POST-AUTHORISATION SAFETY STUDY

Non-Interventional Study Protocol

Study Title

Effectiveness of the Mysimba® Physician Prescribing Checklist (PPC): Focus group to assess understanding, attitude, and behaviour for usage of the PPC and for key safety messages

Sponsor/Name and address of MAH:	Orexigen Therapeutics Ireland Limited 2nd Floor, Palmerston House Dublin 2 Ireland
Active substance:	Naltrexone hydrochloride / bupropion hydrochloride ATC Code: A08AA62
Product name:	Prolonged-release naltrexone hydrochloride/bupropion hydrochloride (Mysimba®)
Form/Route:	Prolonged-release tablets/Oral
Indication for this study (EU):	Mysimba is indicated, as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients (≥18 years) with an initial body mass index (BMI) of ≥30 kg/m^2 (obese), or ≥27 to <30 kg/m^2 (overweight) in the presence of one or more weight-related co-morbidities (e.g., type 2 diabetes, dyslipidaemia, or controlled hypertension). Treatment with Mysimba should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight.
Date of authorisation in the EU:	26 March 2015
Joint PASS (If applicable):	Not applicable

Study code	NB-453
Study type	EU RMP category 3 (required)
EU PAS study number:	TBD
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Version:	2.0, dated 05 December 2022

This post-authorisation safety study (PASS) protocol was developed further to a request by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) in the context of procedure EMEA/H/C/003687/II/0054 (review outcome and list of Request for Supplementary Information dated June 10th, 2022). The Agency asked the MAH to submit a qualitative research protocol for a PASS that aims at conducting a root cause analysis of the reason(s) for inadequate knowledge of selected key safety messages and low usage of the Physician Prescribing Checklist (PPC), that was observed in a cross-sectional survey of Mysimba prescribers in the EU ((PASS protocol version 1.2 was approved with procedure EMEA/H/C/003687/MEA/0004.6, EU PAS Register Number 42491, Study NB-452).

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1. List of Abbreviations

ADR	Adverse drug reaction
AE	Adverse event
aRMM	Additional risk minimisation measure
BMI	Body mass index
CRO	Contract research organisation
EC	European Commission
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GDPR	General Data Protection Regulation
HCl	Hydrogen chloride
HCP	Health care professional
IRB	Institutional Review Board
KAU	Knowledge and understanding
MAH	Marketing authorisation holder
MAOI	Monoamine oxidase inhibitor
PPC	Physician Prescribing Checklist
PASS	Post-authorisation safety study
PQI	Product quality issue
PRAC	Pharmacovigilance Risk Assessment Committee
QPPV	Qualified Person responsible for Pharmacovigilance
RMP	Risk management plan
SAE	Serious adverse event
SSR	Special situation report
TBD	To be determined

2. Responsible parties

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Contract Research Organisation (CRO):
TBD

3. Abstract

Background and rationale
Mysimba (naltrexone HCl 8 mg / bupropion HCl 90 mg prolonged-release tablets) is indicated in the European Union (EU), as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients (≥18 years) with an initial body mass index (BMI) of ≥30 kg/m^2 (obese), or ≥27 to <30 kg/m^2 (overweight) in the presence of one or more weight-related comorbidities (e.g., type 2 diabetes, dyslipidaemia, or controlled hypertension). Treatment with Mysimba should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight. Mysimba was first approved in the EU on 26 March 2015, and marketing authorisation renewal with unlimited validity was granted with the European Commission (EC) Decision dated 16 January 2020.

As per the EU risk management plan (RMP) for Mysimba, the additional risk minimisation measure (aRMM) tool consists of a Physician Prescribing Checklist (PPC) targeting physicians who prescribe Mysimba. The goal of the PPC is to verify key safety elements, including indications and contra-indications, at the time of treatment initiation for each patient. The PPC was distributed to potential prescribers at the time of product launch in each EU country, following a review and approval by each national competent authority.

A post-authorisation safety study (PASS), consisting of a cross-sectional survey of Mysimba prescribers was conducted over the period Q1-Q2 2021 to evaluate the effectiveness of the PPC (PASS protocol version 1.2 was approved with procedure EMEA/H/C/003687/MEA/0004.6, EU PAS Register Number 42491, Study NB-452). The survey was conducted in EU countries where Mysimba had been launched and with sufficiently high prescription rates. These consisted of the Czech Republic, Poland, Hungary, Greece, and Norway. Of the 3,971 physicians who were invited to take part in this study, 281 (7.1%) returned the survey, with 249 (6.3%) completing at least one screening question. The completer set (i.e., eligible physicians who gave consent, had prescribed Mysimba in the past 12 months, and completed all survey questions) consisted of 223 respondents (5.6%).

