NON-INTERVENTIONAL PASS PROTOCOL

Title	**Health Care Professional survey on understanding of key risk minimisation measures related to interstitial lung disease (ILD) / pneumonitis with Trastuzumab Deruxtecan treatment**
Protocol version identifier	Final 1.0
Date of last version of protocol	Not applicable
EU PAS register number	-not registered yet-
Active substance	Trastuzumab deruxtecan (T-DXd) ATC code: L01XC41
Medicinal product	Enhertu
Product reference	EU/1/20/1508/001
Procedure number	EMEA/H/C/005124
Marketing authorisation holder(s)	Daiichi Sankyo Europe GmbH (DSE) Zielstattstrasse 48 81379 Munich Germany
Joint PASS	No
Research question and objectives	The aim of this study is to evaluate the effectiveness of T-DXd's risk minimisation measures for the important identified risk of ILD/pneumonitis by assessing their correct implementation among physicians expected to prescribe T-DXd. Physicians' knowledge and understanding of the educational material proposed by DSE will be evaluated. Primary objective: • To assess physicians' awareness, knowledge, and implementation of additional risk minimisation measures related to the risk, early detection, diagnosis, and management of ILD/pneumonitis. Secondary objectives: • To measure physicians' awareness of the ILD/pneumonitis risk and its related minimisation measures • To assess the extent to which physicians are aware of having received the educational material (HCP guide and patient card) • To measure physicians' knowledge on the requirement for treatment modifications in case of suspected ILD/pneumonitis • To measure physicians' knowledge on the requirement to monitor specific signs and symptoms that allow early detection of ILD/pneumonitis • To assess whether physicians implement the recommended talking points to patients at the recommended frequency • To assess the extent to which physicians implement the distribution of the patient card to their patients

Country(-ies) of study	Austria, Denmark, France, Germany, Sweden, Spain, UK
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Marketing authorisation holder(s)

Marketing authorisation holder(s)	Daiichi Sankyo Europe GmbH Zielstattstrasse 48 81379 Munich Germany
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3 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADC	Antibody Drug Conjugate
AE	Adverse Event
aRMM	additional Risk Minimisation Measure
ASOCS	Association of Opinion and Behaviour in health field research companies
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
DSE	Daiichi-Sankyo Europe
EM	Educational Material
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EphMRA	European Pharmaceutical Marketing Research Association
EU	European Union
GVP	Good Pharmacovigilance Practices
HCP	Health Care Professional
HER2	Human Epidermal growth factor Receptor 2
ILD	Interstitial lung disease
ISPE	The International Society for Pharmacoepidemiology
MAH	Market Authorisation Holder
PC	Patient Card
PAS	Post Authorisation Study
PASS	Post Authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOP	Standard Operating Procedure
STROBE	Strengthening the Reporting of Observational studies in Epidemiology
T-DXd	Trastuzumab Deruxtecan
UK	United Kingdom
USA	United States of America

4 RESPONSIBLE PARTIES

Sponsor: Daiichi Sankyo Europe

Project Manager: [redacted]

Contractor: IQVIA

The execution of this protocol will be the responsibility of the IQVIA Real World Evidence Solutions, acting as contracted principal investigator.

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SIGNATURE PAGE

Reviewed and approved by:

5 ABSTRACT

Title

Health Care Professional survey on understanding of key risk minimisation measures related to interstitial lung disease (ILD) / pneumonitis with Trastuzumab Deruxtecan treatment

Final Version 1.0; 20 December 2021

Rationale and background

In January 2021, the European Commission has granted Trastuzumab Deruxtecan (T-DXd) a conditional approval for use as a monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens.

Interstitial lung disease (ILD) and/or pneumonitis have been identified as important risks for patients treated with T-DXd, and fatal outcomes have been observed.

To prevent / minimize the occurrence of severe ILD/pneumonitis, the Marketing Authorization Holder (MAH) Daiichi-Sankyo Europe (DSE) proposed additional risk minimisation measures (aRMM) for ILD/ pneumonitis and developed educational material (EM), which includes:

- a Healthcare Professional (HCP) Guide and
- a Patient Card (PC).

A prescriber survey will be performed in the EU Member States where T-DXd is marketed to evaluate effectiveness of these key risk minimisation measures for ILD/ pneumonitis.

Research question and objectives

The aim of this study is to evaluate the effectiveness of T-DXd's aRMMs for the important identified risk of ILD/pneumonitis by assessing their correct implementation among physicians expected to have prescribed or will potentially prescribe Enhertu (T-DXd). Physicians' awareness, knowledge and implementation pertaining the key messages of the aRMMs distributed by DSE will be evaluated.

The primary objective for this study is:

- To assess physicians' awareness, knowledge, and implementation of additional risk minimisation measures related to the risk, early detection, diagnosis, and management of ILD/pneumonitis.

