locally advanced or metastatic urothelial carcinoma who have received platinum and PD-1/L1 inhibitor therapy), approximately 5 000 individuals in Europe are eligible for Padcev™ therapy [Ferlay et al, 2013]. The target sample size represents the number of participants needed to complete the questionnaire in order to produce results that exhibit a desired degree of precision (acceptable margin of error). To produce the potential sample sizes presented in [Table 2], assumptions were made regarding the confidence level, margin of error, proportion of correct responses, and population size. The objectives of the survey are to assess participants' levels of knowledge of the risk associated with Padcev™ therapy as detailed in the PC. With these objectives in mind, a confidence level of 95% was selected. Margins of error of ± 5%, ±7.5%, and ± 10% and proportions of correct responses of 50%, 60%, 70%, 80%, and 90% were selected.

Based on these considerations, 62 fully completed questionnaires of the survey will be the target for the final analysis. Using a normal approximation to the binomial distribution, and assuming a proportion of correct responses to individual questions of 80%, we have 95% confidence that the true response rate is between 70% and 90% when the sample size is 62. This sample size takes into account the limited size of the target population at the time of the survey administration as well as typical response rates for surveys among the patient population [Artime et al, 2019].

Table 2 Precision and 95% Confidence Intervals for Various Combinations of Sample Size and Knowledge Levels*

Margin of Error	Respondent Knowledge Levels				
	50%	60%	70%	80%	90%
±5 %	358	344	304	235	135
±7.5 %	166	159	140	108	61
±10 %	96	92	80	62	34

*Calculation of sample sizes are based on a true population size of N = 5,000.

8.6.2 Statistical Analysis

A SAP will be developed and will describe all planned analyses in detail, along with any specifications for tables, listings, and figures to be produced. The SAP will be finalised prior to database close. Any changes to analyses outlined in the SAP will be captured in the final study report.

8.6.2.1 Analysis Populations

The primary analysis set will include patients and caregivers who have completed the question in the survey associated with the primary endpoint, see [Section 7.1.2.1]. Participants will be required to answer each question before moving on to the next one. Denominators used to calculate knowledge levels for individual survey questions will reflect the number of respondents who completed the particular survey question including responses of 'I don't know/am not sure.'

8.6.2.2 Statistical Methods

General Considerations

Data analysis will be performed by ICON qualified personnel in accordance with ICON's SOPs for statistical analysis and programming. All analyses will be performed using SAS® Version 9.0 or higher. A report summarizing the results of the survey will be developed.

Missing Data

Missing data will be reviewed, but no replacement or imputation will be performed. Descriptive statistics for continuous variables will include the available n, and descriptive statistics for categorical variables will include a category of "missing" when applicable.

Effectiveness Endpoints

Effectiveness endpoints (i.e., survey responses that assess knowledge and behaviour) are defined in [Table 3]. The primary endpoint is knowledge level of patients, or their caregivers, of the risk of skin reactions associated with the use of Padcev™, corresponding to question 8 in the survey [Section 7.1.2.1]. The secondary endpoints are assessments of (1) awareness of the PC, (2) knowledge of the symptoms and recommended care for skin reactions associated with the use of Padcev™, and (3) reported behaviours to minimise risk associated with the

use of Padcev™. Knowledge endpoints will be presented as percentages of respondents with appropriate answers to key questions, corresponding to questions 9 to12 in the survey [Section 7.1.2.2].

Awareness and reported behaviour endpoints, questions 1 to 7 in the survey [Section 7.1.2.2], do not have correct responses, and percentages will be presented for each category. Each question will be analyzed individually.

Table 3 Effectiveness Endpoints

Study objective assessed	Correct response to corresponding variable	Operational definition
Primary: Knowledge levels of patients, or their caregivers, of the risk of skin reactions associated with the use of Padcev™	Knowledge that severe skin reactions are a known complication associated with Padcev™	Calculated as the percentage of participants who tick 'severe skin reactions' for question 8
Secondary: Knowledge of the symptoms and recommended care for skin reactions associated with the use of Padcev™	Knowledge of the severe skin reactions listed on the Padcev™ PC	Calculated as the percentage of participants who tick 'all of the above' for question 9
	Knowledge that chest pain is not known side effect associated with Padcev™	Calculated as the percentage of participants who answer "No" to question 10A
	Knowledge that skin blistering or peeling is a known side effect associated with Padcev™	Calculated as the percentage of participants who answer "Yes" to question 10B
	Knowledge that painful sores or ulcers in the mouth or nose, throat, or genital area, are known side effects associated with Padcev™	Calculated as the percentage of participants who answer "Yes" to question 10C
	Knowledge that a bloody nose is not a known side effect associated with Padcev™	Calculated as the percentage of participants who answer "No" to question 10D
	Knowledge that painful urination is not a known side effect associated with Padcev™	Calculated as the percentage of participants who answer "No" to question 10E
	Knowledge that fever or flu like symptoms are a known symptom indicating a severe complication associated with Padcev™	Calculated as the percentage of participants who answer "Yes" to question 10F
	Knowledge that severe skin complications listed on the Padcev™ PC can happen at any time during treatment	Calculated as the percentage of participants who answer "False" to question 11
	Knowledge that patients should seek medical treatment immediately if they have one of the symptoms listed on the PC	Calculated as the percentage of participants who answer "Immediately" to question 12

