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InductOs®

Dibotermin alfa/ACS

INN: Dibotermin alfa
EU/1/02/226/001-002

Protocol

A cross-sectional study to evaluate the effectiveness of additional Risk Minimisation Measures: A Survey among surgeons to assess their knowledge and understanding of selected risks of InductOs (dibotermin alfa/ACS) in Europe

Version 2.0. 25 May 2020
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PASS information

Title	A cross-sectional study to evaluate the effectiveness of additional Risk Minimisation Measures: A Survey among surgeons to assess their knowledge and understanding of selected risks of InductOs (dibotermin alfa/ACS) in Europe
Protocol version identifier	2.0
Date of last version of protocol	Not applicable
EU PAS register number	EUPAS32916
Active substance	M05BC01 Dibotermin Alfa
Medicinal product	InductOs
Product reference	EU/1/02/226/001-002
Procedure number	EMEA/H/C/000408
Marketing authorisation holder(s)	Medtronic BioPharma B.V.
Joint PASS	No
Research question and objectives	Primary questions: Do physicians administering InductOs understand the potential for heterotopic ossification occurrence after spinal interbody fusion? Do physicians administering InductOs know the appropriate measures to be taken to minimize the risk of heterotopic ossification occurrence? Secondary question: Was the knowledge on the risk of heterotopic ossification and minimization measures obtained from the SmPC, educational materials, professional training and literature, or a combination of these?
Country(-ies) of study	France, Germany, Ireland, United Kingdom
Author	Koen van der Heijden, MSc dl.biopharmapharmacovigilance@medtronic.com

Marketing authorisation holder(s)

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MAH contact person	Koen van der Heijden, MSc dl.biopharmapharmacovigilance@medtronic.com

1. Table of contents

2. List of abbreviations

ACS	Absorbable Collagen Sponge
AE	Adverse Event
ALIF	Anterior Lumbar Interbody Fusion
ANSM	Agence Nationale de Securité du Médicament et des produits de santé
aRMM	Additional Risk Minimisation Measures
ATC	Antomical Therapeutic Chemical
BfARM	Bundesinstitut für Arzneimittel und Medizinprodukte
CA	Competent Authority
CI	Confidence Interval
DALYs	Disability Adjusted Life Years
EMA/EMEA	European Medicine Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS	European Post Approval Study
GDPR	General Data Protection Regulations
GVP	Good Pharmacovigilance Practices
HPRA	Health Products Regulatory Authority
HROoL	Health-Related Quality of Health
ICD	International Classification of Diseases
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MHRA	Medicines and Healthcare products Regulatory Agency
MSc	Master of Science
OLIF	Oblique Lateral Interbody Fusion
PAS	Post Approval Study
PASS	Post Approval Safety Study
PIR	Product Information Report
PLIF	Posterior Lumbar Interbody Fusion
PLF	Posterior Lumbar Fusion
PRAC	Pharmacovigilance Risk Assessment Committee
QALYs	Quality Adjusted Life Years
rhBMP-2	Recombinant human Bone Morphogenetic Protein-2
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TLIF	Transforaminal Lumbar Interbody Fusion
WHO Drug Dictionary	World Health Organisation Drug Dictionary
XLIF	Extreme Lateral Interbody Fusion

3. Responsible parties

Sponsor

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4. Abstract

4.1 Title

A cross-sectional study to evaluate the effectiveness of additional Risk Minimisation Measures: A Survey among surgeons to assess their knowledge and understanding of selected risks of InductOs (dibotermin alfa/ACS) in Europe.

Version 2.0; May 2020

Koen van der Heijden, MSc, Medtronic BioPharma B.V.

4.2 Rationale and background

The active ingredient of InductOs is dibotermin alfa or recombinant human Bone Morphogenetic Protein 2. Its osteoinductive properties result in the induction of new bone tissue at the site of implantation.

InductOs is approved for:

- single-level lumbar interbody spine fusion as a substitute for autogenous bone graft in adults with degenerative disc disease who have had at least 6 months of non-operative treatment for this condition.
- treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary unreamed nail fixation.

Additional risk minimisation measures (aRMM) to increase awareness about the identified risk of heterotopic ossification (especially in posterior surgical approaches for lumbar interbody fusion) and the potential risk of medication errors and misuse are available in the form of educational materials. This study is set up to measure the effectiveness of InductOs educational materials.

4.3 Research question and objectives

Primary questions:

- Do physicians administering InductOs understand the potential for heterotopic ossification occurrence after spinal interbody fusion ?
- Do physicians administering InductOs know the appropriate measures to be taken to minimize the risk of heterotopic ossification occurrence ?