The secondary objectives for this study are:

- To measure physician's awareness of the ILD/pneumonitis risk and its related minimisation measures
- To assess the extent to which physicians are aware of having received the educational material (HCP guide and patient card)
- To measure physician's knowledge on the requirement for treatment modifications in case of suspected ILD/pneumonitis
- To measure physicians' knowledge on the requirement to monitor specific signs and symptoms that allow early detection of ILD/pneumonitis
- To assess whether physicians implement the recommended talking points to patients at the recommended frequency
- To assess the extent to which physicians implement the distribution of the patient card to their patients

Study design

This is a cross-sectional, multi-national survey conducted among physicians who are prescribers or potential prescribers of T-DXd in a selection of European countries where T-DXd is marketed.

Population

The survey will be conducted among office and hospital-based physicians in European countries approximately 12 months after the distribution of EM for T-DXd. According to the launch sequence of T-DXd in European countries planned for 2021-2022, the following 7 countries will be included in the survey: Austria, Denmark, France, Germany, Sweden, Spain, UK.

The population to be surveyed in the selected countries will comprise physicians from the distribution list for the EM who are prescribers or potential prescribers of T-DXd. Physicians will be further selected on the basis that they treat patients for their breast cancer and that they are aware of T-DXd.

Variables

Variables related to physician characteristics, practice information, their awareness of the important identified risk of ILD/pneumonitis, and clinical actions related to the identified risk will be collected. Physicians will be asked to indicate their knowledge of the requirement to monitor specific signs and symptoms for early detection of ILD/pneumonitis, their management, and the implementation of proposed risk mitigation measures. In addition, physicians' opinions on the usefulness of EM (HCP guideline) will be sought.

Data sources

The survey is a primary data collection of the responses provided by physicians via a web-based questionnaire.

Physicians from the distribution list of the EM will be contacted in a random order.

Study size

The survey aims to recruit 262 physicians from different European countries in the project. The target is to collect responses from at least 165 prescribers of T-DXd and up to 97 potential prescribers.

Based on the number of physicians on the distribution list of the education material, it is assumed that approximately 78 physicians will complete the survey.

Data analysis

The statistical analysis will be done descriptively and conducted using the software SAS® V9.3 or higher.

The statistical results of the physician survey data will be presented in one report, by country, and combined.

In addition, analyses will be stratified by physicians' prescribing status (prescriber vs. potential prescriber) and, if applicable, by specialty.

Analysis of submitted questionnaires will be performed for 3 domains:

- Awareness questions
- Knowledge questions
- Implementation questions

Milestones

Milestone	Planned date
T-DXd approval	January 2021
Protocol submission to PRAC	May 2021
Registration in the EU PAS register	After approval of the protocol and before start of data collection
Start of data collection	March 2022
End of data collection	December 2023
Final report of study results	June 2024

6 AMENDMENTS AND UPDATES

None.

7 MILESTONES

Milestone	**Planned date**
T-DXd approval	January 2021
Protocol submission to PRAC	May 2021
Registration in the EU PAS register	After approval of the protocol and before start of data collection
Start of data collection	March 2022
End of data collection	December 2023
Final report of study results	June 2024

8 RATIONALE AND BACKGROUND

Background

Trastuzumab Deruxtecan (T-DXd) is an antibody drug conjugate (ADC) indicated for the treatment of adult patients with unresectable or metastatic human epidermal growth factor receptor 2- (HER2) positive breast cancer who have received 2 or more prior anti-HER2 regimens.

HER2 is a tyrosine kinase receptor growth-promoting protein expressed on the surface of many types of tumours including gastric, breast and lung cancers. Approximately 15 to 20% of metastatic breast cancers are characterized by overexpression or amplification of HER2 which is often associated with aggressive disease (1–3). Despite recent improvements and approvals of new medicines, significant clinical needs remain for patients with HER2 positive metastatic breast cancer.

ADCs are targeted cancer medicines that deliver cytotoxic chemotherapy (“payload”) to cancer cells via a monoclonal antibody that binds to a specific target expressed on cancer cells.

T-DXd is a HER2 directed ADC. It is comprised of a humanized HER2 monoclonal antibody attached to a novel topoisomerase I inhibitor payload by a tetrapeptide-based linker. This linker is stable in plasma and is selectively cleaved by cathepsins that are up-regulated in tumour cells (4–7). Unlike other trastuzumab-containing drugs, T-DXd has a payload that, after release, easily crosses the cell membrane, which potentially allows for a potent cytotoxic effect on neighbouring tumour cells regardless of target expression (5). In addition, the released payload has a short half-life, which is designed to minimize systemic exposure. (4–7)

In January 2021, European Commission has granted T-DXd (5.4 mg/kg) a conditional approval for use as a monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens.

Rationale

Risk

Interstitial lung disease (ILD) and/or pneumonitis have been identified as important risks for patients treated with T-DXd, and fatal outcomes have been observed. In clinical studies (HER2-pos. BC 5.4 mg/kg pool, n = 234), adjudicated ILD occurred in approximately 15.0% of patients (grade 1 in 3.0%, grade 2 in 8.5%, grade 3 in 0.4%, grade 5 in 3.0% of patients (8)).

