

**STUDY PROTOCOL**

**AN OBSERVATIONAL POST-AUTHORIZATION MODIFIED  
PRESCRIPTION-EVENT MONITORING SAFETY STUDY TO MONITOR  
THE SAFETY AND UTILIZATION OF EXENATIDE ONCE WEEKLY  
(BYDUREON®) IN THE PRIMARY CARE SETTING IN ENGLAND**

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**Glossary of terms**

<b>Abbreviation</b>	<b>Term</b>
AE	Adverse Event
BMI	Body Mass Index
BP	Blood Pressure
CHM	Commission on Human Medicines
CHMP	Committee for Medicinal Products for Human Use
DM	Diabetes Mellitus
DSRU	Drug Safety Research Unit
ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drugs Administration
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
GLP-1	Glucagon Like Peptide-1
GP	General Practitioner
HLT	Higher Level Term
ID	Incidence Density
IQR	Interquartile Range
LLT	Lower Level Term
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
M-PEM	Modified Prescription-Event Monitoring
MTC	Medullary Thyroid neoplasm
NHS	National Health Service
NHSRxS	National Health Service Prescription Services
OTC	Over-The-Counter
ODS	Organisation Data Service
PEM	Prescription Event Monitoring
PSUR	Periodic Safety Update Report
RAIDAR	Rare and Iatrogenic Adverse Reactions
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SOC	System Organ Class
SmPC	Summary of Product Characteristics
T2DM	Type 2 Diabetes Mellitus
UK	United Kingdom
US	United States

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## EXECUTIVE SUMMARY

Bydureon® (exenatide) is a once weekly injection indicated for the treatment of type 2 diabetes mellitus (T2DM) in combination with metformin, sulphonylurea or thiazolidindione alone, metformin and sulphonylurea or metformin and thiazolidinedione for patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies alone. On 18<sup>th</sup> April 2011, the European Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion recommending the granting of marketing authorization for once weekly exenatide injection (Bydureon®) for the treatment of type-2 diabetes in adults.

A predecessor to Bydureon® is Byetta®, which is an exenatide twice daily injection that has been marketed in the United States since May 2005 and in regions outside of the United States (US), including the European Union (EU), since April 2007. A total of 5682 unique patients are recorded in the clinical trial database as having received Byetta® for a total exposure of 4377 patient-years (pyrs), with a mean exposure time of 0.89 years per patient. Of these, 1168 patients are recorded as having been exposed for 54 or more weeks.(1) The clinical trial safety database for Bydureon® comprises of 2611 unique patients with a total exposure of 2049 pyrs and a mean exposure per patient of 0.82 years. Of these, 566 have been exposed for 12 or more months.(1) Thus additional information from larger numbers outside the clinical trial setting, in conditions of routine clinical practice, may be helpful to further monitor possible adverse events in users of exenatide. A Risk Management Plan (RMP) has been developed for exenatide by the manufacturer. This plan includes tools designed to monitor the important identified and potential risks.

This post-marketing Modified Prescription-Event Monitoring (M-PEM) safety study of exenatide (Bydureon®) is to be carried out by the Drug Safety Research Unit (DSRU) as part of the Risk Management Plan required by the Committee for Medicinal Products for Human Use (CHMP) to further investigate the safety profile of Bydureon® in clinical practice. The aim of this study is to proactively capture safety and drug utilisation data in the post-marketing phase of license approval of Bydureon® as prescribed to patients by general practitioners in England. This M-

PEM study will enable the systematic collection and reporting of drug utilisation and safety data on patients newly initiated on treatment with exenatide once weekly in the primary care setting. The study aims to collect exposure and outcome data for a cohort of approximately 5000 evaluable patients.