Secondary question:

- Was the knowledge on the risk of heterotopic ossification and minimization measures obtained from the SmPC, educational materials, professional training and literature, or a combination of these ?

Objective:

The goal of this study is to assess the awareness of InductOs-using spine surgeons concerning heterotopic ossification in relation to the InductOs Risk Management Plan. A supplementary goal of this study is to gauge the clinician's awareness about the development of heterotopic ossification and the risk minimisation measures; specifically identifying from which source was any knowledge obtained.

4.4 Study design

An anonymous, cross sectional and non-interventional (online) survey of a sample of physicians from Germany, France, Ireland and the United Kingdom who have implanted InductOs in the last 2 years.

4.5 Population

Inclusion criteria

Participants of this study must meet the following inclusion criteria to be eligible to participate in this study:

1. Physicians that have implanted InductOs in a lumbar interbody spine fusion procedure at least once in the 24 months prior to taking this survey

Exclusion criteria

Participants meeting any of the following criteria will not be included in the study:

1. Physicians that participated in the testing of this survey, if there are substantial changes made to the survey post-pilot i.e. changes which, in the view of the research team, make the participants contributions invalid or potentially compromising of the study objectives.
2. Physicians that either themselves work for or have immediate family members who work for Medtronic, third parties involved in this study, or a regulatory agency (EMA, MHRA, HPRA, ANSM, BfARM).

4.6 Variables

Information is collected on three main categories. The first category is used to describe the population and includes variables around demographics, type of practice, and level of experience in using InductOs. The second category of variables is aimed at measuring the awareness on the risk of heterotopic ossification, the educational materials and knowledge about safe use of InductOs presented in the educational materials. The third set of variables covers the different sources where information on the key messages in the educational materials could have been obtained.

4.7 Data sources

Data will be collected using a standardized online questionnaire that has been translated into the local languages of the countries where the survey is being conducted.

4.8 Study size

The minimum sample size needed to obtain a proportion with confidence interval with the lower limit above the 80 % minimum awareness was calculated. For this calculation an alfa of 0.05 with a two-sided interval and a distance from proportion to limit of 0.1 was used with the expected proportion of 90 %. This leads to a minimum sample size of 35.

To ensure inclusion of data from the different participating countries, this study aims at collecting responses from physicians covering roughly 10 % of purchasing pharmacies that have received InductOs in the past 2 years in each target country. This brings the total to 55 completed surveys which is above the calculated minimum sample size. Taking into account response rate of roughly 60 % and screening failures an estimated 120 surgeons will be screened for eligibility.

4.9 Data analysis

The study population will include all physicians who are screened, are eligible for this study, and completed the questionnaire. All statistical summaries in this study will be descriptive. Frequencies and percentages, with 95 % confidence intervals (CIs) where appropriate, will be presented. Country specific data will be presented. Additional exploratory analyses and sensitivity analyses may be conducted to identify difference between groups of responders.

The primary analysis is aimed at evaluating the proportion of physicians that is aware of the risk of heterotopic ossification and measures described in the educational materials to minimize that risk. A respondent is considered to be aware if they answer 75 % of the questions with regards to heterotopic ossification and the applicable minimization measures correctly. The aRMM will be considered effective if 80 % of the respondents are aware of the described risk of heterotopic ossification and the appropriate measures to minimize them.

The secondary analysis is aimed at identifying the source of physician knowledge. Based on the received data it will be determined to what extent the educational materials are used and are considered an important source of information for the respondents.

Milestones:

- Start of data collection: September 2020
- End of data collection: November 2020
- Registration in the EU PAS register of the approved protocol: September 2020
- Final report of study results: December 2020

5. Amendments and updates

None after the start of data collection.

6. Milestones

Milestone	Planned date
Start of data collection	September 2020
End of data collection	November 2020
Registration in the EU PAS register of the approved protocol	September 2020
Final report of study results	December 2020

7. Rationale and background

The active ingredient of InductOs is dibotermin alfa or recombinant human Bone Morphogenetic Protein 2. Its osteoinductive properties result in the induction of new bone tissue at the site of implantation.

InductOs is approved for:

- single-level lumbar interbody spine fusion as a substitute for autogenous bone graft in adults with degenerative disc disease who have had at least 6 months of non-operative treatment for this condition.
- treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary unreamed nail fixation.