Risk minimisation measures

To prevent / minimize the occurrence of severe ILD/pneumonitis, the Marketing Authorization Holder (MAH) Daiichi-Sankyo Europe (DSE) proposed additional risk minimisation measures (aRMM) for ILD/ pneumonitis and developed educational material (EM), which includes:

- a Healthcare Professional (HCP) Guide and
- a Patient Card (PC).

According to the guidelines on good pharmacovigilance practices (GVP) Module V, VIII, and XVI effectiveness of risk minimisation activities should be assessed. Therefore, the MAH proposed to conduct a prescriber survey to evaluate effectiveness of these key risk minimisation measures for ILD/ pneumonitis. The MAH plans to verify that in the European countries where T-DXd is marketed, physicians expected to prescribe T-DXd are aware of, knowledgeable of and implementing the key risk minimisation measures of the EM.

9 RESEARCH QUESTION AND OBJECTIVES

9.1 Research question

The aim of this study is to evaluate the effectiveness of T-DXd’s risk minimisation measures for the important identified risk of ILD/pneumonitis by assessing their correct implementation among physicians expected to have prescribed or will potentially prescribe Enhertu (T-DXd). Physicians’ awareness, knowledge and implementation pertaining the key messages of the aRMMs distributed by DSE will be evaluated.

9.2 Objectives

The primary objective for this study is:

- To assess physicians' awareness, knowledge, and implementation of aRMMs related to the risk, early detection, diagnosis, and management of ILD/pneumonitis.

The secondary objectives for this study are:

- To measure physicians' awareness of the ILD/pneumonitis risk and its related minimisation measures
- To assess the extent to which physicians are aware of having received the educational material (HCP guide and patient card)
- To measure physicians' knowledge on the requirement for treatment modifications in case of suspected ILD/pneumonitis
- To measure physicians' knowledge on the requirement to monitor specific signs and symptoms that allow early detection of ILD/pneumonitis
- To assess whether physicians implement the recommended talking points to patients at the recommended frequency
- To assess the extent to which physicians implement the distribution of the patient card to their patients

10 RESEARCH METHODS

10.1 Study design

This is a cross-sectional, multi-national survey conducted among physicians who are prescribers or potential prescribers of T-DXd in a selection of European countries where T-DXd is marketed.

An online multiple-choice questionnaire will be used to capture the physicians' responses in the survey.

The print version of the questionnaire is available in Annex 3.

The survey will be completed in a web-based format or, alternatively, by phone if preferred by participating physicians. Details on conduct of the study are provided in section 10.4.3.

10.2 Setting

The survey will be conducted among office and hospital-based physicians in European countries approximately 12 months after the distribution of EM for T-DXd. According to the launch sequence of T-DXd planned for 2021-2022, the following 7 European countries will be included in the survey: Austria, Denmark, France, Germany, Sweden, Spain, UK (Table 1 below). It is planned that the distribution of the EM will be performed at launch or shortly after launch. However, the list of countries is subject to change and might be updated before the start of the survey.

Table 1 Country specific T-DXd launch schedule in European countries

Country	Planned launch date (month / calendar year)
Austria	March 2021
France	April 2021
UK	April 2021
Denmark	June 2021
Sweden	July 2021
Germany	March 2022
Spain	December 2022

10.2.1 Population

The population to be surveyed in the selected countries will comprise physicians who are prescribers or potential prescribers of T-DXd.

All physicians who were planned to receive the EM based on the distribution lists and have not provided their general opt-out will be considered as the target population for the survey. The physicians from the distribution list will be contacted in a random order and invited to participate in the survey until the target number of physicians for that country is reached or the list is exhausted.

Inclusion criteria:

Physicians of the relevant specialties (i.e. either oncologists or gynaecologists) must meet all of the following inclusion criteria:

- Physicians on the distribution list for the EM

Exclusion criteria:

- Physicians who may have conflicts of interest with the survey (i.e., physicians employed by pharmaceutical industry or contracted by regulatory bodies, e.g. EMA)
- Physicians who are not actively treating patients for their breast cancer
- Physicians who are not aware of T-DXd

10.3 Variables

The following variables are recorded in the survey:

1) Variables related to physician's characteristics and practice information:
   - Location (country)
   - Physician's age group
   - Physician's primary speciality
   - Type of care setting (office-based, hospital based or both)
   - Duration of practice (years of practice as a physician)
   - Past experience with T-DXd (number of patients treated)
2) Variables related to the physician's awareness about the important identified risk of ILD/pneumonitis as well as the physicians' awareness of clinical measures with respect to the identified risk:
   - Awareness of important identified risk of ILD/pneumonitis (yes/no)
   - Awareness of having received EM (yes/no)
3) Variables related to the physician's knowledge on the requirement to monitor specific signs and symptoms that allow early detection of ILD/pneumonitis and its management - percentages of physicians with correct answers:
   - Specific measures to early detect ILD/pneumonitis (tick boxes with correct and false answers)
   - Specific signs and symptoms of ILD/pneumonitis that should be monitored closely (tick boxes with correct and false answers)
   - Management in case of suspected diagnosis of ILD/pneumonitis (tick boxes with correct and false answers)
4) Variables related to the implementation of the proposed risk minimisation measures by the physicians:

- For potential prescribers: Points to address with respect to the risk of ILD/pneumonitis before first treatment (tick boxes with correct and false answers)
- For prescribers and potential prescribers: Actions to perform immediately to manage a suspected T-DXd related ILD/Pneumonitis
- For prescribers:
    - Performance of risk minimisation tasks to check at visits with the required frequency
    - Distribution of patient card

5) Other variables:

- Physician's opinion on usefulness of EM (HCP guide) (closed question: very useful to not useful)
- Physicians involvement as investigator in clinical trials regarding T-DXd

10.4 Data sources

The survey is a primary data collection of the responses provided by physicians via a web-based questionnaire.

The survey will be conducted by IQVIA.

10.4.1 Identification of physicians

In each country, the physicians on the distribution lists of the EM comprise the target population of this study. The distribution list will include physicians of relevant specialties as agreed with the local authorities. Physicians on the distribution list will be matched with IQVIAs OneKey database so information on opt-outs and updated contact information is available.

Prescribers and potential prescribers of T-DXd will be considered as the target population and will be recruited in a random order.

10.4.2 Questionnaire

The questionnaire will focus on evaluating the participants' knowledge and understanding of the EM related to the important risk of ILD/pneumonitis. It will include multiple-choice and closed questions, as appropriate. The link to the web questionnaire will be sent to the participating physicians to collect information on their awareness, knowledge and implementation of the key messages of the aRMM regarding risk, early detection, diagnosis, and management of ILD/pneumonitis. Information regarding distribution of the Patient Card to patients will also be collected. In the main part of the survey, participants will not be able to go back in the questionnaire to correct their responses. This is prevented because subsequent questions could indicate correct answers.

Validation

The original survey questionnaire will be generated in English and tested by at least 3 physicians of relevant specialties for its comprehensibility, consistency and the appropriateness of medical terms. Physicians' comments will be implemented in the final version.

The questionnaire will be translated into the relevant local languages. Local medical experts will review and approve the localised questionnaires.

It is estimated that it takes a physician about 15 minutes to complete the questionnaire.

10.4.3 Conduct of survey

The data collection period in each of the selected countries will start approximately 12 months after the country's specific launch of T-DXd. The fieldwork start date will vary by country based on the date of local market launch and the time when the EM was distributed (anticipated earliest launch date: March 2021, Table 1). The fieldwork of the survey will last about 8-12 weeks in each participating country. According to the current status of market launch sequence in the countries, the anticipated end of data collection is in December 2023, approximately 12 months after the latest expected launch of T-DXd in the selected countries. Details on project timelines are provided in section 7 "Milestones".

To ensure that the invitation and the survey are well understood, the entire physician outreach will be conducted in the respective country's local language with exception of Denmark and Sweden, where the English version will be used.

Physicians will be contacted mainly via email or phone call by the IQVIA Primary Intelligence team. The recruitment process will be executed as follows:

- Physicians will be invited to participate in the survey (via email or phone call). The survey background and objectives, the contact information for questions, and the proposed compensation will be explained to the physicians at this step. IQVIA will ensure that the compensation is in line with relevant guidelines of each country (fair market value) and that it only constitutes a compensation for the actual effort and time that is needed to fill-in the questionnaire
- Physicians can also choose to participate in the survey by phone. In this case, an appointment for a phone interview will be scheduled with the physician.
- If they agree to participate in the web survey, they will receive an invitation email with the access link to the online survey platform and the instructions for completing the web questionnaire
    - If the questionnaire is not completed within one week, a reminder to complete the questionnaire will be sent to the participating physician by email.
    - If the questionnaire is not completed within two weeks, a second reminder to complete the questionnaire will be sent to the participating physician by email.
- For physicians that do not respond to the initial invitation to the survey and the maximum sample size for the country is not reached:
    - Physicians will be approached by three follow-up call attempts or email reminders.
    - Physicians will be contacted more often in case it is expected that this may lead to participation

A physician will be considered as contacted if he/she:

- has completed the web-based questionnaire
- has refused to participate
- considered as not reachable (has been approached at least 3 times without any response).

For each physician of the sample, the number of contacts, and the date and time when he/she completed the web questionnaire will be recorded. The recruitments in each country will be stopped once the target is reached. If all contacts on the distribution lists have been contacted in a country, the recruitment in this country will be ended.

The number of physicians passing the screening questions and the survey response rate will be monitored regularly by IQVIA.

Approaches for increasing response rate

People are increasingly contacted to participate in web or phone surveys. The overall response rate of participation remains low according to international studies (9–11): Holbrook et al. showed that the response rate to surveys continues to decline over time, but a lower rate does not appear to reduce the representativeness of a demographic survey (10). Van Geest et al. conducted a systematic review of 66 published reports on efforts to perform for improving response rates (12). Two general strategies were explored: incentives-based approaches and survey design-based approaches. Monetary incentives, even little ones, were effective in improving physician response rates while non-monetary incentives e.g. use of a short questionnaire were much less effective.