Patients will be identified from dispensed National Health Service (NHS) prescription data for exenatide, sent to the Drug Safety Research Unit by the National Health Service Prescription Services (NHSRxS) in England. At least 12 months after the first identified prescription has been issued for each patient, the prescribing doctor will be sent a M-PEM questionnaire to gather data on Bydureon<sup>®</sup> treatment prescribing patterns and baseline patient characteristics such as: the year of birth, sex, Blood Pressure (BP), IFCC-HbA<sub>1C</sub> and Body Mass Index (BMI) of the patient (closest available measurement prior to initiation), duration of clinical indication (date of first ever diagnosis); start dose and date of starting treatment, reasons for prescribing, past medical history, current (anti-diabetic) medication use; events occurring during and after stopping treatment up to the end of the observation period, including cause of death (where applicable); date of stopping treatment (including reason for discontinuing therapy if treatment was stopped) and changes in selected patients characteristics and medications during treatment.

In addition to the routine pharmacovigilance activities (which include regular analysis of spontaneously reported post-marketing safety data), this modified prescription event monitoring study will monitor clinically important identified and potential risks within a cohort of patients treated with Bydureon<sup>®</sup>. The primary focus of the study will be to quantify the incidence rate of the selected important identified risk of acute pancreatitis, as the risk of acute pancreatitis with exenatide use is unclear. One secondary focus will be to describe the baseline health profile of patients on treatment with Bydureon<sup>®</sup> in the primary care setting and the treatment they received (and by whom), to advance the understanding of the Bydureon<sup>®</sup> patient population in actual clinical practice. The other secondary focus will be to describe the risk profile of events reported in the 12 month observation period in the overall cohort and in special populations (arising from contraindications and those for which: precautions for use are recommended; appropriate clinical monitoring is recommended; and limited

information is available). The study also includes an exploratory focus to describe the characteristics of selected important identified and potential risks (such as cases of thyroid and pancreatic cancer)<sup>1</sup> in the first 12 months after starting treatment and to quantify the incidence of other frequently and rarely reported events (including other important identified and potential risks not mentioned in the primary objective).

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<sup>1</sup> It is important to note that this M-PEM study will only characterise any cases of thyroid neoplasm and pancreatic neoplasm that are reported during the twelve month observation period. This study cannot give any inference on the incidence of these cancers in the M-PEM cohort, as the study length and size has not been designed for this.

## **1.0 BACKGROUND**

### **1.1 Post-marketing surveillance**

The clinical safety information available when a new medicine is marketed relates to a limited number of patients.(2) This applies to new formulations of licensed medicines. Pre-marketing data will usually give little information on drug utilisation and safety post-marketing. In the UK, the Yellow Card spontaneous reporting scheme and Prescription-Event Monitoring (PEM) provide complementary systems of post-marketing surveillance on a national scale of newly marketed drugs prescribed by general practitioners (GPs) in the primary care setting.

### **1.2 Prescription-Event Monitoring**

Standard Prescription-Event Monitoring (PEM) studies provide active surveillance on a national scale. Using a study questionnaire, general practitioners (GPs) who prescribe the new medicine are asked to report all events\* that have been recorded in the patients' notes during a specific time-period after beginning treatment with the medicine, regardless of whether any events are thought to be associated with any specific drug or treatment. PEM removes the need for the prescribing doctor to give an opinion about whether an event might have been caused by the medicine and provides an opportunity to generate safety signals not previously associated with the drug under surveillance. The technique of PEM, a records-based observational cohort methodology, has been described previously.(3)

### **1.3 Modified Prescription-Event Monitoring**

The technique of PEM can be used to examine a variety of issues relating to the use of prescription drugs. In certain situations however, it may be desirable to modify this methodology – such studies are referred to as Modified Prescription-Event Monitoring studies (M-PEM). Customized data-collection questionnaires are designed for such studies. Examples of the modifications may relate to establishing

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\* The term 'event', as used in this study, is defined as, “any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any alteration of clinical importance in laboratory values, or any other complaint that was considered of sufficient importance to enter into the patient's notes”.



baseline characteristics of patients in relation to pre-specified risks, identifying physician prescribing and decision making behaviour and evaluating risks of adverse events over various timeframes, including periods prior to starting or after discontinuation of treatment.