Instructions for proper preparation and administration of dibotermin alfa/ACS are provided in the Summary of Product Characteristics (SmPC) and instructions for reconstitution are provided in the labelling of the pack. The aforementioned instructions consist of routine measures to minimise important identified (heterotopic ossification, osteolysis/resorption bone increased, fluid collection) and potential risks (medication errors and incorrect use, malignancies, antibody formation) by providing information on the measures to take during administration of dibotermin alfa/ACS or situations to avoid.

Additional risk minimisation measures (aRMM) to increase awareness about the identified risk of heterotopic ossification (especially in posterior surgical approaches for lumbar interbody fusion) and the potential risk of medication errors and misuse are available in the form of educational materials. These educational materials also aim at providing guidance on how to manage these risks. The aRMM present the information from the Summary of

Product Characteristics (SmPC) supported with visual aids, e.g. a demonstration of the correct preparation technique. The aRMM and related educational materials contain no information which is not contained in the SmPC.

InductOs educational materials consist of a preparation guide, two videos (one for each indication), and the SmPC. The educational materials can be accessed through a dedicated website, or upon request to the MAH.

The results from measuring the educational materials effectiveness as described in the Risk Management Plan (RMP), were considered suboptimal by the Pharmacovigilance Risk Assessment Committee (PRAC) in view of the context of administration and availability of data. An assessment of outcome indicators, i.e. the occurrence of heterotopic ossification and medication errors and misuse using the available data sources in the EU, was deemed unfeasible. The PRAC agreed that the effectiveness evaluation could be based exclusively on careful interpretation of data on newly chosen process indicators. Specifically, Medtronic BioPharma considered the use of a survey to determine the available knowledge of physicians administering InductOs. Therefore, Medtronic BioPharma is conducting this cross-sectional knowledge check with the aim of obtaining a better understanding of the knowledge of the physicians regarding the risks and minimisation instructions that are described in the educational materials.

8. Research question and objectives

The goal of this study is to assess the awareness of InductOs-using spine surgeons concerning heterotopic ossification in relation to the InductOs Risk Management Plan. A supplementary goal of this study is to gauge the clinician's awareness about the development of heterotopic ossification and the risk minimisation measures; specifically identifying from which source was any knowledge obtained.

Primary questions:

- Do physicians administering InductOs understand the potential for heterotopic ossification occurrence after spinal interbody fusion?
- Do physicians administering InductOs know the appropriate measures to be taken to minimize the risk of heterotopic ossification occurrence?

Secondary question:

- Was the knowledge on the risk of heterotopic ossification and minimization measures obtained from the SmPC, educational materials, professional training and literature, or a combination of these?

9. Research methods

9.1 Study design

This study is a cross-sectional cohort analysis of InductOs-using spine surgeons to establish:

- their current level of knowledge regarding heterotopic ossification,

- the current level of knowledge, and degree of access to or utilisation of educational materials about the potential for post-surgical heterotopic ossification and practical risk minimisation measures.

A cross-sectional cohort study methodology was judged to be appropriate to meet the expectations of the European Medicines Agency (EMA) based on:

- The nature of the medicinal product: single use implantation in a relatively small target population
- The nature of heterotopic ossification which is not an uncommon adverse event of many orthopaedic procedures and it does not always manifest clinically
- The lack of appropriate data fields captured in the national spine registries across Europe,
- The period over which the educational materials have been available (since summer 2017)

The cohort study will be composed of an anonymous, online survey (see Annex 3) with the aim of answering the study questions outlined in section 8.

The screening for eligibility and online interviews will be conducted in the surgeon's native language. All materials will be prepared using the English master questionnaire as the baseline (see Annex 3). Translations will undergo appropriate quality checks prior to sign off by the research team.

The researchers will secure responses from 55 individuals from the four selected countries split proportionally based on usage, see section 9.5.

A pilot project of 2 surgeons will test the survey for clarity and accuracy of response and translated materials in an iterative manner. If no changes are made, then the pilot recruits will be included in the main cohort.

9.2 Setting

As the national spine registries at the time of this study do not record InductOs use or the incidence of heterotopic ossification, and no database of physicians who prescribe InductOs exists, a random or probability sample is not feasible for this cohort study.

A non-probability sample (i.e. convenience sample) of orthopaedic surgeons and neurosurgeons who have administered InductOs in the last 2 years (recent users) will be chosen from a pool of the four countries comprising the largest InductOs-selling countries (France, Germany, United Kingdom and Ireland).