In order to increase the response rate among physicians, three actions will be applied to this survey:

- A compensation fee will be proposed to physicians for their participation in the survey.
- All physicians will be sent an email or contacted by experienced operators of IQVIA with extensive experience in conducting health related surveys.
- Each physician will be emailed or called at least 3 times before being considered as “not reachable”.

10.5 Study size

The survey aims to recruit 262 physicians from different European countries in the project. The target is to collect responses from at least 165 prescribers of T-DXd and up to 97 potential prescribers. In the concept sheet of the study, the planned number of recipients for the EM was 2,800 physicians and the expected sample size of 262 physicians. As currently, only 1,538 HCPs (including 1,351 physicians) are planned to receive the EM in the countries for the study, the achievable sample size is smaller than anticipated to when the concept sheet was drafted.

Based on the number of physicians on the distribution list of the education material, it is assumed that approximately 78 physicians will complete the survey:

Table 2 Estimated sample size based on the available source population for the survey

Step in the derivation of sample size	Number
HCPs on distribution list (see Table 4)	1,538
Physicians on list with gynaecological or non-surgical oncology specialty	1,351
Physicians expected to respond to invitation (8%)	108
Physicians expected to treat breast cancer (85%)	92
Physicians expected to be aware of T-DXd (95%)	87
Physicians expected to complete survey (90%)	78

Although the assumed realistic sample size is lower, reasonable efforts (see section 10.4.3) will be made to reach the originally planned sample size of 262.

Expected precision of the estimates

The sample size formula based on the normal approximation to the binomial is the following:

$$n = \frac{P \cdot (1-P) \cdot \left(Z_{1-\alpha/2}\right)^2}{e^2},$$

Where P is the expected proportion, e is one half of the desired width of the confidence interval, and Z1–α/2 is the standard normal Z value corresponding to a cumulative probability of 1 – α/2 (e.g., if α = .05 then Z = 1.96).

The proportions of interest (p) here are the proportions mentioned under specific objectives above. As p is not known in advance, we consider it to be 50% (maximum uncertainty). Such a hypothesis yields the most conservative i.e., the largest sample size. For example, the required sample size would be 100 for precision levels of 10%. Table 3 below provides precision of the estimate (width of 95% CI around the estimate) for a range of sample sizes.

Table 3 Margin of Error of the Estimate for a Range of Sample Sizes

Sample Size	Margin of error (%)
100	±9.8
150	±8.0
200	±6.9
250	±6.2
300	±5.7
350	±5.2
400	±4.9
78	±11.1
165	±7.6
262	±6.1

Sampling distribution in the participating countries

All physicians that are on the distribution list of the EM will be contacted, if needed to reach the targeted number per country. At least 30 physicians from each country will have the opportunity to participate in the survey, even if this exceeds the target size in the study countries. To avoid that one country is highly overrepresented in the study, a maximum number of 60 physicians per country is set.

Table 4 Number of HCPs on the distribution lists for the educational material

Country	Planned number of HCPs
Austria	50
Denmark	26
France	616
Germany	207
Spain	236
Sweden	48
United Kingdom	355
Total	**1,538**

10.6 Data management

The survey will be conducted according to the Standard Operating Procedures (SOPs) of IQVIA's Primary Intelligence and IQVIA's Real World & Analytics Solutions.

Collected data will be entered and stored in a central database specific to the survey.

The study database will be locked once validated.

Data Quality Assurance

IQVIA's QC team will be responsible for the data management of this study, including quality checking of the data. IQVIA will produce a Data Management Plan that describes the content of the database.

Quality of data (plausibility and consistency) will be validated at data entry and before data analysis including:

- Removal of duplicates (if required)
- Data labelling and data formatting
- Range and consistency checks for each variable to identify potential non-admissible values.

IQVIA will not query physicians' answers to questions in the questionnaire.

Non-admissible values will be avoided by implementation of the appropriate controls in the questionnaire at the time of its completion by the physicians. Any non-admissible values identified after database lock (if any) will be excluded from the analysis.

10.7 Data analysis

10.7.1 General statistical considerations

The statistical analysis will be conducted using SAS® software Version 9.3 or higher (SAS Institute, North Carolina, USA).

The statistical results of the physicians survey data will be presented in one report, by country and combined (Table 5 as example).

In addition, selected analyses will be stratified by physicians' prescribing status (prescriber vs. potential prescriber) and, if applicable, by specialty. Stratification by specialty will be performed in countries where at least 10 physicians in a specialty have completed the questionnaire. Each specialty for which there are at least 10 questionnaires is presented separately, the remainder will be presented combined as "others".

It is aimed to consider weightening of results with respect to country and physician specialty to account for under- or overrepresentation of participants. The feasibility of weightening is dependent on the compilation of final sample (e.g. more than one speciality take part per country) because the universe of HCPs for this survey is determined by the final distribution lists of the EM for the target countries.