Planned Analyses

Survey administrative details (e.g., number of invited participants, number and percentage of responding participants, number and percentage of eligible vs. ineligible participants, number and percentage of patients vs. caregivers, number and percentage of participants with fully completed surveys) will be described overall and by country. Participant characteristics will be summarised overall and by country.

Frequencies, percentages, and corresponding 95% 2-sided CIs will be used to summarise the primary and secondary effectiveness endpoints overall and by country. The primary endpoints will also (if supported by the distributions of data within each subgroup) be stratified by items with potential to confound the knowledge level (e.g., length of time patient was given Padcev™ or whether the participant was a patient or a caregiver).

A threshold of success for the primary endpoint is to have 80% or more patients/caregivers providing correct responses to this question.

Other Analyses

A descriptive analysis of the distribution of all response choices to questions 1 to 20 [Annex 4] will be performed.

8.7 Quality Control

Steps to be taken to ensure the accuracy and reliability of data will include the selection of qualified study personnel and review of data collection and processing procedures with the study personnel before the study is launched. ICON will ensure data quality and integrity, which includes archiving of statistical programs, appropriate documentation of data cleaning and validation of derived variables, and description of available data. Guidelines for data collection and data quality checks will be described in the study-specific Data Management Plan.

Data will be stored in a secure validated database and shall be treated in compliance with all local applicable laws and regulations. The collection and processing of personal data from participants will be limited to those data that are necessary to fulfill the objectives of the study. Participants' personal data will be collected and processed in accordance with General Data Protection Regulation of Europe. Survey responses will be anonymous and reported in aggregate.

8.7.1 Non-Interventional Study Monitoring

Not applicable.

8.7.2 Direct Access to Source Documents

Not applicable; participants will complete surveys directly on-line.

8.8 Strengths and Limitations of the Research Methods

A primary limitation of this cross-sectional survey is potential selection bias due to use of a convenience sample and/or low response rates. Moreover, the small population of patients

eligible for Padcev™, the poor prognosis of bladder cancer, and the relatively recent approval of Padcev™ (meaning reimbursement in many EU countries may not yet or may only recently be available) may compromise the ability to identify a sufficiently large number of Padcev™ patients to complete the survey. To improve response rates and expedite recruitment, countries with robust physician networks were considered for participation. If a patient is unable to participate in the survey, their caregiver will be asked to participate.

Analyses will be performed stratified by patients versus caregivers, assuming numbers permit. Countries with robust physician networks were also considered for participation to bolster response rates and ease recruitment efforts.

For this survey, to minimise selection bias, patients (or caregivers) from a broadly representative sample of European countries, geographically and via market-share, will be invited to participate. Countries were selected based on the following considerations:

- Countries where Padcev™ is commercialised and reimbursed, and
- Countries with reasonable product uptake.
- After considering the above, countries were selected to ensure reasonable geographic representation (e.g., covering Southern, Eastern, Northern, and Western Europe), and
- Feasibility/logistics (e.g., patient/caregiver familiarity with non-interventional research studies, ability to conduct a patient survey without unduly long timelines for ethical and other regulatory reviews).

Generalizability of the study results may be limited in that the study population is based on a convenience sample. To improve generalizability, there will be several avenues of recruitment for patients and caregivers, discussed in [Section 8.2.1]. To further endeavor to minimise selection bias:

- Participants who have not responded will receive up to two reminders to encourage their participation.
- Caregivers will be invited to participate when a patient is unable to participate.
- Participants will be offered a small reimbursement, based on FMV, for their time to complete the survey.

Another limitation is reliance on self-reporting which can result in social desirability reporting bias [Mazzaglia et al, 2018]. However, a meta-analysis of three studies found no association between social desirability and self-reported health risk behaviours in web-based research, indicating that the online platform may increase respondents perception of privacy and reduce the risk of social desirability bias [Artime et al, 2019]. Conducting qualitative interviews will also help to alleviate this risk by allowing for more open-ended responses. Recall bias can also impact study results, e.g., if there is a long lag time between receiving the Padcev™ PC and completing this survey. This will be assessed by stratifying the primary endpoint analyses by duration between the patient receiving the aRMM and completion of the survey.