Hospitals who have purchased the medicinal product in the 24 months prior to the cut-off date for confirmation of the 'involved study accounts' with the study researchers, will be identified from Medtronic sales records. The appropriate hospital clinicians will then be approached by the study researchers to identify and screen for surgeons meeting the inclusion/ exclusion criteria. Eligible surgeons will be invited to participate in an online interview to quantitatively extract the required information via a personal link by email, and up to two reminders will be sent if needed. The first reminder is sent by email after 2 days, the second reminder is sent after 5 days and the surgeon will be given a call at that time as well.

Any surgery where InductOs is implanted is conducted under supervision of a surgeon, including the preparation of the medicinal product. The main risk minimization measures are under the control of the surgeon, e.g. placing an additional barrier between implanted matrix and the spinal canal. Therefore, the target population for the survey has been determined to be surgeons only.

Participating physicians have the option to receive compensation for their time. The amount will be determined based on the maximum allowed for each country and a fair market value assessment, appropriate reporting or disclosure of physician reimbursement will comply with appropriate regulations and codes of practice; dependant on physician location.

Inclusion criteria

Participants of this study must meet the following inclusion criteria to be eligible to participate in this study:

1. Physicians that have implanted InductOs in a lumbar interbody spine fusion procedure at least once in the 24 months prior to taking this survey

Exclusion criteria

Participants meeting any of the following criteria will not be included in the study:

1. Physicians that participated in the testing of this survey, if there are substantial changes made to the survey post-pilot i.e. changes which, in the view of the research team, make the participants contributions invalid or potentially compromising of the study objectives
2. Physicians that either themselves work for or have immediate family members who work for Medtronic, third parties involved in this study, or a regulatory agency (EMA, MHRA, HPRA, ANSM, BfARM)

During the initial phone call, screening questions will be asked to determine the eligibility of the physician for participation.

9.3 Variables

Information is collected on three main categories, details are described below. The first category is used to describe the population and includes variables around demographics, type of practice, and level of experience in using InductOs. The second category of variables is aimed at measuring the awareness on the risk of heterotopic ossification, the educational materials and knowledge about safe use of InductOs presented in the educational materials. The third set of variables covers the different sources where information on the key messages in the educational materials could have been obtained. A transcription of the intended survey is included in Annex 3.

First category:

- Physician specialty
- Practice type/hospital
- Years of practicing physician
- Years InductOs is used

- Last time InductOs was implanted
- Number of patients implanted with InductOs in the past 2 years
- Surgical approaches used
- Amount of rhBMP2 used in lumbar interbody spine fusion in one intervertebral space

Second category:

- Awareness of common adverse reactions that are associated with InductOs when administering InductOs during lumbar interbody fusion
- Knowledge on safe use of InductOs during pre-implantation, implantation and post-implantation of InductOs

Third category

- Used sources for guidance on InductOs administration
- Use of educational materials

9.4 Data sources

Data will be collected using a standardized online questionnaire that will be translated into the local languages of the countries where the survey is being conducted. The majority of the questions will evaluate the knowledge of physicians on heterotopic ossification and the measures to reduce the risk of occurrence of heterotopic ossification communicated in the educational materials.

The questionnaire will be pre-tested as described in section 9.1.

9.5 Study size

The minimum sample size needed to obtain a proportion with confidence interval with the lower limit above the 80 % minimum awareness was calculated. For this calculation an alfa of 0.05 with a two-sided interval and a distance from proportion to limit of 0.1 was used with the expected proportion of 90 %. This leads to a minimum sample size of 35.

To ensure inclusion of data from the different participating countries, this study aims at collecting responses from physicians covering roughly 10 % of purchasing pharmacies that have received InductOs in the past 2 years in each target country. However, if a greater number of respondents complete the questionnaires for a given target group, these responses will be integrated into the analyses.

The following number of completed surveys are planned per country:

- France: 15
- Germany: 15
- United Kingdom: 15
- Ireland: 10

This brings the total to 55 completed surveys which is above the calculated minimum sample size. Taking into account response rate of roughly 60 % and screening failures an estimated 120 surgeons will be screened for eligibility.

Recruitment rate will be monitored by the researchers; and if it becomes apparent that the there is a risk of the study not meeting the recruitment target then other countries with InductOs sales will be included in the study to widen the pool of potential participants. In the selection of additional countries for recruitment, priority will be given to countries where the existing translated materials are used.

9.6 Data management

Questionnaires will be completed on-line and data will be stored on a secure server. Participants must log in using a unique login identification. Every effort will be made to protect participant confidentiality. Participant identifiers will not be disseminated or placed on any reports from this study. Analyses will be conducted with anonymized data. Unless authorized by the participant (for example, in the case of adverse event [AE] or product complaint reporting), only anonymized data will be made available to Medtronic BioPharma in accordance with privacy protection rules as dictated by applicable regulations.