In this survey, 71.3% (95%CI 64.9%, 77.1%) of Mysimba prescribers met the overall knowledge and understanding (KAU) criteria (primary outcome), which did not reach the pre-specified threshold of 85% for effectiveness of the PPC. Key safety elements associated with sub-optimal

KAU were precise indication for Mysimba as well as contra-indications with respect to concomitant use of bupropion and MAOI. Lack of knowledge was identified in particular for cardiovascular risk factors and hepatic impairment, which represent medical conditions that may increase the risk of adverse reactions. Furthermore, only 58.7% of prescribers remembered having received the PPC.

Prior to developing a strategy for improving the awareness, usage and understanding of the Mysimba PPC, or making any modification to the risk minimisation strategy, it is necessary to conduct a root cause analysis of low awareness of the PPC as well as of incorrect responses to survey questions related to knowledge and understanding of selected key safety messages. Key safety messages targeted by the proposed study are those relating to comorbidities which may put the patient at risk (i.e., cardiovascular and hepatic conditions), along with the following other relevant key safety messages that were also not well understood by survey respondents: Indication for an initial BMI ≥27 kg/m2 to <30 kg/m2 (overweight) in the presence of one or more weight-related co-morbidities (79.8%), depression as a contra-indication (77.6%), and contraindicated concomitant use of bupropion (72.6%) and MAOI (74.4%) within the past 14 days.

Mysimba is contraindicated for patients receiving chronic opiate therapy. In patients requiring intermittent opiate treatment, Mysimba should be temporarily discontinued, and opiate dose should not be increased above the standard dose. Although the great majority of respondents (>94%) answered correctly the two survey questions related to this safety concern, there have been observed cases of concomitant use of Mysimba and opioids. The concomitant chronic opioid use will therefore also be addressed in the proposed research.

This PASS will help determine the adequacy of the PPC and, potentially, guide strategies to improve the understanding of key safety messages described in the EU RMP for Mysimba.

Objectives

Main objective: To identify factors that could explain the low awareness and usage of the PPC as well as the inadequate responses to selected questions on key safety messages.

Specific Objectives:

1) To identify the reasons for low awareness and usage of the PPC;

2) To assess the understanding of the cardiovascular risk factors, hepatic impairment messages, and the other less understood key safety messages, as perceived by the prescribers;
3) To determine prescriber's attitudes/agreement with the key safety messages;
4) To identify problems in the understanding of the cardiovascular risk factors, hepatic impairment messages, and other less understood key safety messages;
5) To obtain insights from prescribers into the observed contraindicated concomitant chronic opioid use;
6) Based on findings, to discuss strategies to improve awareness and understanding of key safety messages.

Methods

Study Design: A qualitative research study, based on a grounded theory using thematic analysis, will be conducted. A qualitative research strategy will be adapted to answer the research objectives that aim at uncovering domains of attitude, perceptions, and knowledge from prescribers. The conceptual framework consists of an inductive process whereby theoretical insights (themes and domains) are generated. Web-based (virtual) focus groups of prescribers of Mysimba will be conducted to gain a better understanding of reasons and factors associated with the inadequate responses to selected KAU survey questions. This methodology is deemed valid to explain relationships or results found in surveys.

Setting: The study targets physicians who have prescribed Mysimba at least once in the past 12 months in Greece, Czech Republic, and Norway. Greece was selected for the following reasons: (i) accounts for almost half of the participants in the survey, (ii) offered further risk minimisation measures not conducted in the other study countries, and (iii) represents the south of the EU. Czech Republic was selected because, in the survey, it offered the largest number of survey participants from Eastern Europe, and Norway because respondents were the least likely to recall receipt of the PPC.

Study population: A purposive sample will be selected to obtain richly textured information, using a strategy to capture maximum variation of prescribers according to specialties and settings. There will be two focus groups/country, each of approximately 3-4 participants (recommended size for a virtual focus group during the COVID-19 pandemic) in each of Greece, Czech Republic, and Norway (six focus groups in total). Selection of participants will not be influenced by their

previous participation or performance in the survey. Physicians who were initially contacted for the survey will be invited. No unblinding will be necessary for the MAH.

Data Collection: Each web-based focus group will last between 1-2 hours and will include approximately 3-4 participants, with an over-recruitment of one person if possible, in case some participants may not be available on the date of the meeting. The focus group sessions will be led by one moderator and one assistant moderator, in local languages based on a set of questions (see interview guide in Appendix 1). The first set of questions will apply to the PPC in order to gather prescribers' opinion on the usefulness and relevance of this tool as well as their perspectives and/or suggestions about the diffusion (distribution) means employed by the MAH. A national physical copy of the PPC will be shown to the participants to elicit their awareness of the tool, as some participants may remember the tool but not its name.