9 PROTECTION OF HUMAN PATIENTS

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

9.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) / Competent Authorities (CA)

It is the responsibility of ICON to seek approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms, recruitment advertisements), from independent ethics committees (IEC). Where applicable, all correspondence with IEC will be retained in ICON's study-specific file.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in Good Pharmacoepidemiology Practice issued by the International Society for Pharmacoepidemiology, the EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and GVP Module VIII – PASS.

9.3 Patient Information and Consent

Consent will be collected via a digital informed consent form (ICF), which will appear as part of the script between the screening questions and the main questionnaire and shall:

- enable the participant to understand:
  - the nature, objectives, benefits, and inconveniences of the study.
  - the conditions under which the study is to be conducted, including the expected duration of the participant's involvement in the study.
- be kept comprehensive, concise, clear, relevant, and understandable to a layperson.
- include the study ISN number and information about the future availability of the study results in terms understandable to a layperson.
- include information about why, how and for how long patient's personal information will be processed; with whom his/her personal information may be shared and if it is transferred beyond the country of origin; how participants can exercise their data protection rights and how they can contact the Sponsor and the Sponsor's data protection office.
- include any other information that may be required according to the applicable local laws and regulations.

Participants will be informed that their participation is voluntary and shall have their protective rights and guarantees explained, including their privacy rights. In particular, their right to refuse to participate and the right to withdraw from the study at any time without any resulting detriment and without having to provide any justification shall be explained.

Participants will be required to sign a statement of informed consent that meets the requirements of the IEC and includes consent about the processing of personal information.

A copy of the ICF(s) will be provided to the participant.

9.4 Patient Confidentiality

Astellas maintains confidentiality standards by ensuring that it does not receive from Investigators names or other directly identifying personal information of participants in any case report forms (CRFs) or other documents submitted to the sponsor (unless this is required by law for reporting of adverse events). In particular, a participant identification number will be used at inclusion to serve as the participant's identifiers in the study, as well in the study database retained by the Sponsor. Documents not for submission to ICON or the Sponsor, such as participant contact information, payment information, or signed ICFs (where required and applicable), are maintained in strict confidence by the recruiter.

The sponsor will use the personal information processed as part of the study in order to run the study and publish the results of the study. Any personal information that may be processed in relation to reported adverse events during the study will be processed in order to comply with pharmacovigilance obligations.

Data generated by this study, including personal information of the participants and their medical information, must be available for inspection by the Sponsor, the Sponsor's authorized representative(s), the IRB/IEC and, when necessary, representatives of the relevant regulatory health authorities. Only authorized persons will have access to identifiable personal information, if required. All study reports will contain aggregate data only and will not identify any individual participants.

The sponsor will inform the participants about their privacy rights and how to exercise them under the Informed Consent Form which participants will sign in order to participate in the study.

Participants will be entitled to contact Astellas Group Data Protection Officer at privacy@astellas.com with questions about the use and protection of their personal information when they participate in a study.

Data protection and privacy regulations will be observed in collecting, forwarding,

processing, and storing participant's personal information. The Sponsor affirms the participant's right to protection against invasion of privacy. Only a participant identification number will identify participant data retrieved by the Sponsor in accordance with applicable data privacy requirements. However, the Sponsor requires the Investigator to permit the Sponsor, Sponsor's representative(s), the IRB/IEC and, when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

9.5 Insurance of Participants

Not applicable.

10 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

10.1 Primary Data Collection

Information on all adverse events associated with the use of Astellas products should be collected and reported to Astellas Pharmacovigilance per the timelines and email addresses described in [Section 10.4]. A causality assessment from the primary source should be obtained as described in [Section 10.2]. If this is not available, enough information should be collected to allow the sponsor to perform the causality assessment.

Events related to non-Astellas drugs are not required to be reported to Astellas Pharmacovigilance; however, it is the investigator's responsibility to forward these events to the relevant MAH.