The survey will be conducted using Lighthouse Studio version 9.8.0 or higher from Sawtooth Software. The statistical software used will be SAS version 9.4 or higher.

9.7 Data analysis

The study population will include all physicians who are screened, are eligible for this study, and completed the questionnaire. All statistical summaries in this study will be descriptive. Frequencies and percentages, with 95 % confidence intervals (CIs) where appropriate, will be presented. Country specific data will be presented. Additional exploratory analyses and sensitivity analyses may be conducted to identify difference between groups of responders.

The primary analysis is aimed at evaluating the proportion of physicians that is aware of the risk of heterotopic ossification and measures described in the educational materials to minimize that risk. A respondent is considered to be aware if they answer 75 % of the questions with regards to heterotopic ossification and the applicable minimization measures correctly. In the questionnaire there are 12 (sub)questions raised on the occurrence of heterotopic ossification and the related risk minimization measures. Hence a surgeon needs to answer 9 of these correct to be considered aware. In Annex 3 the (sub)questions included in the scoring of awareness are marked. The aRMM will be considered effective if 80 % of the respondents are aware of the described risk of heterotopic ossification and the appropriate measures to minimize them. With the targeted 55 respondents, this means 44 or more need to be aware.

The secondary analysis is aimed at identifying the source of physician knowledge. Based on the received data it will be determined to what extent the educational materials are used and are considered an important source of information for the respondents.

9.8 Quality control

A pre-test of the questionnaire will be performed to ensure its comprehensibility and consistency (see section 9.4).

Suazio will follow its procedures for quality control during the conduct of the survey, which includes but is not limited to:

- Randomization of answer options
- Consistency checks for plausible data
- Checks for completeness of data and perform follow-up as needed

Medtronic BioPharma will follow Medtronic BioPharma procedures and study specific plans will be followed for quality control, which includes but is not limited to:

- Documenting all statistical analysis programs used, including version number
- Archiving the original database and any derived data sets, and all relevant study documents in an electronic document system

9.10 Limitations of the research methods

Potential limitations to using this online survey include:

- Non-response bias: This is an inherent limitation in the survey study design. The non-response rate is reduced through the use of a telephone screening, short survey and the potential for compensation for time.
- Social desirability response bias: Surgeons may respond positively rather than truthfully. In order to reduce the probability of this type of bias, surveys are anonymous, questions are not leading, and are designed to elicit truthful responses.
- Sample is not random: A random sample of individuals meeting the selection criteria equalises the potential for bias to occur, making the sample potentially useful for generalising to the overall population. However, the small number of potential surgeons who would meet the selection criteria effectively removes the potential for randomisation.
- Self-selection bias: Even with the selection criteria it may be only the most motivated, experienced or engaged surgeons who participate leading to artificially high rates of awareness. This is reduced by decreasing the non-response bias, see above. Furthermore, the sample is chosen from all current users in the countries, regardless of quantity of InductOs provided in the past years.

These limitations are acknowledged and, given the nature of the data collected, should not greatly impact the conclusions drawn from the data collected from respondents. Efforts, where possible, will be made to address and reduce the impact of these limitations, see bullets above.

9.11 Other aspects

Not applicable.

10. Protection of human subjects

Any regulatory required ethics assessment or permissions will be obtained prior to the study start.

Participant Information and Consent

The participants will receive a thorough briefing on the nature and purpose of the study to enable and inform their consent decision, see the questionnaire in Annex 3. Their consent will be recorded.

Personal Data

Following the implementation of the General Data Protection Regulations (GDPR) participants will be required to demonstrate that they agree to the completion of the survey. Participants (data subjects) will be informed of the data processing activities using their data, and organisations who may require access under what conditions. Privacy notices will set out how personal information is used and what the data subjects' rights are.

The research participant will be allowed to withdraw their consent for use of their personal information at any time regardless of any implications for the research project.

Confidentiality

Every effort will be made to protect participant confidentiality. Participant identifiers will not be disseminated or placed on any reports generated by this study. Analyses will be conducted with anonymized data. Unless authorized by the participant (for example, in the case of an AE or product complaint report), only anonymized data will be made available to Medtronic BioPharma in accordance with privacy protection rules as dictated by applicable regulations.

The researchers will abide by any and all appropriate laws and codes related to their activities.