The specific aims of this M-PEM study are:

#### Primary

- Quantify the incidence rate of the important identified risk of acute pancreatitis in patients prescribed Bydureon<sup>®</sup> in the primary care setting

#### Secondary

- To describe the baseline health profile of patients on treatment with Bydureon<sup>®</sup> in the primary care setting and the treatment they received (and by whom), to advance the understanding of the Bydureon<sup>®</sup> patient population in actual clinical practice
- To describe the risk profile of events reported in the 12 month observation period in the overall cohort and in special populations (arising from contraindications and those for which: precautions for use are recommended; appropriate clinical monitoring is recommended; and limited information is available).

#### Exploratory

- To describe the characteristics of selected important identified and potential risks in the first 12 months after starting treatment, which are:
  - Acute pancreatitis (plus signs and symptoms)
  - Pancreatic cancer<sup>2</sup>
  - Thyroid neoplasm (benign and malignant sub-types)<sup>2</sup>

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<sup>2</sup> It is important to note that this M-PEM study will only characterise any cases of thyroid neoplasm and pancreatic neoplasm that are reported during the twelve month observation period. This study cannot give any inference on the incidence of these cancers in the M-PEM cohort, as the study length and size has not been designed for this.

- Where possible, to quantify the incidence of other frequently and rarely reported events (including other important identified and potential risks not mentioned in the primary objective)

Modified PEM studies involve a payment to GPs for the data-collection questionnaires that are returned completed. Requests for 'follow-up' data are made, as in standard PEM studies, using a postal questionnaire. GPs receive an additional payment to cover any administrative costs for completed questionnaires for 'follow-up' information returned to the DSRU. Modified PEM studies are carried out under the same ethical guidelines as standard PEM studies (Section 3.0).

## **1.4 Bydureon<sup>®</sup> (exenatide once weekly)**

### ***1.4.1 Administration, mode and mechanism of action***

Bydureon<sup>®</sup> (exenatide) is a once weekly injection indicated for the treatment of type 2 diabetes mellitus (T2DM) in combination with metformin, sulphonylurea, thiazolidinedione alone, metformin and sulphonylurea or metformin and thiazolidinedione for patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies alone.(4) Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist that exhibits several antihyperglycaemic actions of GLP-1. It has been shown to bind to and activate the known human GLP-1 receptor *in vitro*. Exenatide increases, on a glucose-dependent basis, the secretion of insulin from pancreatic beta cells.(4) It suppresses glucagon secretion which is known to be inappropriately elevated in patients with T2DM. Lower glucagon concentrations lead to decreased hepatic glucose output. Exenatide also slows gastric emptying thereby reducing the rate at which meal-derived glucose appears in the circulation and has been shown to reduce food intake, due to decreased appetite and increased satiety.

Bydureon<sup>®</sup> once weekly is an extended-release formulation that consists of exenatide-containing polymeric microspheres for suspension in an aqueous diluent and thus provides extended release of medication for predictable and controlled periods of time. The recommended dose of Bydureon<sup>®</sup> is 2mg weekly, by subcutaneous injection. The dose can be administered at any time of day, with or without meals(4),

which is in contrast to the twice daily version of exenatide (Byetta<sup>®</sup>) which must be taken within 60 minutes before the morning or evening meal.(5) After discontinuation, the effect of Bydureon<sup>®</sup> may persist as plasma levels of exenatide decline over 10 weeks. Choice of other medicinal products and dose selection for continued treatment of T2DM should be considered accordingly.