10.2 Criteria for Causal Relationship to the (Study) Drug

When making an assessment of causality, the following factors are to be considered when deciding if there is evidence and/or arguments to suggest there is a 'reasonable possibility' that an AE/SAE may have been caused by the study drug (rather than a relationship cannot be ruled out) or if there is evidence to reasonably deny a causal relationship:

- Plausible temporal relationship between exposure to the study drug and AE/SAE onset and/or resolution. Plausibility: i.e., could the event have been caused by the Astellas
- product? Consider biologic and/or pharmacologic mechanism, half-life, literature evidence, drug class, etc.
- Results of Dechallenge/Dose reduction/Rechallenge:
  - Did the AE/SAE resolve or improve after stopping or reducing the dose of the suspect drug? Also consider the impact of treatment for the event when evaluating a dechallenge experience.
  - Did the AE/SAE reoccur if the suspected drug was reintroduced after having been stopped?
- Laboratory or other test results; a specific lab investigation supports the assessment of the relationship between the AE/SAE and the study drug (e.g., based on values pre-, during and post-treatment).
- Available alternative explanations independent of study drug exposure, such as other concomitant drugs, past medical history, concurrent or underlying disease, risk factors including medical and family history, season, location, etc. and strength of the alternative explanation.

There may be situations in which an AE/SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the medically qualified investigator always make an assessment of causality for every event before the initial transmission of the AE/SAE data to the Sponsor. With limited or insufficient information about the event to make an informed judgment and in absence of any indication or evidence to establish a causal relationship, a causality assessment of 'no' is to be considered. In such instance, the investigator is expected to obtain additional information

regarding the AE/SAE as soon as possible and to re-evaluate the causality upon receipt of additional information.

10.3 Procedure in Case of Pregnancy

Should a cognitive interview or survey participant report a female patient, or partner of a male patient, becoming pregnant having been exposed to Padcev™, study personnel must report the pregnancy as specified in [Section 10.4].

10.4 Notification of Adverse Events (Serious and Non-serious) by Study Personnel to Sponsor

For a new Serious/Fatal Adverse Event, the reporter must complete and submit an Astellas Safety Information Report Form containing all information that is required by the Regulatory Authorities to the Sponsor by fax or e-mail immediately (within 24 hours of awareness). If the faxing or e-mailing of an Astellas Safety Information Report Form is not possible or is not possible within 24 hours, the local drug safety contact should be informed by phone.

In the case of a new non-serious AE, the investigator must contact the Sponsor by fax or email within 72 hours of awareness.

When submitting an Astellas Safety Information Report Form, the following information is required:

- International Study Number (ISN)/Study number
- Participant identifier (i.e., participant number, sex, age, etc.)
- The date of report
- A description of the adverse event
- Causal relationship to Astellas drug (including reason)
- The drug provided

In addition, the reporting of the batch number is strongly encouraged, when available. The Astellas Safety Information Report Form must be signed by a medically qualified Investigator or Sub-Investigator (as identified on Delegation of Authority Log). Signature confirms accuracy and completeness of the SAE data as well as the Investigator causality assessment.

In the case of all other new non-serious AEs, the investigator also must contact the Sponsor by fax or email within 72 hours of awareness using the Astellas Safety Information Report Form. Reporting is to begin following consent and will continue to the end of the qualitative interviews or the survey. All new AEs collected for the study will be recorded, organized, and summarized for inclusion in the final study report.

Guidance for Reporting AEs/Special Situations to Astellas PV:

Reporting to Pharmacovigilance	Timelines
Serious AEs	within 24 hours of awareness
Fatal AEs	within 24 hours of awareness
Non-serious AEs	within 72 hours of awareness
Special Situations	within 72 hours of awareness
Pregnancy	within 72 hours of awareness

For reporting to Pharmacovigilance EU:
Europe:
Fax: +31 71 545 5208
Email: Safety-EU@astellas.com

10.5 Definitions

10.5.1 Definitions of Adverse Events

An AE is defined as any untoward medical occurrence in a participant administered a study drug, which occurrence does not necessarily have to have a causal relationship with the study drug 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 it is considered related to the medicinal (investigational) product.

Use the following criteria to determine if an abnormality identified during a medical assessment should be identified as an AE:

- 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 (S)AE.
- Any clinically significant abnormal laboratory finding or other abnormal safety assessment which is associated with the underlying disease does not require reporting as an (S)AE, 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.

10.5.2 Definitions of Adverse Drug Reaction

An Adverse Drug Reaction is defined as 'Any noxious and unintended response associated with the use of a drug in humans, at any dose, where a causal relationship (drug-event) is at least a reasonable possibility'.

10.5.3 Definitions of Serious Adverse Events (SAEs)

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 patient 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)
- Other medically important events

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The sponsor has a list of events that they classify as "important medical events". If an adverse event is reported that is considered to be an "important medical event", additional information on the event may be requested by the Sponsor.

10.5.4 Definitions of Special Situations

The following special situations are not considered AEs, but they do require collection and communication to Astellas as per timelines described in the table above: Guidance for Reporting AE/Special Situations to PV.