11. Management and reporting of adverse events/adverse reactions

This study does not involve data collection on clinical outcomes of individual patients. However, any information with regards to adverse events or product complaints voluntarily offered by a participant during the course of this study will be handled as described below.

Suazio's employees performing the screening interviews and the initial data analysis are trained to recognize adverse events and product complaints per Suazio's procedure. For this study any noted adverse event or product complaint will be reported on a Product Information Report (PIR, see Annex 1) and sent to Medtronic BioPharma's designated contact. The reported information will be further processed as per local requirements and Medtronic BioPharma's procedures. Suazio may be asked to support in requesting follow-up information.

12. Plans for disseminating and communicating study results

The final study report will be published via the EU PAS register and provided to the EMA and to the local Competent Authorities as relevant.

13. References

None

Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	500231	01 May 2019	Product Information report

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:

EU PAS Register® number: EUPAS32916 **Study reference number (if applicable): N/A**

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

[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.

Comments:

Given the short planned duration of the study, there are no progress or interim reports foreseen.

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)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☒	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

This study is set up to measure the awareness of surgeons at the time of the study. There is no hypothesis set to be tested.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1, 9.3
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:

This study doesn't study a particular disease or risk factor. The study examines the awareness of information of surgeons at the time of the study. Therefore no measures of occurrence or association are collected.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2
4.2.2 Age and sex	☐	☒	☐	
4.2.3 Country of origin	☒	☐	☐	9.2, 9.5
4.2.4 Disease/indication	☒	☐	☐	9.3
4.2.5 Duration of follow-up	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

There is no difference made for the inclusion in this based on age or sex as this is not relevant for the research questions and objective.

This is a cross-sectional study; hence the duration of follow-up is not defined.

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:

The objective of this study is to measure awareness of surgeons. There is no exposure measured.

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?	☐	☐	☒	
6.2 Does the protocol describe how the outcomes are defined and measured?	☐	☐	☒	
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:

This study doesn't measure outcomes but awareness of surgeons.

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

Comments:

Given the nature of the study, confounders are not expected. Therefore, these are not measured.

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:

Given the nature of the study effect modifiers are not expected. Therefore, these are not measured.

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:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☒	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☐	☐	☒	
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3
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)	☐	☐	☒	
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
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:

There is no coding planned for covariates and other characteristics, nor is there a linkage foreseen between different data sources.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☐	☒	☐	
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?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7

Comments:

There are no confounders (see above) or outcomes measured in this study.

As the study population will only include completed questionnaires there is no description needed for the handling of missing data.

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)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

There is no independent review of the study results planned as part of the study, however, the study results will be shared with the PRAC and relevant CA.

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?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
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)	☒	☐	☐	9.1

Comments:

As described above, there is no confounding expected for this study.

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☒	

Section 13: Ethical / data protection issues	**Yes**	**No**	**N / A**	**Section Number**
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

For this study no ethical committee review is required.

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)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Koen van der Heijden

Date: Captured with electronic signature

Signature: Signed electronically

Annex 3. Questionnaire

Invitation

Good morning/afternoon/evening, I am …….. and I am approaching you on behalf of SuAzio Consulting, an independent Market Research Company with focus on the medical field and working on behalf of pharmaceutical and MedTech companies. We would like to invite you to participate in an **online Risk Minimisation assessment study.**

We are currently conducting this online study among specialists in Europe on behalf of **Medtronic BioPharma**, to assess the knowledge of healthcare professionals administering **InductOs** (recombinant human Bone Morphogenetic Protein-2; rhBMP-2), on the **risks and minimisation measures** of InductOs in its **approved use** for lumbar interbody spine fusion.

We would be happy to count on your insights and spend **15 minutes** in an easy to use **online survey**. The access to the online survey will be highly secure and all information encrypted end-to-end and treated anonymized.

As appreciation for the time you will dedicate to completion of the questionnaire you will be **compensated with** *[to be adapted to the specialty and country, e.g. XX Euros]* Alternatively, you can donate your portion to our charity project, a local community care center in Guayaquil, Ecuador, "Dispensario Medico suAzio".

Finally, let me stress that **confidentiality** is a high priority to us, and we guarantee that your information is used solely for statistical research purposes. Our institute does not intend to promote or sell certain products. We focus entirely on industry research and medical development. For more information on our company, please visit our website: www.suAzio.com

Are you willing to answer a few questions to ensure you qualify to participate in this research project? Y/N

Screening criteria

Have you used InductOs for a lumbar interbody spine fusion procedure at least once within the last two years?