#### ***1.4.2 Synopsis of safety data***

Exposed population to Bydureon<sup>®</sup> is likely to be comprised of patients with T2DM who have not achieved adequate control with selected other antidiabetic treatments as well as from patients switching from Byetta<sup>®</sup>. Transient alterations to blood glucose levels (hypo- and hyperglycaemic) are likely in such populations during treatment initiation. Special populations for whom clinical experience is limited includes elderly patients aged 75 or more years, patients with moderate renal impairment, pregnant and breast feeding women and children/adolescents aged 17 years or less. Specific contraindications are listed as patients who have reported previous hypersensitivity to exenatide, whilst use in individuals with type 1 DM, or for treatment of diabetic ketoacidosis are both listed as special warning and precaution for use in the Summary of Product Characteristics (SmPC). Other Special warnings and precautions for use include use in patients with: end-stage renal disease or severe renal impairment (creatinine clearance < 30 ml/min); severe gastrointestinal disease; concurrent use of insulin, D-phenylalanine derivatives (meglitinides), alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors or other GLP-1 receptor agonists. Pharmacokinetic drug-drug interactions of note include combination of Bydureon<sup>®</sup> with warfarin and sulphonylureas, however there is the potential for pharmacodynamic interactions due to delayed gastric emptying.

Common adverse events (incidence > 1%) listed in the SmPC include hypoglycaemia, nausea/vomiting and diarrhoea, allergic (injection site) reactions and rapid weight loss. Very rare (incidence < 1/10000) adverse events include severe allergic reactions and acute inflammation of the pancreas.[1] There have been spontaneous case reports of acute pancreatitis with exenatide twice daily.(6;7)

A total of 5682 unique patients had been recorded in the clinical trial database as having received Byetta<sup>®</sup> for a total exposure of 4377 patient-years (pyrs), with a mean

exposure time of 0.89 years per patient. Of these, 1168 patients are recorded as having been exposed for 54 or more weeks. The clinical trial safety database for Bydureon® comprises of 2611 unique patients with a total exposure of 2049 yrs and a mean exposure per patient of 0.82 years. Of these, 566 have been exposed for 12 or more months.(1) Thus additional information from larger numbers outside the clinical trial setting, in conditions of routine clinical practice, may be helpful to further monitor possible adverse events in users of exenatide. A Risk Management Plan (RMP) has been developed for exenatide by the Marketing Authorisation Holder (MAH). This plan includes tools designed to monitor the important risks (including class effects and off-label use. Evaluation by the MAH) of all safety data and possible risk factors related to the use of exenatide or related to a therapeutic class effect, revealed the following important risks:

Important identified risks are

- Pancreatitis
- Acute Renal Failure
- Rapid Weight Loss

Important potential risks are:

- Anaphylactic-Type Reactions
- Cardiovascular effects (coronary artery disease; arrhythmia; heart failure) and related adverse events
- Malignant neoplasms (pancreatic and thyroid)
- Food-Drug and Drug-Drug Interactions

Important missing information includes use in:

- Paediatric population ( $\leq 17$  years)
- Very elderly population ( $\geq 75$  years)
- Pregnancy and lactation
- Combination with TZDs
- Severe gastrointestinal disease
- Impaired renal and hepatic function