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. 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 (e)CRF 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 refers to an inadvertent, unintentional, or unsupervised action by either HCP, participant, 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 an HCP, 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.
- (Suspicion of) Transmission of infectious agent
- Pregnancy: the pregnancy itself is not considered to be an (S)AE but is a special situation, in addition, any pregnancy complication, pregnancy termination (including elective termination), congenital anomaly of an infant is to be collected

11 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this study will be summarised in a study report that, after review and approval by Astellas, will be communicated to the applicable health authorities within the agreed timeframe. Protocol details and an abstract of results will be posted on the EU-PAS register as per guidelines for studies meeting the criteria for PASS. A scientific publication may be considered. Authorship of any publications resulting from this study will be determined based on the International Committee of Medical Journal Editors Recommendations for the

ISN 7465-PV-0002
PAS register No: EUPAS104456

Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals [ICMJE 2023].

12 REFERENCES

Artime E, Qizilbash N, Garrido-Estepa M, et al. Are risk minimization measures for approved drugs in Europe effective? A systematic review. Exp Op Drug Safety. 2019;18(5):443-54.

Astellas. Highlights of Prescribing Information. In:2022.

Burger M, Catto JW, Dalbagni G, et al. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol. 2013;63(2):234-241.

EMA. Padcev. 2022. https://www.ema.europa.eu/en/medicines/human/EPAR/padcev. Accessed 23 September, 2022.

Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374-1403.

Guest G BA, Johnson L. How many interviews are enough? An experiment with data saturation and variability. Field Methods. 2006;18(1):5982.

ICMJE. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. http:www.ICMJE.org. Accessed.

Mazzaglia G, Straus SMJ, Arlett P, et al. Study Design and Evaluation of Risk Minimization Measures: A Review of Studies Submitted to the European Medicines Agency for Cardiovascular, Endocrinology, and Metabolic Drugs. Drug Saf. 2018;41(2):191-202.

Miyazaki J, Nishiyama H. Epidemiology of urothelial carcinoma. Int J Urol. 2017;24(10):730-734

Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma. N Engl J Med. 2021;384(12):1125-1135.

Rosenberg J, Sridhar SS, Zhang J, et al. EV-101: A Phase I Study of Single-Agent Enfortumab Vedotin in Patients With Nectin-4-Positive Solid Tumors, Including Metastatic Urothelial Carcinoma. J Clin Oncol. 2020;38(10):1041-1049.

13 ANNEXES

Annex 1: List of stand-alone documents

Number	Document reference number	Date	Title†
1	N/A	N/S	Padcev Patient Card

†The English version has been included as this was the master version from which country specific translations were made

Annex 2: ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is “Yes”, the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer ‘N/A’ (Not Applicable) can be checked and the “Comments” field included for each section should be used to explain why. The “Comments” field can also be used to elaborate on a “No” answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: A Non-Interventional Post-Authorization Safety Study (NI-PASS) as an Effectiveness Check of a Patient Card for Padcev™
EU PAS Register® number:
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection †	☒	☐	☐	6
1.1.2 End of data collection ‡	☒	☐	☐	
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.	☒	☐	☐	

† 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.

‡ Date from which the analytical dataset is completely available.

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
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)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.4
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	8

Comments:

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)	☒	☐	☐	9.3
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1, 9.2, 9.8
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	☒	
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)	☒	☐	☐	11

Comments:

Measures of occurrence are levels of knowledge, expressed as the percentages of respondents with correct answers to questions regarding knowledge of information included in the Padcev Patient Card.

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.1, 9.4

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.1.1, 9.3, 9.11
	4.2.2 Age and sex	☐	☐	☒	
	4.2.3 Country of origin	☒	☐	☐	9.1.1, 9.3, 9.11
	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)	☒	☐	☐	9.1.1, 9.3, 9.4, 9.7, 9.11

Comments:

This is a cross-sectional study of patients and caregivers of patients who have received Padcev therapy. Age, sex, and duration of follow-up are all not applicable.

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)	☐	☐	☒	
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
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:

This is a non-interventional study that aims to test knowledge related to risk minimisation for Padcev.