(1) Yes
(2) No
→ End if "(2) No"

Have you previously participated in a pre-test of this survey about InductOs?

(1) Yes
(2) No
(3) I do not remember
→ End if "(1) Yes" or (3) I do not remember

Are you or one of your close family members currently employed or contracted by regulatory bodies (e.g. EMA, MHRA, ANSM, Bfarm, HPRA) or an involved company (Medtronic BioPharma, another Medtronic entity or Suazio)?
(1) Yes
(2) No
→ End if "(1) Yes"

If criteria are not met: Thank you for your time and interest in this research. Unfortunately, we are sorry to inform you that you do not qualify to participate at this point.
If all criteria are met: Thank you for answering these questions. Based on your answers, we would like to invite you to take part in this project.

Do you agree to take part in this survey about InductOs?
(1) Yes
(2) No
→ End if "(2) No"

Thank you for agreeing to participate in this study. You will shortly receive a link that will direct you to the online survey. Please complete it at your earliest convenience. Should you have any problems or issues using the app you will be able to report us, and we will assist you asap in order to you be able to complete the exercise
Once it is completed, we reach back to you to begin processing your compensation

If you wish to contact us about this survey, please contact: _____
You are about to enter a market research survey.

Survey presentation.

The survey aims to assess the knowledge of healthcare professionals administering InductOs (dibotermin alfa; recombinant human Bone Morphogenetic Protein-2 (rhBMP-2)), on the risks and minimisation measures of InductOs in its approved use for lumbar interbody spine fusion. The survey has been requested by the European Medicines Agency (EMA) and it is funded by Medtronic BioPharma, the Marketing Authorisation Holder (MAH). The study will run in four European countries (France, Germany, Ireland, and United Kingdom).
The questionnaire will take approximately 15 minutes to complete, partly depending on your responses.
The survey will be conducted in an anonymous way. The information collected will remain absolutely confidential and will only be used for the purposes of this survey. Respondents' answers will be pooled together and presented to the research sponsor in the aggregate and anonymously. Furthermore, real names and addresses will never appear on the online community. Only SuAzio and Medtronic BioPharma will have access to the answers.

The results obtained will be presented in aggregated form to the MAH and regulatory agencies, mainly the EMA. No connections will be made between your identity and your answers to the survey.
The survey does not involve any promotional material and you will not be contacted for marketing purposes based on your answers to the survey, be sure that your information is used solely for research purposes. Neither the survey sponsor nor its contractors will sell or rent your information. You have the right to withdraw from the study at any time during the survey process and to withhold information. Your answers will not affect your ability to administer InductOs.
Are you willing to proceed with the survey?
(1) Yes – **Proceed**
(2) No – **Terminate**

Demographic questions

Please indicate your specialty (select one response):
(1) Neurosurgery
(2) Traumatology
(3) Orthopaedic surgery
(4) Other

Please indicate your practice type (select one response):
(1) General / non-university public hospital (not affiliated with university hospital)
(2) Academic teaching hospital
(3) Private Hospital or Clinic
(4) Other (please specify): [MULTILINE INPUT]

In total, how many years have you been a practicing physician?
(1) ≤5 years
(2) 6-10 years
(3) ≥10 years
(4) Prefer not to answer

Questionnaire on InductOs

How many years have you been using InductOs?
(1) ≤5 years
(2) 6-10 years
(3) ≥10 years
(4) Prefer not to answer

When was the last time you implanted InductOs?
(1) 0 – <3 months ago
(2) 3 – <6 months ago
(3) 6 – <9 months ago
(4) 9 – <12 months ago
(5) 12 – 24 months ago
(6) I don't remember

Approximately how many patients have you implanted with InductOs in the past 2 years?
(1) <5
(2) 5-<10
(3) 10-<15
(4) 15-<20
(5) >20
(6) I don't know

Please indicate in percentages how much of your time is spent in the following approaches during your procedures with InductOs. Must sum to 100%.
(1) Anterior Lumbar Interbody Fusion (ALIF)
(2) Posterior Lumbar Interbody Fusion (PLIF)
(3) Transforaminal Lumbar Interbody Fusion (TLIF)
(4) Oblique Lateral Interbody Fusion (OLIF) / eXtreme Lateral Interbody Fusion (XLIF)
(5) Posterolateral Fusion (PLF)
(6) Others (*textbox*)

When using InductOs in lumbar interbody spine fusion, how much rhBMP-2 do you usually implant in one intervertebral space?
1- Less than 4 mg
2- Between 4 mg and 8 mg
3- Between 8 mg and 12 mg
4- More than 12 mg

What best describes your use of the following tools, provided to physicians, when considering the use of InductOs or administering InductOs to a patient?