#### 1.4.2.1 Pancreatitis

Acute pancreatitis is an inflammatory condition of the pancreas. It is characterized by abrupt onset severe abdominal pain, which often radiates to the back. Necrosis or haemorrhage of the pancreas and other systemic complications occur in 15-20% of cases.(8;9) Annual incidence rate of acute pancreatitis in U.S. adults is estimated at 0.7 per 1000 in the general population.(10;11) Patients with T2DM appear to be at nearly a 3-fold greater risk than non-diabetics for developing pancreatitis and at nearly 2- fold increased risk for developing biliary disease, (12) making it difficult to make any causal inference. Results from a recent observational study conducted in a pharmacy claims database in the US which examined the incidence risk and rate of acute pancreatitis in exenatide (Byetta<sup>®</sup>) new users, sitagliptin new users, other antidiabetic medication users and a non diabetic cohort reported a crude incidence rate ( per 100,000 pyrs ) of 569.9, 554.4, 571.9 and 190.5 respectively(13); the crude incidence risk from these data is estimated to be 0.34%, 0.42%, 0.40% and 0.23% over the study period, respectively. It was noted that patients with a past history of pancreatic disorders were included within these analyses. The cumulative reporting rate for exenatide (bd) from post-marketing data is 0.88 per 1000 patient-years exposure (1654 reports as of 30/9/2011). The product label for Byetta<sup>®</sup> contains precautionary information concerning the risk of acute pancreatitis with exenatide use. (14) An FDA alert was issued in August 2008 regarding several serious cases of necrotizing or hemorrhagic pancreatitis and a small number of deaths.(15) However, to date, no definite biological mechanism for exenatide-induced pancreatitis has been identified.

#### 1.4.2.2 Carcinogenicity

In a two year carcinogenicity study with Bydureon<sup>®</sup> an increased incidence in thyroid C-cell tumours (adenomas and / or carcinomas) was reported in both sexes of rats at all doses administered (0.3, 1, or 3 mg/kg given in alternate weeks, which is 1.4 - to 26 - fold higher than human clinical exposure to Bydureon<sup>®</sup>) compared to controls. The human relevance of these findings is currently unknown. There have been a total of 44 spontaneously reported cases of thyroid neoplasm with Byetta<sup>®</sup> (1.45 cases per 100,000 subject-years exposure) in postmarketing experience (up until the 30<sup>th</sup> September 2010).(16) No reports of medullary thyroid neoplasm (MTC) have been recorded through to 30<sup>th</sup> September 2010. The background incidence rate of thyroid

neoplasms in the US general population is 9.1 per 100,000 subject-years (National Cancer Institute data). In animal studies, GLP-1 medications similar to exenatide have been reported to cause malignant tumours of the thyroid gland. MTC is rare in humans, and approximately 20% to 25% of MTC cases are familial.(17)

Cumulatively through 30 September 2010, three cases of pancreatic cancer were reported in exenatide clinical trials.(16) Among them, one case was in the comparative (insulin) arm; the remaining two cases were in exenatide twice daily arms. From launch to 30 September 2010, there have been 60 cases reporting some type of pancreatic cancer in patients using Byetta®. The global cumulative reporting rate for pancreatic neoplasm is 3.8 cases per 100,000 subject year to 30 September 2010. The estimated incidence rate for pancreatic neoplasms in the general adult population is approximately 10 cases per 100,000 persons per year.(16) Of note, patients with diabetes have approximately a two-fold increased risk of developing pancreatic neoplasm compared with patients without diabetes.

It is important to note that this M-PEM study will only characterise any cases of thyroid neoplasm and pancreatic neoplasm that are reported during the twelve month observation period. This study cannot give any inference on the incidence of these cancers in the M-PEM cohort, as the study length and size has not been designed for this. Any cases that are reported during the study will be described in a case-series.

### **1.5 Study Rationale**

In addition to the routine pharmacovigilance activities (which include regular analysis of spontaneously reported post-marketing safety data), this modified prescription event monitoring study will monitor clinically important identified and potential risks within a cohort of patients treated with Bydureon®. The primary focus of the study will be to describe the incidence rate of the selected important identified risk of acute pancreatitis and associated events, as the risk of acute pancreatitis with exenatide use is unclear. The secondary focus will be on advancing the understanding of the patient population (including special populations for which there is limited information available from preauthorisation phase) prescribed Bydureon® in the primary care setting, to understand how the product is been used in 'real life' in England. The study also includes an exploratory focus to characterise any cases of acute

pancreatitis, pancreatic and thyroid neoplasm that are diagnosed after starting treatment, since these are identified potential risks that are not well characterised.