Following these general considerations, the discussion will focus on the KAU survey questions related to cardiovascular risk factors, hepatic impairment, and the other relevant key safety messages (i.e., indication for an initial BMI ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of one or more weight-related comorbidities, contraindicated concomitant use of bupropion and MAOI within the past 14 days, and depression). Participants will be expected to express their point of view regarding the correct answer to each question. In addition, contraindicated concomitant Mysimba and chronic opioid use will be included in the discussion. The following set of initial themes has been developed, which will be enriched based on focus group discussions:

- Understanding of the cardiovascular risk factors, hepatic impairment, as well as the other less understood key safety messages, as perceived by the focus group participants;
- Determination of their attitudes/agreement with the safety messages;
- Identification of problems in the communication of the cardiovascular risk factors, hepatic impairment, and the other less understood key safety messages;
- Identification of potential reasons why concomitant Mysimba and chronic opioid use has been observed;
- Recommendations for changes or improvements of these safety messages, mainly with respect to education reinforcement of their importance;
- Discussion on how the corresponding questions in the survey are understood by prescribers.

Variables: As this is qualitative research, there are no endpoints. Instead, themes will be sought with the aim of reaching saturation (i.e., when no more new themes emerge from the discussions).
Data Analysis: The technique of thematic analysis will be used, which involves searching across discussion verbatim and meeting notes in order to identify, organize, describe, and report repeated patterns. The verbatim of the focus group discussions will be transcribed and analyzed along with field notes constructed by the moderator and assistant moderator, and any notes extracted from the debriefing meeting. Coding will be conducted using a qualitative data analysis software program (QSR NVivo, version 13 March 2020 or later). Analysis will include systematic coding using constant comparison analysis. Codes will be reviewed to identify themes, opinions, and beliefs that are recurrent (referred to as nodes). Coding will be deductive (pre-set coding scheme, based on hypotheses regarding less well understood key safety messages) and inductive (nodes will be generated while examining the collected data). The most significant nodes will be grouped through "focused coding" to identify recurrent patterns and multiple layers of meaning, and to delineate variations and interconnections among sub-themes within the general topic. To enhance the reliability of analysis, coding will be performed independently by two researchers and conflicts will be resolved by consensus or by a third researcher where there is no consensus. Dissents and argumentative interactions between focus group participants and nonverbal communication will also be documented to increase the richness of the data.

Study limitations and potential sources of bias

Potential sources of bias in this qualitative research project are the following:
Participant bias: Questions in the focus groups will be open-ended to avoid participants from simply agreeing or disagreeing with the moderator, minimize social-desirability and moderator bias.
Researcher bias: To avoid interpretation of the data to support researcher's hypothesis, data will be coded by assessors who will not be involved in the focus group discussions.
Selection bias: Prescribers initially invited to participate in the KAU cross-sectional survey (NB-452) will be invited to the focus group, with no consideration of their participation or response to the initial survey.

Generalizability: As this is qualitative research, an in-depth analysis will aim at understanding circumstances rather than collecting representative data, and a maximum variation purposive sample will be sought.

Compensation

Participants in the focus groups will be compensated according to fair market value and according to applicable laws in each study country.

Protection of Human Subjects

The study protocol will be submitted for ethics approval to local or national institutional review boards (IRBs) according to applicable laws in each study country. Prescribers will sign an informed consent for participation in the focus group. Their names will be known only for the purposes of scheduling the meeting and processing payment. Their names will not appear in the study report or in any other study materials (only a participant number will appear, not the actual name).

Milestones: Study is expected to start in Q1 2023. A final report will be submitted to the European Medicines Agency (EMA) six months after the start of data collection.

4. Amendments and Updates

Version	Amendments
2.0	Updated submitted version, dated 05/12/2022, requested by the PRAC.
1.0	Initial submitted version, dated 26/07/2022, requested by the PRAC.

5. Milestones

Milestone	Planned date
Registration in the EU PAS register	Upon protocol finalization and prior to the start of data collection
Start of data collection	Q1 2023
End of data collection	3 months after the start of data collection
Interim report	Not applicable
Final Study report	6 months after the start of data collection

6. Rationale and Background

As part of the conditional renewal of marketing authorisation in the European Union (EU) for Mysimba (naltrexone HCl 8 mg / bupropion HCl 90 mg prolonged-release tablets), this non-interventional study is designated as a post-authorisation safety study (PASS) category 3 and is a commitment to the European Medicines Agency (EMA). This qualitative research will serve as a root cause analysis of inadequate knowledge and understanding (KAU) related to selected Mysimba key safety messages, that was observed through the conduct of a cross-sectional study (PASS protocol version 1.2 was approved with procedure EMEA/H/C/003687/MEA/0004.6, EU PAS Register Number 42491, Study NB-452).

Mysimba was first approved in the EU on 26 March 2015 as a fixed combination medicinal product under article 10(b) of Directive 2001/83/EC as amended. Marketing authorisation renewal with unlimited validity was granted with EC Decision dated 16 January 2020.