Data will be analysed descriptively. Continuous variables will be presented by their number (of valid cases), mean, standard deviation, median, first and third quartiles (Q1, Q3), minimum, and maximum. Categorical variables will be tabulated with absolute and relative frequency per category. Percentages will be presented to one decimal place.

In case of multiple-choice questions, the frequency of each option provided by the physicians will be reported in the statistical results. Different combinations of the answers provided will not be considered.

Confidence intervals of 95% will be estimated, as appropriate.

A detailed description of planned analyses and table templates will be provided in the statistical analysis plan (SAP), which will be generated prior to the start of the survey.

Table 5 Mock tables to implement in the Statistical and Study Reports

Question …			
Country	**Specialty (oncologists)**	**Specialty (…..)**	**All**
Country 1	(N=xx)	(N=xx)	(N=xx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…			
Country 2	(N=xx)	(N=xx)	(N=xx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…			
Country 3	(N=xx)	(N=xx)	(N=xx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…			
Country x	(N=xx)	(N=xx)	(N=xx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…			
Overall-results	(N=xx)	(N=xx)	(N=xx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
…			

Note: the table structure may be adjusted for the final study report

10.7.2 Questionnaire analysis

Analysable questionnaires are those where physicians passed the screener and questionnaires submitted at least one of the questions in the main part of the survey via internet or by phone.

The proportions of correct and appropriate answers to selected questions asked in the questionnaire will be expressed among physicians who provided answers to those questions. The numbers of missing data will be indicated. Missing values are expected to be few and distributed at random. Remaining questions of participants that start the main part of the questionnaire but do not complete will be considered as missing. Missing values will not be replaced and the number of missing responses for each question will be reported.

Analysis will be performed for 3 domains:

- Awareness questions (question Q3 of physicians' questionnaire)
- Knowledge questions (questions Q4, Q5 and Q7 of physicians' questionnaire)
- Implementation questions (questions Q6, Q8 and Q10 of physicians' questionnaire)

Individual physician's domain scores will be descriptively analysed and reported as the percentage correctly answered questions. Scores will range from 0% to 100% with 100% representing the case of all domain questions being answered correctly. For each question comprised of sub-questions, the number and percentage of physicians answering correctly each sub-question will be reported.

Assessment of success

A successful outcome on the effectiveness of the aRMMs is defined based on specific proportions of correct answers by the following target levels in study population (please see secondary outcomes for criteria for each question). The proportion of physicians who answer correctly to all questions within the criteria (2) and (3) will be used to evaluate success.

The **primary outcome** of the aRMMs for T-DXd will be evaluated as effective if all of the following success criteria are met (1.-3.):

1. Proportion of physicians being aware of the important identified risk of ILD/pneumonitis (Question Q3 of physicians' questionnaire) – Success: ≥80%
2. Proportion of physicians knowledgeable about the important risk of ILD/pneumonitis (Questions Q4, Q5 and Q7 of physicians' questionnaire) – Success ≥60%
3. Proportion of physicians answering the implementation questions correctly
   - For non-prescriber (Questions Q6a and Q8 of physicians' questionnaire) – Success ≥75%
   - For prescriber (Questions Q6b, Q8 and Q10 of physicians' questionnaire) – Success ≥75%

The **secondary outcomes** will be evaluated as follows:

- Physicians' awareness of the ILD/pneumonitis risk and its related minimisation measures:
  Q3 ≥ 80% (proportion that selected at least "Interstitial lung disease (ILD) / pneumonitis")
- Awareness of having received the educational material (HCP guide and patient card):
  Q2 ≥ 80% (proportion that selected "yes")
- To measure physicians' knowledge on the requirement for treatment modifications in case of suspected ILD/pneumonitis:
  Q4 ≥ 80% (proportion that selected "yes")
- To measure physicians' knowledge on the requirement to monitor specific signs and symptoms that allow early detection of ILD/pneumonitis:
  Q5 ≥ 80% selected at least all 4 correct responses
- To assess whether physicians implement the recommended talking points to patients at the recommended frequency
  - For non-prescribers, correct if at least 80% prescribers selected Q6a all correct items
  - For prescribers
    a. Correct if at least 80% prescribers responded Q6b "At most visit" OR "At each visit" to the correct items that should be performed at each visit
    b. Correct if at least 80% prescribers responded Q6b "At first visit" OR "Occasionally" OR "At most visit" OR "At each visit" for the correct items that should be performed at the first visit
- To assess the extent to which physicians implement the distribution of the patient card to their patients:
  Q10 ≥ 80% responded correctly

The thresholds used are in accordance with success rates applied in other studies approved by PRAC and provide a balance between the ideal scenario of achieving a 100% rate of awareness, knowledge and compliance and what can be realistically expected from routine aRMMs in the clinical practice. A success criterion is considered met when the point estimate exceeds the success threshold.