Tool	Never use	Sometimes use	Frequently use	Always use
Summary of Product characteristics / Package insert				
Educational materials				
Other information provided by the Market Authorisation Holder				
Information from peers				
Scientific publications				

Would you consider that the available information on the use and administration of InductOs is easy to access?
Y/N
(Note: for the questions below the following legend applies:

- *Green text indicates a correct answer*
- *Orange text indicates a (sub)question which is considered for assessing awareness)*

Which of the following are common adverse reactions you associate with InductOs when administering InductOs during lumbar interbody fusion?

1-	*Urinary retention*	Y / N
2-	*Fluid collection, like localised edema or (pseudo)cyst*	Y / N
3-	*Malignancies*	Y / N
4-	*Neuralgia*	Y / N
5-	*Osteolysis / increased bone resorption*	Y / N
6-	*Pseudarthorsis*	Y / N
7-	*Radiculopathic complaints (radiculitis, radicular pain, radiating pain, sciatica)*	Y / N
8-	*Heterotopic / ectopic ossification / additional bone growth*	Y / N
9-	*Back pain*	Y / N
10-	*Infections*	Y / N
11-	*Retrograde ejaculation*	Y / N
12-	*Others, please specify*	Y / N

As the terms ectopic and heterotopic ossification are used interchangeably in some publications, we will use heterotopic ossification to describe both concepts. Heterotopic

ossification is one of the known adverse reactions to InductOs. Can you please indicate for each of the following statements whether it is true or false?

1	Heterotopic ossification can occur during lumbar arthrodesis	True / False
2	Heterotopic ossification occurs with and without the use of InductOs	True / False
3	Heterotopic ossification forms quickly	True / False
4	Heterotopic ossification can lead to nerve compression	True / False
5	Radicular pain is never the result of heterotopic ossification	True / False
6	Heterotopic ossification can occur asymptomatic	True / False
7	Heterotopic ossification occurs more often in patients undergoing a surgery with an anterior approach than in surgery with a posterior approach.	True / False

Pre-implantation

In the operating theatre InductOs is reconstituted and added to the collagen matrix. When filling the hollow geometry of the lumbar interbody fusion device, a surgeon needs to:

(1) Loosely fill the lumbar interbody fusion device with the wetted matrix, while preventing compression of the matrix and overfilling of the volume intended for new bone formation
(2) Firmly fill the lumbar interbody fusion device with the wetted matrix, while preventing compression of the matrix and overfilling of the volume intended for new bone formation
(3) Loosely fill the lumbar interbody fusion device with the wetted matrix, while allowing compression of the matrix and overfilling of the volume intended for new bone formation
(4) Firmly fill the lumbar interbody fusion device with the wetted matrix, while allowing compression of the matrix and overfilling of the volume intended for new bone formation

Implantation

A surgeon is performing a posterior lumbar interbody fusion (PLIF). Besides inside the lumbar interbody fusion device, the surgeon can place the wetted matrix (multiple answers possible):

(1) Anterior to the lumbar interbody fusion device
(2) Posterior to the lumbar interbody fusion device
(3) Lateral to the lumbar interbody fusion device

In the same PLIF procedure, the surgeon considers creating a physical barrier between the matrix and the spinal canal. Which of the following statements are true (multiple answers possible):

(1) It is not needed to create a physical barrier if the matrix is placed to the anterior side of the interbody space only
(2) A physical barrier may be created using e.g. local bone or allograft
(3) A physical barrier is needed when there is potential leakage into the spinal canal or nerve root
(4) A physical barrier may be created using a fibrin-based sealant

Post-implantation

After implantation of InductOs, irrigation of the surgical site and placing of a drain may occur as part of regular surgical practices. For each of the following with regards to irrigation and drains please indicate whether it is true or false (multiple answers possible):

(1) The inside of the intervertebral disc space may be irrigated
(2) When irrigating the surgical field, any fluid loss from the wetted matric should be washed away
(3) A surgical drain may be placed close to the implantation site
(4) A surgical drain is preferably placed one layer superficial to the implantation site

You have now completed the survey.
Thank you for your participation in this Risk Minimisation assessment study! We appreciate all the feedback that you have shared. We hope it was an interesting experience for you as well to participate.
You will receive [XX Euros] to thank you for your time. We will reach out to you to collect all your remuneration details and preferred payment method.