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?	☒	☐	☐	8, 9.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.2
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)	☒	☐	☐	9.1, 9.2
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:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.9.2.2
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.11
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time- related bias)	☒	☐	☐	9.1.2

Comments:

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)	☒	☐	☐	9.9.2.2

Comments:

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)	☐	☐	☒	

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.1, 9.2
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.6
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)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.1, 9.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co- morbidity, co-medications, lifestyle)	☒	☐	☐	9.6

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))	☐	☐	☒	
9.3.3 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?	☒	☐	☐	9.9
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.9.1
10.3 Are descriptive analyses included?	☒	☐	☐	9.9
10.4 Are stratified analyses included?	☒	☐	☐	9.9
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.9
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.9.2.1
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.9.2.2

Comments:

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
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8, 9.10
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?	☒	☐	☐	9.11
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)	☒	☐	☐	9.1.2, 9.7, 9.8

Comments:

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
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

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)?	☒	☐	☐	1 2
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	1 2

Comments:

Name of the main author of the protocol: _____

Date: _____

Signature: _____

Annex 3: Survey Invitation Letter

Survey for Users of the

Padcev™ (enfortumab vedotin) Patient Card

Study objective. On behalf of Astellas Pharma Europe B.V. (Astellas), ICON is inviting you to participate in a survey being conducted among patients and caregivers of patients who have received Padcev™ therapy. **Astellas is performing this survey as part of the requirement to assess the Padcev™ Patient Card in the Risk Management Plan submitted to the European Medicines Agency (EMA).** The overall goal of this study is to assess the effectiveness of the risk minimisation measures for Padcev™. Your participation is highly valued, and the information you provide will help Astellas in providing important information to patients and caregivers in the future. Participation in this survey is voluntary.

Survey duration. This survey will take no more than 15 minutes to complete. The survey is recommended to be completed during one sitting, although you may save the survey and completed it another time. You will receive an honorarium of €XX <*replace with local currency equivalent where applicable*> in consideration of your time and inconvenience.

Confidentiality. In the course of conducting this survey, ICON will process your personal information, including your name, contact information, and bank details if the honoraria payment is made via electronic transfer. ICON may share your personal information with third parties including Astellas and ICON's survey software tool supplier solely for the purpose of conducting the study. Your individual survey responses will not be linked with your personal information in any data shared with Astellas, and will be processed by ICON such that you will not be able to be identified without the use of additional information that is kept separate and secure by ICON (this is known as 'pseudonymization'). ICON may process your personal information outside the European Economic Area. ICON will treat your data with care and sensitivity in accordance with data protection legislation, and the detailed Privacy Information Notice at *https://www.iconplc.com/privacy/privacy-policy/*. If necessary, you may be contacted to obtain additional information regarding potential adverse events, as per the applicable law.

Adverse Events. This survey is not designed to collect adverse event information that may have occurred in specific individuals. To report information on potential adverse events or quality issues, please notify Astellas Safety either by email at Safety-EU@astellas.com or by facsimile at +31 (0)71 545 5208.

Access to Survey. To access the survey, go to: <Link to be supplied once survey has been launched>

If you do not wish to be considered for further surveys, please contact Data_Privacy_Officer@ iconplc.com.

[1] For emailed survey invitations, this is replaced with a custom URL that is embedded directly in the emailed invitation.

Annex 4 Survey Questionnaire

Please enter your Unique ID to participate in the survey. Your Unique ID was provided in your survey invitation.
Unique ID: _____ ➔ **IF ENTERED, PROCEED TO COUNTRY AND LANGUAGE SELECTION, OTHERWISE, TERMINATE SURVEY**

All questions will be included in the "full survey".

Items in RED font are programming instructions and will not be seen by participants who complete the survey.

The above section will only appear for respondents who did not receive their invitation directly by email from the Confirmit survey software.

Correct responses are ticked as ✓ and will be removed for the versions used for pre-testing and the actual survey

Place Questions 13-20 on the same page.

Please select your country and language from the list below:

- ☐ Country 1 (language) ➔ **PROCEED TO SURVEY INTRODUCTION**
- ☐ Country 2 (language) ➔ **PROCEED TO SURVEY INTRODUCTION**
- ☐ Country 3 (language) ➔ **PROCEED TO SURVEY INTRODUCTION**
- ☐ Country 4 (language) ➔ **PROCEED TO SURVEY INTRODUCTION**
- ☐ Country 5 (language) ➔ **PROCEED TO SURVEY INTRODUCTION**
- ☐ Country 6 (language) ➔ **PROCEED TO SURVEY INTRODUCTION**
- ☐ My country is not listed ➔ **THANK AND TERMINATE**

[Termination Language for Non-Qualified Candidates:]

Thank you for your interest in participating in this survey. However, we are required to limit participation to patients and caregivers located in one of the listed countries. We look forward to your potential participation in a future survey.

Survey Introduction

This survey is being conducted by ICON, on behalf of Astellas Pharma Europe B.V. (Astellas), among patients, or caregivers of patients, who have been prescribed Padcev™ for the treatment of bladder cancer. The overall goal of this study is to assess how well the Padcev™ Patient Card worked to inform patients and caregivers about the potential risks of Padcev™. **Astellas is performing this survey as part of the requirement to assess the Padcev™ Patient Card in the Risk Management Plan submitted to the European Medicines Agency (EMA).** Participation in this survey is voluntary.