Analysis of Physicians' Participation Rate

Physicians' participation rates in the survey will be examined as follows:

- Complete response rate = C/RE
- Partial response rate = P/RE
- Response rate = (C+P)/RE
- Refusal rate = R/RE

where

- **RE** (reachable physicians): physicians who were reachable and received the invitation to participate in the survey
- **P** (partial completer): physicians who partially responded to the questionnaire and passed the screener questions
- **C** (completer): physicians who completed the entire questionnaire
- **R** (physicians who refused to participate): physicians who explicitly indicated their refusal to participate

The participation rates will be presented by country and by specialty (if applicable).

Characteristics (questions D1-D5: age, country, setting, experience, clinical trial physician) of participating (i.e. physicians that passed the screener) and non-participating physicians (i.e. physicians that did not pass the screener) will be compared to assess possible selection bias.

10.8 Quality control

10.8.1 Validation of questionnaire

The physicians' questionnaire will be tested by targeted physicians (at least 3) in the UK for comprehensibility, consistency, and the appropriateness of medical terms used. The translated questionnaires will be checked by native speakers with medical expertise.

10.8.2 Approaches for quality control of results

The quality control for validating the results will be conducted at five levels:

1. At IQVIA Primary Intelligence management level, every effort will be undertaken to collect complete and valid data:
    - Verification of the reliability and security of the web questionnaire interface by the data management team,
    - Monitoring of the quality and datasets definition by a qualified data manager
2. At the study database level, final data quality checks will be applied (beyond data management process):
    - Identification and count of non-analysable questionnaires: estimation of the percentage of physicians without complete analysable questionnaire,
    - Any changes in the database will be tracked and documented. The country-specific datasets will be stored in a dedicated database. Once data validated and quality checked, the database will be locked.

3. At the statistical analysis level: all data management and statistical analysis programs developed and used in the analysis will be documented. All versions generated will be dated, kept with accompanying documentation and archived. The original database will be stored. A derived database will be created for the new versions of the data in order to include recoding and computing of new variables, especially stratification of continuous variables, combination of modalities for categorical variables, calculation of composite indicators.
4. At the results level, a data review will be done to ensure data integrity. A statistical analysis report including all the results will be provided for review and discussion. The final statistical report will take into account the reviewers' comments.
5. At the study level, all aspects of the study will be conducted according to the SOPs of IQVIA Real World Evidence Solutions and Primary Intelligence divisions. The study documents have been approved by people competent in medical and safety areas of IQVIA. According to the SOPs, an independent review of the survey results and report will be conducted by a person who was not in charge of their preparation.

10.8.3 Record retention

The study documentation will be stored in the study master file.

The data from the web questionnaires and the phone interviews will be stored on the survey database for 10 years.

Data storage will be in line with national data protection requirements for each of the countries where the study will be conducted.

All documentation pertaining to the study, including paper and electronic records will be retained for a minimum of 10 years after the end of the study, in accordance with IQVIA Standards.

10.9 Limitations of the research methods

Selection bias

The potential for selection bias of physicians participating in a survey is an inherent bias/limitation to any study based on volunteer participation. In order to quantify any selection bias, will be compared between participating (i.e. physicians that passed the screener) and non-participating physicians (i.e. physicians that did not pass the screener) of the study. In this survey, the order in which physicians are contacted in a country will follow a stratified randomized method which contributes to the representativeness of the contacted population to limit selection bias due to voluntary participation.

Selection bias inherent to participation via internet

Most physicians take part in the survey via internet. To participate via internet, physicians need an active email address and need to be willing (and able) to answer a questionnaire online. This might restrict generalisation and external validity of the results as these physicians may not be fully representative of the whole targeted population (13).

Social desirability bias

Web surveys may promote social desirability bias which refers to the tendency of physicians to give socially desirable/expected responses instead of choosing those reflecting their current knowledge or behaviour, e.g. physicians can copy-paste information gathered online instead of giving their own opinions (13). Social desirability can affect the validity of survey research findings, but the use of prepopulated items in the questionnaire could reduce this bias (14).

Stakeholder bias

Stakeholder bias (multiple answers of people who have a personal interest in survey results and/or who incite peers to fulfil the survey in order to influence the results) or unverified respondents (when it is not possible to verify who responds) are not applicable for this survey, because the access to the web questionnaire interface will be strictly limited to the invited participants, with the possibility to participate only once.

Non-response bias

Targeted physicians may also have activated filters in their mailbox in order to block spams and unsolicited emails. They may not even see the invitation to participate in the survey if a very strict degree of message filtering is set. Having multiple email addresses could also be a critical situation. If the one used is not the primary address or if the physicians do not check their email box frequently, they will not receive the invitation during the recruitment period. Some physicians who were sent an email may not have received it. This is one of the reasons why the physicians will also be contacted by phone.

Generalisability of results

The survey results will be valid for the physician population included in the country specific distribution lists. Generalizability to the overall target population will be restricted due to possibly low number of participants in some countries and unequal distribution of specialties in the study- and target population.