Mysimba is indicated, as an adjunct to a reduced-calorie diet and increased physical activity, for the management of weight in adult patients (≥18 years) with an initial body mass index (BMI) of ≥30 kg/m^2 (obese), or ≥27 to <30 kg/m^2 (overweight) in the presence of one or more weight-related comorbidities (e.g., type 2 diabetes, dyslipidaemia, or controlled hypertension). Treatment with Mysimba should be discontinued after 16 weeks if patients have not lost at least 5% of their initial body weight.

The Physician Prescribing Checklist (PPC) is an additional risk minimisation measure (aRMM) to help prevent the prescription of Mysimba to patients who are at an increased risk of adverse events (e.g., seizures) or patients who do not meet the approved indication. A cross-sectional web-based survey of Mysimba prescribers was conducted to evaluate the effectiveness of the PPC through an evaluation of process indicators that included physician awareness and utilisation of the PPC in clinical practice, knowledge of the contraindications, warnings and precautions of Mysimba, knowledge of factors that may increase the risk of adverse reactions and impact upon a physician's behaviour with respect to mitigating the risks in patients receiving Mysimba therapy.

The survey was conducted in EU countries where Mysimba had been launched and with sufficiently high prescription rates. These consisted of the Czech Republic, Poland, Hungary, Greece, and Norway. Of the 3,971 physicians who were invited to take part in this study, 281 (7.1%) returned the survey, with 249 (6.3%) completing at least one screening question. The completer set, (i.e., eligible physicians who gave consent, had prescribed Mysimba in the past 12 months and completed all survey questions), consisted of 223 respondents (5.6%). Although the geographical distribution was well chosen, the actual representation of countries included in the completer set was unbalanced (Czech Republic – 23.8%, Greece – 43.0%, Hungary 0.9%, Poland - 18.4%, Norway 13.9%) and seemed not to reflect the proportion of invited physicians. The majority of invites were sent to physicians in Norway (2000), with a similar number of invites sent to physicians in Poland, Czech Republic and Greece (669, 636, and 626 respectively), and with a much lower number sent to physicians in Hungary (40). The proportion of invited physicians vs. physicians included in the completer set was 5.6%, but highly varied across countries [Greece - 15.3% (96/626), Czech Republic - 8.3% (53/636), Poland - 6.1% (41/669), Hungary - 5.0% (2/40), Norway - 1.6% (31/2000)]. Furthermore, the target minimum of 20 completed surveys per country was not reached in Hungary.

According to specialty, most of the physicians in the completer set were from primary care (35.0%), internal medicine (27.8%) and endocrinology (19.7%). According to practice setting, private practice (60.1%), outpatient clinic (14.8%), public practice (8.1%) and academic centre (7.6%) were most represented, but the distribution of specialty and practice setting was highly variable between countries.

Overall, 58.7% recalled receiving the Mysimba PPC. Respondents in Norway were least likely (22.6%) and respondents in Greece (82.3%) and Hungary (100%) most likely to recall receipt. It was noted that a recent re-distribution of the PPC by e-mail or mail to physicians in all participating countries, except for Norway, may partly explain such differences in results. The reason for the re-distribution of the PPC was an update to reflect the outcome of the II/0023 variation procedure i.e., the removal of the contraindication for patients with severe renal impairment. In Norway, the new version of the PPC was uploaded to the website of the Norwegian Pharmaceutical Compendium without repeated distribution.

The measure of success of the Mysimba PPC was based on a minimum acceptable threshold of knowledge and understanding (KAU), defined as 85% of physicians whose correct response rate for the general PPC knowledge and risk-related questions was ≥80% (a score of ≥20 out of 25 possible points). Overall, this threshold was not reached. In total, 71.3% (95%CI 64.9%, 77.1%) of physicians from the completer set achieved this target. The percentage of success by country was as follows: Czech Republic – 71.7%, Greece – 77.1%, Hungary – 100%, Norway – 45.2%, and Poland – 80.5%.

The questions achieving inadequate KAU most often concerned the following medical conditions, which may put patients at increased risk of adverse reactions:

- Controlled hypertension (29.1% correct)
- Mild or moderate hepatic impairment (57.0% correct)
- Angina or recent myocardial infarction (65.5% correct)
- Depression (77.6% correct)

Further questions answered correctly by <80% of respondents concerned the indication and contraindicated drug interactions:

- Concomitant bupropion use (72.6% correct)
- Monoamine oxidase inhibitor (MAOI) within the past 14 days (74.4% correct)
- Approved indication for Mysimba use (79.8% correct)

Approximately 74.8% of respondents considered the PPC either extremely (30.9%) or very helpful (43.9%). However, only 39.9% of the respondents indicated utilising the PPC always (22.0%) or most of the time (17.9%) when prescribing Mysimba, which are contradictory results. Furthermore, 29.6% of respondents indicated they either rarely (9.4%) or never (20.2%) used the Mysimba PPC. The percentage of responders, receipt recall, level of success and PPC use was the lowest in Norway.