To complete the survey, you must meet study eligibility criteria (based on a series of Yes/No questions). Please be assured that your individual answers will be held confidential. Your results will be combined with other participants results and will then be summarized to protect the confidentiality of your individual answers.

By participating, you agree that ICON may contact you only about this survey. You may withdraw from the survey at any time, in which case the information you provide will not be used in the final study report.

Please click on the NEXT button to verify that you qualify for this survey and to complete the required documentation for participation.

[BEGIN SURVEY SCREENING QUESTIONS]

S1. Have you received or are you currently receiving Padcev™ therapy for the treatment of bladder cancer?

☐ Yes ➔ **PROCEED TO S4**
☐ No ➔ **PROCEED TO S2**

S2. Are you a caregiver of a patient who has received or is currently receiving Padcev™therapy for the treatment of bladder cancer?

☐ Yes ➔ **PROCEED TO S3**
☐ No ➔ **THANK AND TERMINATE**

S3. Has the person you provided care for passed away?

☐ Yes ➔ **THANK AND TERMINATE**
☐ No ➔ **PROCEED TO S4**

S4. Are you 18 years of age or older?

☐ Yes ➔ **PROCEED TO S5**
☐ No ➔ **THANK AND TERMINATE**

S5. Do you give your permission to share your anonymized survey responses, combined with all other survey responses, with the European Medicines Agency or national competent authorities, if requested?

☐ Yes ➔ **PROCEED TO S6**
☐ No ➔ **THANK AND TERMINATE**

S6. Did you previously participate in an interview to assess the questionnaire for Padcev™ used in this survey?

☐ Yes ➔ **THANK AND TERMINATE**
☐ No ➔ **PROCEED TO S7**

S7. Have you (or an immediate family member) been a direct employee of Astellas, ICON, the European Medicines Agency, or other European-based National Competent Authorities within the past 5 years?

☐ Yes ➔ **THANK AND TERMINATE**
☐ *No* ➔ **PROCEED TO MAIN SURVEY**

[Termination Language for Non-Qualified Candidates:]

Thank you for your interest in participating in this survey. However, we are required to limit participation to patients or caregivers who meet the survey eligibility requirements. We look forward to your potential participation in a future survey.

[Language for Qualified Candidates of Full survey:]

Thank you for your responses. You qualify for this survey. The survey consists of 2 questions related to your awareness of Padcev™ safety information available, 5 questions related to your behaviours related to Padcev™ treatment, 5 questions related to your knowledge of the safety risks, and finally additional demographic questions. We look forward to your participation. This survey should take no more than 15 minutes.

[END SURVEY SCREENING QUESTIONS]

AWARENESS

[Preamble 1]: Please tell us about your awareness of the Padcev™ Patient Card. THERE ARE NO CORRECT ANSWERS FOR THIS SECTION.

1. Are you aware of the Padcev™ Patient Card?
   a. Yes
   b. No ➔ **PROCEED TO Q8**
   c. I don't know/am not sure

2. How did you access the Padcev™ Patient Card?
   a. The doctor who prescribed Padcev™ gave me the card
   b. I found it online
   c. I have not accessed the Patient Card ➔ **PROCEED TO Q8**
   d. I don't know/am not sure

BEHAVIOURS

[Preamble 1]: Please tell us about the practices concerning the Padcev™ Patient Card, whether yours or for the person you care for. THERE ARE NO CORRECT ANSWERS FOR THIS SECTION.

3. Did you review information in the Padcev™ Patient Card?
   □ Yes
   □ No ➔ **PROCEED TO Q5**
   □ I don't know/am not sure

4. How much of the Padcev™ Patient Card did you review?
   - □ All of it
   - □ Some of it
   - □ I don't know/am not sure

5. How often do you or the patient you care for carry the Padcev™ Patient Card?
   - □ All of the time
   - □ Some of the time / Only when interacting with healthcare professionals
   - □ None of the time
   - □ I don't know/am not sure

6. Have you, or the patient you care for, had a doctor's appointment, interacted with a pharmacist, gone to a walk-in clinic, or had a hospital visit since starting Padcev™?
   - □ Yes
   - □ No ➔ **PROCEED TO Q8**
   - □ I don't know/am not sure ➔ **PROCEED TO Q9**

7. How often did you show the Padcev™ Patient Card when interacting with healthcare professionals?
   - □ At each visit to a healthcare professional
   - □ At each visit, apart from with the prescribing physician
   - □ At some visits. I forgot the Patient Card on at least one occasion
   - □ None of the time
   - □ I don't know/am not sure

KNOWLEDGE

[Preamble 2]: These questions are about information in the Padcev™ Patient Card. Please be sure to review all response choices for each question before answering each question, you will not be able to return to a question once you have clicked on the "Next" button.