10.10 Other aspects

None

11 PROTECTION OF HUMAN SUBJECTS

The survey is non-interventional and totally anonymous to the study sponsor. It will accumulate physicians' opinions rather than healthcare data and will not involve any patient data collection. Data collected will remain absolutely confidential, and only aggregated data will be analysed and communicated in a report. Identifiable data are only processed if a regulatory obligation exists (reporting of adverse events) or if compensation is desired.

Regulatory and ethics considerations

The survey will follow the regulatory and ethical requirements of each country in which the research will be conducted. It will be performed in compliance with the Guidelines for Good Pharmacoepidemiological Practice (GPP) published by the International Society of Pharmacoepidemiology (ISPE) (15) and the European Pharmaceutical Marketing Research Association (EphMRA) code of conduct guidelines (16).

Physicians' information

Physicians participating in the study have to consent for data collection. They will be informed about the purpose of the survey, the nature of the transmitted data, the intended use of data, recipients of these data, and storage of data. IQVIA will ensure that the national and European data protection and ethical requirements are met for the physicians. This will be done electronically.

Physicians' compensation

Physicians will be offered a compensation for the time spent participating in this survey (that they may refuse). The estimated time to complete the survey is estimated to be about 15 minutes.

The amount of this compensation will be determined according to the EphMRA recommendations and the Association of Opinion and Behaviour in health field research companies (ASOCS) charter, which states:

"When it is necessary to compensate an HCP in return to the time spent during an interview or a group meeting, the compensation must not exceed the fees commonly taken by the HCP for his/her advice or consultation and must be proportional to the time provided. The compensations should be clearly stated prior to the physicians' participation in the survey. They must be declared to the tax authorities in accordance with applicable laws".

Data confidentiality / Data security

Participating physicians will access the survey website (https secured site) via a secure unique link.

The answers provided will be collected in an anonymous way, only aggregated data and presented as a synthesis will be transmitted to the MAH.

Data will be recorded in a central database and tracked using an audit trail. The system will enable retrieving all introduced data at any time and will include security elements to prevent others than authorized staff from accessing data. Each user will have a specific profile which will limit his/her use of the database. A security copy of the survey database and the application files will be replicated in a separate location.

Description of all elements of security and traceability will be available upon request. The sponsor is the data controller in the study.

12 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study is a survey to evaluate the effectiveness of EM implemented as aRMM. The survey does not involve individual patients' data collection. Although adverse effects are not being measured directly in this survey, any safety information for an individual patient provided by participating physicians during the study must be reported as described below.

In the event that a participating physician reports a safety event associated with a DSE product, IQVIA will forward any information on adverse event (AE) along with the physician's contact information (upon prior consent of the physicians) to the DSE Clinical Safety and Pharmacovigilance department using the DSE AE reporting form. This will be done within the timeline of 1 working day for serious AE or within 30 days for non-serious AE.

13 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The survey will be registered in the European Union electronic Register of Post-Authorisation Studies (EU PAS Register of ENCePP) (17) by MAH.

The final survey report validated by MAH will be communicated to EMA. An abstract of the study results will be also entered into the ENCePP database.

14 REFERENCES

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST

ENCePP Checklist for Study Protocols (Revision 4)

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

Study title:
Health Care Professional survey on understanding of key risk minimisation measures related to interstitial lung disease (ILD) / pneumonitis with Trastuzumab Deruxtecan treatment

EU PAS Register® number: not registered yet
Study reference number (if applicable): not 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[1]	☒	☐	☐	7
1.1.2 End of data collection[2]	☒	☐	☐	7
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	7
1.1.6 Final report of study results.	☒	☐	☐	7

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	9.1
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)	☒	☐	☐	9.1
2.1.2 The objective(s) of the study?	☒	☐	☐	9.1
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.1, 10.2.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

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

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	10.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	10.4
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)	☒	☐	☐	12

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	10.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	10.4.3
	4.2.2 Age and sex	☐	☐	☒	
	4.2.3 Country of origin	☒	☐	☐	10.2
	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)	☒	☐	☐	10.2.1

Comments:

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

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
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:

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?	☒	☐	☐	10.7.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	10.7.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	10.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	10.9

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)	☐	☐	☒	

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)	☒	☐	☐	10.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	10.4, 10.7.2
9.1.3 Covariates and other characteristics?	☒	☐	☐	10.3
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)	☒	☐	☐	10.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	10.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 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?	☒	☐	☐	10.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	10.5
10.3 Are descriptive analyses included?	☒	☐	☐	10.7
10.4 Are stratified analyses included?	☒	☐	☐	10.7
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	10.7.2
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

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)	☒	☐	☐	10.8
11.2 Are methods of quality assurance described?	☒	☐	☐	10.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	10.9
12.1.2 Information bias?	☒	☐	☐	10.9
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)	☒	☐	☐	10.5., 10.9

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?	☒	☐	☐	11
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	11

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?	☒	☐	☐	6.

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)?	☒	☐	☐	13.
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	13.

Comments:

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

Date: [redacted]

Signature: [redacted]

ANNEX 3. ADDITIONAL INFORMATION

Appendix 1. Questionnaire