Some of the main limitations of the cross-sectional survey were the low response rate and differences in the implementation process of the PPC between countries. Moreover, it is unclear

whether the responders were representative for the prescribers in respective countries and how the reported level of knowledge and understanding translates into actual prescribing behaviour. Another category 3 study, namely NB-451 Drug Utilisation and Safety Study of Mysimba, has not yet been initiated, as the study feasibility and protocol are still under discussion. The final report of study results is currently expected in September 2024 (please refer to EMEA/H/C/003687/MEA/003.11 for more details). Therefore, further data on the Mysimba drug utilisation in the EU is awaited.

Since the target level of success was not reached, the MAH was requested to propose and discuss strategies for improving the awareness, usage and understanding of the Mysimba PPC. To address this request, the MAH proposes to conduct a root cause analysis to identify the reason(s) for lack of knowledge and usage of the PPC as well as for inadequate understanding of selected key safety messages, through a web-based focus group discussion (qualitative research method). The findings from the study will inform on the needs and targets for improving the risk minimisation strategy.

Mysimba is contraindicated for patients receiving chronic opiate therapy. In patients requiring intermittent opiate treatment, Mysimba should be temporarily discontinued, and opiate dose should not be increased above the standard dose. Although the great majority of respondents (>94%) answered correctly the two survey questions related to this safety concern, there have been observed cases of concomitant use of Mysimba and opioids. This safety concern relating to chronic opioid use will therefore also be addressed in the proposed research in order to obtain the prescribers' insights into potential reasons for concomitant use.

This study is classified as a Post-Authorisation Safety Study (PASS) category 3 and has been designed to meet the requirements of the European Medicines Agency Guidelines on Good Pharmacovigilance Practices (GVP) Module VIII – Post-authorisation safety studies (revision 3, 2017) (1). The protocol has been developed using the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (2), the 2016 CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects (3). Study report will follow the Standards for Reporting Qualitative Research (SRQR) (4).

7. Objectives

7.1 Primary objective

To identify factors that could explain the low awareness and usage of the PPC as well as the inadequate responses to selected questions on key safety messages.

7.2 Specific objectives

1) To identify the reasons for low awareness and usage of the PPC;
2) To assess the understanding of the cardiovascular risk factors, hepatic impairment messages, and the other less understood key safety messages, as perceived by the prescribers being interviewed;
3) To determine prescriber's attitudes/agreement with the key safety messages;
4) To identify problems in the understanding of the cardiovascular risk factors, hepatic impairment messages and other less understood key safety messages;
5) To obtain insights from prescribers into the observed contraindicated concomitant chronic opioid use;
6) Based on findings, to discuss strategies to improve awareness and understanding of key safety messages.

8. Hypotheses

Hypotheses have been put forward that will be used as initial theory to conduct the qualitative research. Potential root causes of lack of knowledge about the existence of the PPC include the following:

1. Prescribers are aware of the checklist, but the term "PPC" is not used by clinicians in their routine clinical practice setting
2. Clinicians remember the PPC, but dissemination occurred too long ago, and they forgot about its existence

3. Clinicians did not see the PPC (i.e., inadequate mode of dissemination)

Potential root causes of incorrect answers to the survey regarding key safety messages include the following:

1. Lack of usage of the PPC (i.e., problem of implementation of aRMM)
2. Incorrect processing of information (i.e., problem with understanding the key safety messages)
3. Conflicting sources of information (i.e., clinicians may have been exposed to sources of information other than the SmPC or the PPC, which may not explicitly cover the key safety messages)
4. Inadequate formulation of the questions in the survey (i.e., problem with the evaluation method)

9. Research Methods

9.1 Study design

A qualitative study, based on a grounded theory using thematic analysis, will be conducted. Study will be based on primary data collection using web-based (virtual) synchronous focus groups. Grounded theory is an approach by which a theory (corresponding to the hypotheses listed in Section 8) will be extended from the qualitative analysis conducted on the focus group data (5). As described below, data will be analyzed using a thematic analysis in order to identify, organize, describe, and report repeated patterns (6). Study design and qualitative data analysis will be guided by the Consolidated criteria for reporting qualitative research (COREQ) – a checklist for interviews and focus groups (7).

Compared to quantitative research that tests hypotheses in a representative sample of patients, a qualitative research strategy will be more adapted to answer the descriptive research questions, which involve an in-depth assessment of insights. The conceptual framework is that of an inductive process whereby theoretical insights (themes and domains) will be generated. Data will be collected through focus groups of Mysimba prescribers (that will last 1-2 hours) in order to identify and explore reasons for sub-optimal usage of the PPC and inadequate KAU of key safety messages. There will be two focus groups of approximately 3-4 participants in each study country

(Greece, Czech Republic, and Norway) for a total of six focus groups. Maximum variation purposive sampling will be used to ensure a representation of specialties, practice setting, and awareness/use of the PPC.