## **2.0 AIMS AND OBJECTIVES**

### **2.1 Overall aim**

To study the utilisation and safety of exenatide once weekly (Bydureon<sup>®</sup>) to treat type 2 diabetes mellitus in new user patients (exenatide naïve) and switchers (past exenatide twice daily users) under normal conditions of use in primary care in England.

### **2.2. Specific Objectives**

#### **2.2.1 Primary objective**

This is given below; its purpose is to provide timely information to:

- i. quantify the incidence rate of the important identified risk of acute pancreatitis (see Section 4.4.1 for case definition) in the first 12 months after starting treatment

#### **2.2.2 Secondary objectives**

These are given below. The purpose of these objectives is to provide timely information on:

- i. The baseline health profile of patients on treatment with Bydureon<sup>®</sup> in the primary care setting and the treatment they received (and by whom), to advance the understanding of the Bydureon<sup>®</sup> patient population in actual clinical practice
- ii. To describe the risk profile of events reported in the 12 month observation period in the overall cohort and in special populations (arising from contraindications and those for which: precautions for use are recommended; appropriate clinical monitoring is recommended; and limited information is available).

#### **2.2.3 Exploratory objectives**

The specific objectives that follow are all exploratory. The purposes of these objectives are to provide timely information to:

- i. describe the characteristics of selected important identified and potential risks in the first 12 months after starting treatment, which are:
  - Acute pancreatitis (plus signs and symptoms)
  - Pancreatic neoplasm<sup>3</sup>
  - Thyroid neoplasm (benign and malignant sub-types)<sup>3</sup>
- ii. Where possible, quantify the incidence of other frequently and rarely reported events (including other important identified and potential risks not mentioned in Objective 2.2.1)

### **3.0 ETHICAL CONSIDERATIONS**

This study will be conducted in accordance with the International Ethical Guidelines for Biomedical Research prepared by the Council for International Organisations of Medical Sciences in collaboration with the World Health Organisation (2002).(18) The method of study also complies with the Guidelines on the Practice of Ethics Committees in Medical Research involving Human Subjects, as issued by the Royal College of Physicians.(19) PEM is also included in the BMA report detailing methods in which healthcare professionals can help improve post-marketing surveillance.(20)

In addition, under Section 251 of the NHS Act 2006, the DSRU have received support from the Ethics and Confidentiality Committee of the National Information Governance Board to gain access to and process patient identifiable information without consent for the purposes of medical research (October 2009).(21) Reference to Section 251 is made in the General Medical Council booklets, 'Confidentiality' and 'Confidentiality: disclosing information for education and training purposes' whereby clinicians may disclose identifiable information without consent (if it is required by law), if it is approved under Section 251 of the NHS Act 2006 or if it can be justified in the public interest.(22;23)

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<sup>3</sup> It is important to note that this M-PEM study will only characterise any cases of thyroid neoplasm and pancreatic neoplasm that are reported during the twelve month observation period. This study cannot give any inference on the incidence of these cancers in the M-PEM cohort, as the study length and size has not been designed for this.