In this section, please provide the responses that best reflect your thinking.

8. Which one of the following is a potential complication that may occur while being treated with Padcev™?
   - □ Urinary tract infections
   - ✓ Severe skin reactions

□ Abnormal heart rhythms
□ Stroke
□ I don't know/am not sure

Q9-Q12 only appear if Q1 is answered "YES" and Q2 is answered "The doctor who prescribed Padcev™ gave me the card" or "I found it online."

9. Which of the following are severe skin reactions listed on the Padcev™ Patient Card?

□ Stevens-Johnson Syndrome (SJS)
□ Toxic Epidermal Necrolysis (TEN)
□ Symmetrical drug-related intertriginous flexural exanthema (SDRIFE)
✓ All the above
□ I don't know/am not sure

10. According to the Padcev™ Patient Card, which symptoms below may indicate severe complications associated with Padcev™? Please select "Yes" (symptom may indicate severe complication), "No" (symptom does not indicate severe complication), or "I don't know/am not sure" for each item.

		Yes	**No**	**I don't know/am not sure**
A	Chest pain	☐	✓	☐
B	Skin blistering or peeling	✓	☐	☐
C	Painful sores or ulcers in the mouth or nose, throat, or genital area	✓	☐	☐
D	Bloody nose	☐	✓	☐
E	Painful urination	☐	✓	☐
F	Fever or flu like symptoms	✓	☐	☐

11. The severe skin complications listed on the Padcev™ Patient Card can only occur during the first few weeks of treatment.

□ True
✓ False

□ I don't know/am not sure

12. If you or the person you care for has one of the symptoms listed on the Padcev™ Patient Card, when should you seek medical treatment?

□ When it's convenient
□ Within a week
□ In the next day or two
✓ Immediately
□ I don't know/am not sure

PARTICIPANT CHARACTERISTICS

[Preamble 3]: The following questions will help us interpret the survey results once we have combined your answers with other answers we have received. THERE ARE NO CORRECT RESPONSES. ONE SELECTION FOR EACH QUESTION.

13. How old, in years, are you?

□ 18-29 years old
□ 30-39 years old
□ 40-49 years old
□ 50-59 years old
□ 60-69 years old
□ 70-79 years old
□ 80-89 years old

14. What is the highest level of education that you have achieved?

□ Some high school
□ High school graduate
□ Some college
□ Trade/Technical/Vocational training
□ Some postgraduate work
□ Postgraduate degree

The following only appear if S1 is answered "YES".

15. How many 28-day treatment cycles of Padcev™ did you receive?

□ 1
□ 2
□ 3 or more
□ I don't know/am not sure

16. Approximately, how long ago were you prescribed Padcev™?
- □ <3 months ago
- □ 3 to <6 months ago
- □ 6 to <12 months ago
- □ I don't know/am not sure

The following only appear if S2 is answered "YES".

17. How old, in years, is the person you care for?
- □ 18-29 years old
- □ 30-39 years old
- □ 40-49 years old
- □ 50-59 years old
- □ 60-69 years old
- □ 70-79 years old
- □ 80-89 years old

18. What is the highest level of education that the person you care for has achieved?
- □ Some high school
- □ High school graduate
- □ Some college
- □ Trade/Technical/Vocational training
- □ Some postgraduate work
- □ Postgraduate degree

19. How many 28-day treatment cycles of Padcev™ did the person you care for receive?
- □ 1
- □ 2
- □ 3 or more
- □ I don't know/am not sure

20. Approximately, how long ago was the person you care for prescribed Padcev™?
- □ <3 months ago
- □ 3 to <6 months ago
- □ 6 to <12 months ago
- □ I don’t know/am not sure

CLOSING

Thank you for taking the time to complete this survey.

You may now close this browser.

14 SIGNATURES

PROTOCOL APPROVED BY:

PPD PPD Pharmacovigilance	Date (DD Mmm YYYY)
PPD PPD Pharmacovigilance	Date (DD Mmm YYYY)
PPD PPD Pharmacovigilance	Date (DD Mmm YYYY)
PPD PPD Pharmacovigilance	Date (DD Mmm YYYY)
PPD PPD Medical Affairs	Date (DD Mmm YYYY)
PPD PPD Pharmacovigilance	Date (DD Mmm YYYY)

(e-signature approvals are shown in next page)