9.2 Study setting and Study population

9.2.1 Study setting

The study targets physicians who have prescribed Mysimba at least once in the past 12 months in Greece, Czech Republic, and Norway. Greece was selected for the following reasons: (i) it accounts for almost half of the participants in the survey, (ii) it offered further risk minimisation measures not conducted in the other study countries, and (iii) it represents the south of the EU. Czech Republic was selected as it offered the largest number of survey participants from Eastern Europe (there were three Eastern European countries included in the survey: Czech Republic, Poland, and Hungary, contributing respectively, 53, 41 and 2 physicians in the completer set), and Norway because respondents were the least likely to recall receipt of the PPC (22.6% according to survey), since the last version of the PPC was only available on a website.

9.2.2 Study population and enrolment

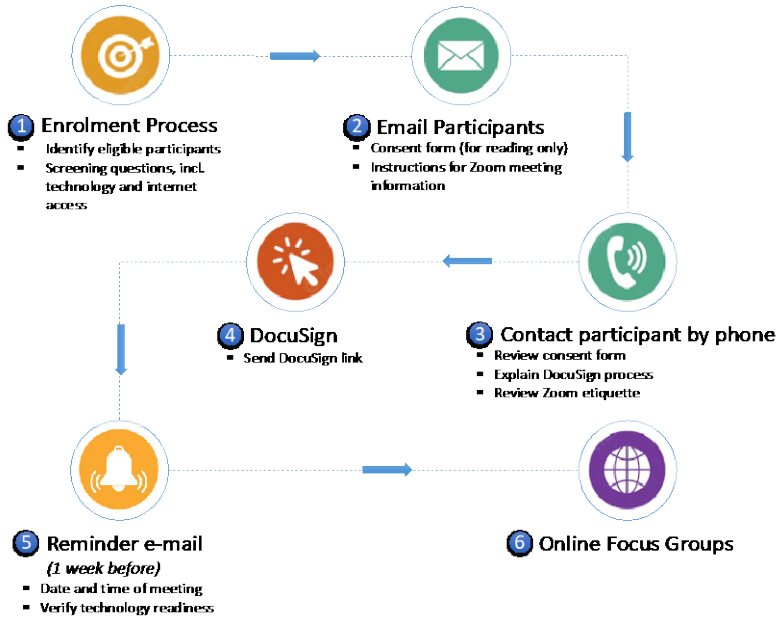
A purposive sample will be selected to obtain richly textured information, using a strategy to capture maximum variation of specialties and settings. In contrast to quantitative research that uses random sampling to ensure adequate generalizability of findings, qualitative research aims at identifying and selecting information-rich participants in order to achieve depth of understanding (8). Consistent with the methods used in implementation science, a maximum variation purposive sample will be used since the purpose will be to document unique or diverse variations that have emerged in the factors influencing the understanding of the Mysimba key safety messages, and to identify important common patterns that cut across variations (9). Sample will represent diverse specialties (primary care, internal medicine, endocrinology, weight loss specialists, etc.) and practice settings (private practice, outpatient clinic, public practice, weight loss centre, community-based centre, academic centre, etc.). Because there was no trend observed in the survey regarding knowledge by specialty or setting, no specific subgroup of prescribers will be

targeted for the focus groups. It will not be possible to select participants on the basis of their scores in the initial knowledge and understanding survey since focus groups will not target only the participants to the initial survey (as this information was confidential). However, quotas will be implemented to include, as much as possible, adequate representation of physicians who 1 –are aware of and use the PPC, 2 –are aware of, but do not use the PPC, and 3 –are not aware of the PPC.

There will be two web-based focus groups, each of approximately 3-4 participants, which was shown to be the optimal size for a virtual focus group (10), in each of Greece, Czech Republic, and Norway (six focus groups in total). Selection of participants will not be influenced by their previous participation in the survey. Since the initial survey was anonymous, it will not be possible to contact only those who have participated. Physicians who were initially contacted for the survey will be invited with a question regarding participation in the previous survey. They will also be asked about their awareness and use of the PPC in order to attempt to ensure adequate representation of each subgroup. Marketing partners in Greece (WinMedica), Czech Republic (Bausch Health) and Norway (Navamedic) will be used to identify potential participants. No unblinding will be necessary for the MAH.

For those who meet the eligibility criteria listed in Section 9.2.3, consent will be explained over the phone and a study information sheet, including Zoom etiquette training material, will be sent by e-mail. Consent form will be sent through DocuSign (DocuSign Inc., San Francisco, CA). Follow-up calls will be made to review the consent form and to provide additional information regarding the use of Zoom and the date of the meeting. Study flow is summarised in Figure 1 below.

Figure 1. Study flow for virtual focus groups



9.2.3 Participant selection criteria

Prescribers will be eligible to participate in the focus groups if they meet the following inclusion and exclusion criteria:

Inclusion criteria:

- Respondent consents to participate in a virtual focus group with an audio recording of the session;
- Respondent is a physician who has prescribed Mysimba in the past 12 months
- Respondent has access to technology (Internet and e-mail)

Exclusion criterion:

- Respondent is employed by or was a family member of someone employed by the EMA, Orexigen Therapeutics Ireland Limited, Currax Pharmaceuticals, Navamedic or Bausch Health.