## 4.0 METHOD

### 4.1 Study Design, Cohort and Time frame

This study will use an observational cohort design. Randomisation will not be required. Prescription data collection will start upon notification of the date of market launch in England (July 2011) and continue for approximately three years, or until the target sample size has been achieved (whichever is the soonest; see Section 4.3.1). The final cohort size and the duration of recruitment will be influenced by the level of prescribing of Bydureon<sup>®</sup> by GPs in England. Current recommendations from NICE for exenatide once weekly is that it should be considered as **third-line therapy** to first-line metformin and a second-line sulfonylurea/thiazolidinedione when control of blood glucose remains or becomes inadequate ( $\text{HbA}_{1\text{C}} \geq 7.5\%$ , or other higher level agreed with the individual). The individual must have a body mass index (BMI)  $\geq 35.0 \text{ kg/m}^2$  if of European descent (with appropriate adjustment for other ethnic groups) and have specific psychological or medical problems associated with high body weight. The patient may also be recommended exenatide once weekly if he/she has a BMI  $< 35 \text{ kg/m}^2$ , and weight loss would benefit other significant obesity-related comorbidities, but therapy with insulin would have significant occupational implications. Once weekly exenatide can also be used in dual therapy regimens (i.e. in combination with metformin or a sulphonylurea) in situations whereby the patient is intolerant to metformin or a sulphonylurea, or if either treatment is contraindicated, or if the patient is intolerant of thiazolidinedione/ dipeptidyl peptidase-4 (DPP-4) inhibitor dual therapy, or if this dual therapy is contraindicated.(24) Thus cohort recruitment rate for this study is based on prescribing data, incidence and prevalence statistics. Slow uptake may impact the ability to meet the study objectives; in this instance due consideration should be given to the need to continue data collection and the feasibility of study completion should be open to re-evaluation. This will be an important area of review by the study team and MAH in order to monitor and agree upon any appropriate remedial actions.

Another important consideration is the capture of data in early use because of the multidisciplinary shared-care approach to management of diabetes. We anticipate that a proportion of patients (% as yet unknown) with more severe diabetes and/or who have co-morbid complications may be initiated within secondary care institutions.

This study design will capture data on patients in primary care who continue therapy that was started in secondary care, as well as patients newly initiated on Bydureon® by the GP. *Therefore, this design will not capture data on patients who start and stop treatment within the hospital/secondary care setting.* This could introduce error through selection bias (see Section 5.3) into interpretation of results because the M-PEM study population may not be entirely representative of the total target population of new users of this product. However, as the data are sampled at national level, the cohort is representative of the population registered within the NHS in England in the general practice setting.

At 12 months, cohort accrual will be examined to determine the proportions of patients initiated in primary care compared to secondary care (based on response to relevant question on treatment initiation on the questionnaire). This is possible because GPs in England typically receive summary information on in-patient episodes and for out-patient care. In addition, in some cases, decisions by hospital doctors to start treatment with medicines are conveyed to GPs who issue the first prescriptions for the medicines recommended by the hospital based doctors.

All patients who receive a prescription from a GP for Bydureon® in the primary care setting will be eligible for inclusion (see Section 4.2.1). Patients will be observed from start of treatment with Bydureon® (index date) and for a minimum of 12 months (or less if patient is censored because of treatment cessation or attrition) in order to allow for detection of acute outcomes associated with treatment initiation and events with delayed onset that might occur within 12 months after starting Bydureon® treatment. The M-PEM questionnaire will be sent at least twelve months after the patient's first Bydureon® prescription and aims to capture information on baseline characteristics and specific risks of interest.

## **4.2 Study Population**

### ***4.2.1 Inclusion Criteria***

Patients will be identified by means of data extracted from dispensed National Health Service (NHS) prescriptions for Bydureon®, written by any GP in England

(irrespective of past participation within PEM studies<sup>4</sup>) and supplied in confidence to the DSRU by the NHS Prescription Services (NHSRxS) of the NHS Business Services Authority for England. M-PEM questionnaires are sent according to the chronological order of prescription issue date to those GPs who prescribed the newly marketed medicine until the target sample size is achieved. Since this is an observational cohort study conducted in a naturalistic setting, open patient entry criteria apply to maximise external validity. Patients, for whom a study questionnaire containing useful information has been returned, will be eligible for inclusion in the evaluable patient study cohort.

#### ***4.2.2 Evaluable patient cohort***

Patients will not be included in the evaluable study cohort if the M-PEM study questionnaire is either not returned or returned with no information (blank) or the GP reports that the patient is no longer registered with the practice and no information is provided (where information is available up to a specific date it will be included). In addition, patients will also not be included in the evaluable study cohort for whom the information provided on the M-PEM questionnaire relates to one or more of the following: the index date is an improbable date (i.e. before market launch date); the GP reports that the patient did not take or was never prescribed Bydureon<sup>®</sup>; and where the dose and/or frequency of administration of Bydureon<sup>®</sup> is improbable for that product.