9.4 Data collection procedures

The key aspect of focus groups is the interactions between participants as a way of collecting qualitative data that would not emerge using individual interviews (11). Synchronous virtual focus groups will be conducted through Zoom videoconferencing technology (Zoom Video Communications, Inc. San Jose, CA). Virtual focus groups ensure the reach of a wide geographical distribution of participants across the three countries. As described by Dos Santos Marques (2021) (10), it also allows for the collection of data in real time, as well as enable interaction between and among the participants and the moderators.

At the time of enrolment, a training on Zoom etiquette will be provided to participants consisting of reminding participants to be alone in a room during the meeting, to turn their camera on, and to avoid outside distractions (e.g., mobile phones etc.).

For security reasons, all meetings will be password protected and a unique invitation will be sent to participants individually. At the time of the meeting, all attendees will first join a waiting room with a co-host. In the waiting room, the participant's identity will be confirmed, and their screen name will be changed, allowing for confidentiality between participants. Once all the attendees join, the meeting will be locked. Sessions will be audio recorded only, which will preserve the identity of the participants while still allowing for data collection for qualitative analyses.

The research team will include a moderator and an assistant moderator from external vendors who specialize in the conduct of focus groups. The moderator will be responsible for facilitating the discussion, prompting members to speak, requesting overly talkative members to let others talk, and encouraging all the members to participate. Furthermore, the moderator will take notes that inform potential emergent questions to ask. The moderator will present the focus group participants with a series of questions (see Appendix 1 for focus group interview guide) and will also show prescribers a physical copy of the PPC as stimulus material and ask them to respond to it. The assistant moderator will record the session, take notes, greet latecomers, conduct any

troubleshooting, and provide verification of data, when necessary. The assistant moderator will also take notes on non-verbal communication such as face expressions and reactions to other participants' comments. Due to the web-based nature of the data collection, only face expressions and reactions will be examined as non-verbal communication.

9.5 Study size

Each focus group will include approximately 3-4 participants, which is the recommended size for a virtual focus group. Previous research has shown that virtual focus groups using web-based video conferencing platform is considered as a valid and feasible tool to collect qualitative data (12; 13). Through additional research conducted during the COVID-19 pandemic, virtual focus groups were shown to offer the possibility to cover a wider geographical range and feasibility is highest with 3-4 participants as opposed to the minimum of 6 recommended for in-person focus groups (10). A higher number of participants may result in technological difficulties (more troubleshooting during the sessions) and hamper online interactions between participants to share their thoughts, opinions, beliefs, and experiences.

Because some of the eligible and confirmed participants might not be available on the day of the focus group, one additional participant per focus group will be recruited, if possible, which is within the recommended over-recruitment of 20% (14).

There will be two focus groups per study country, which is consistent with recommendations that 3 to 6 different focus groups are adequate to reach data saturation and/or theoretical saturation (i.e., when no more themes or theories emerge from the discussions) (14; 15).

9.6 Data management

If possible, transcripts of focus group discussions will be generated automatically through the Zoom platform followed by a manual verification of the text. Session recordings will be used to verify wording on transcripts if unclear. Alternatively, if there is no automation of transcripts in local languages through Zoom, a manual transcription of verbatims will be produced. Transcripts

(verbatims) and meeting notes will be translated in English, followed by a manual verification of the translation.

Study data (recordings, transcripts, notes) will be stored on secure servers and will be maintained to ensure compliance with applicable local or national regulations regarding information security and data privacy. Access to study data will be possible only to a limited number of study staff based on roles and responsibilities and will require authentication protocols. Prior to transmission to coders, any identifiers from transcripts will be removed (e.g., individuals' names or clinics names).

Standards and processes will be governed by data privacy and protection standard operating procedures (SOPs) to ensure compliance and adherence. Those standards follow the General Data Protection Regulation (GDPR).

No participant name or contact information will be included in the tables or in any of the study materials or reports.

9.7 Data analysis

The techniques of thematic analysis will be used. The translated versions (in English) of verbatims of the focus group discussions will be analyzed along with field notes constructed by the moderator and assistant moderator, and any notes extracted from the debriefing meeting. Coding will be conducted using a qualitative data analysis software program (QSR NVivo, version 13 March 2020 or later) by an external vendor with expertise in qualitative analysis. Analysis will include systematic coding using constant comparison analysis. Codes will generate nodes that correspond to themes, opinions, and beliefs that are recurrent amongst participants. The most significant nodes will be grouped through "focused coding". To enhance the reliability of analysis, coding will be performed independently by two researchers and conflicts will be resolved by consensus or by a third researcher where there is no consensus. Dissents and argumentative interactions between focus group participants will also be documented to increase the richness of the data.

The availability of multiple focus groups will allow to assess saturation of themes in general and across groups. Because focus group data are analyzed one focus group at a time, it will be possible to determine whether the themes that emerged from one group also emerged in the other. The main themes identified in the first focus group of each country will therefore be tested in the second focus groups in order to enhance data saturation (16), to assess the meaningfulness of the themes and to refine themes (17).

Because in a focus group the unit of analysis is the group and not the individual, focus group members who did not contribute to a discussion are not acknowledged, such as those who are silent (e.g., do not want to reveal that they have a different opinion, attitude or beliefs, level of knowledge, or who are uninterested to the issue being discussed, or those who agree with the majority of participants and simply nod). Consensus in the themes may actually be due to the group context as it does not reflect the views of the individual group members. It is therefore necessary to analyse information of group members who had dissenting views as well as the participants who did not express any views at all. Non-verbal communication, through facial expressions, will also be analysed to identify acquiescence, dissent or absence of views. A matrix will be developed whereby for each focus group question, agreement, dissent, or neither will be indicated (verbal or non-verbal). Non-verbal data may also include length of silence in the conversion, variations in volume, pitch, face expression, in order to enrich the verbal data. A descriptive analysis of views and opinions expressed by each member for each theme will be provided in the final report.

10. Study limitations

10.1 Sources of bias

Participant bias: Participants may respond to the questions based on what he/she thinks is the right answer or according to social acceptability or to agree with the moderator. Questions in the focus groups will be open-ended in order to avoid participant from simply agreeing or disagreeing with the moderator and will not be able to use a simple "yes" or "no" answer. In order to minimize social desirability or observer bias, questions will be phrased in a manner that will allow the participant to feel accepted, regardless of his/her answer or KAU.

Selection bias: Prescribers initially invited to participate in the KAU survey will be invited to the focus group, with no consideration of their participation or response to the initial survey.

Researcher bias: may occur if a researcher interprets the data to support his or her hypothesis. There will be no *a priori* hypothesis communicated to the moderator, and data will be analyzed independently by two assessors who will not be involved in the interviews in order to provide consistency between interpretations. Questions will be kept simple, and no leading questions will be used that could prompt participants to respond in favour of a particular assumption.

10.2 Generalizability

As this is qualitative research, an in-depth analysis will aim at understanding circumstances rather than on achieving the collection of representative data. As such, a maximum variation purposive sample will be used instead of a random sample, since the purpose will be to document unique or diverse variations and will attempt to include representatives from as many relevant specialties and settings as possible.

11. Compensation

Prescribers who participate in the focus group will be remunerated at fair market value and according to applicable laws in each study country.

12. Protection of human subjects

12.1 Informed consent

Participant consent will be obtained prior to attending the focus groups and confidentiality of information will be enforced throughout the study. Due to the virtual nature of the study, electronic consent will be sought through the DocuSign platform. Participants will be able to withdraw their consent. If requested, their focus group responses can be removed from the analysis database and not used in the final study report. In addition, any of their statements can be deleted at the end of the focus group sessions should they wish to do so. Similarly, their participation in the focus group session can end whenever they wish to withdraw their participation.

12.2 Institutional Review Board or Ethics Committee

This protocol will be submitted to local and national ethics committees, as per applicable laws.

12.3 Privacy and Confidentiality

The privacy rights of individuals will be protected in accordance with all applicable laws, regulations, and guidelines. All contact information and processes will be compliant to the General Data Protection Regulation (GDPR). Personal identifier and contact information will only be collected for the purpose of scheduling focus groups and processing compensation, if applicable. Identifiers will be stored in a database that is separate to the focus group data. For the Zoom sessions and the transcription of verbatim, a prescriber identification (ID) or fake name will be assigned.

13. Management and reporting of adverse events/adverse reactions

If during the conduct of the focus group discussions, the moderator or moderator's assistant is spontaneously informed by a Health Care Professional (HCP) of a serious adverse event (SAE), adverse event (AE), adverse drug reaction (ADR), special situation report (SSR) or product quality issue (PQI), where the event/issue pertains to an Orexigen product (or unbranded generic), such information should be notified to the relevant Orexigen Pharmacovigilance department at PVUS.AENalpropion@primevigilance.com (and cc: drugsafety@nalpropion.com) within 2 calendar days from the time of awareness. Essential information (i.e., gender of patient, description of adverse event, product, and reporter) should be collected, where possible, but at a minimum the reporter information for the purpose of follow-up.

14. Plans for disseminating and communicating study results

Study will be registered in the EU PAS register prior to the start of data collection. The PASS protocol and a summary of the final report will be published in the EU PAS register, upon study completion. There are no progress or interim reports planned. The final study report will be submitted to the EMA and included in updates of the Risk Management Plan (RMP), as required by GVP V revision 2 (18).

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