#### ***4.2.3 Evaluable patient cohort accrual considerations.***

The anticipated use of Bydureon<sup>®</sup> in the first year of marketing in England is projected to be modest, but is difficult to predict. Based on previous knowledge of levels of other new antidiabetic agents prescribed in general practice in England (from previous PEM studies) and assuming these prescribing rates apply in the absence of any specific prescribing uptake figures from the MAH, it is estimated that 8,500 prescriptions will be identified in the first year after market launch, identifying approximately 2,800 patients (3:1 ratio of prescriptions to patients). In the second

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<sup>4</sup> Those GPs who have informed the DSRU that they do not wish to participate in PEM studies are excluded from receiving questionnaires

year, it is estimated that 41,000 prescriptions will be identified, identifying approximately 7,300 further patients (5:1 ratio of prescriptions to patients). Assuming a 50% response rate, this would provide information on a total of 5,050 eligible evaluable patients after two years. In order to account for an exclusion rate of 10% and a possibly lower response rate, it is predicted that cohort accrual will need to run beyond two years is the target sample size (see Section 4.3) is to be achieved.

### 4.3 Sample size

The ability to detect an adverse event is dependent on the expected incidence rate of the adverse event in those exposed to the drug, the background rate in those not exposed to the drug, and the total number of patients. As described in Section 4.2.3 above, the anticipated use of exenatide once weekly in the first years of marketing in the UK is projected to be modest, but is difficult to predict.

#### *4.3.1 Sample size for general safety surveillance of events where background event rate is known*

It is possible to estimate a sample size necessary to detect a specified adverse event with known background incidence rate (BR) by effect size (Table 1).(25) Table 1 displays the sample sizes for a given power across a range of background rates and rate ratios or incidence density ratios (IDR).(25) The table may also be used to interpret sample sizes for risk differences or incidence density differences (IDD) by the following formula:

$$\text{IDD} = (\text{BR} \times \text{IDR}) - \text{BR}$$

For this M-PEM study, a sample size of 5000 evaluable patients (see Section 4.2.3) is desirable for analysis of the important identified risk within the primary objective (Section 2.2.1). Data taken from pre-authorisation clinical trials has shown that the reported incidence of pancreatitis (as defined by MedDRA preferred terms<sup>5</sup>) in the exenatide twice daily cohort is 4.4 per 1000 person-years. The incidence in the placebo control group of diabetic patients (diet controlled) used in clinical trials for

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<sup>5</sup> MedDRA preferred terms: Hereditary pancreatitis; Ischaemic pancreatitis; Oedematous pancreatitis; Pancreatitis; Pancreatitis acute; Pancreatitis chronic; Pancreatitis haemorrhagic; Pancreatitis necrotising; Pancreatitis relapsing.

exenatide twice daily is 1.8 per 1000 person-years. For Exenatide once weekly, the incidence reported in long-term active comparator-controlled studies was 4.6 per 1000 person-years. For this M-PEM study, it is desirable to have appropriate sample size sufficient to detect at least a two-fold increase in the primary event of interest (i.e. pancreatitis) assuming the hypothesised background rate is uncommon (0.2%) or more in that population (as reported for the diet controlled diabetic patients in the clinical trials for exenatide twice daily ). Thus, at the 5% significance level and with a power of 80%, a minimum of 5000 evaluable patients would be required to be analysed [Table 1].(25)

**Table 1. Sample sizes of evaluable patients for detection of a specified adverse event with known background incidence rate by effect size**

	Rate Ratio > 1.5	Rate Ratio > 2.0	Rate Ratio > 3.0	Rate Ratio > 3.5	Rate Ratio > 4.0
<b>Background Rate (%)</b>	<b>Power 80%</b>				
<b>0.1</b>	35,778	9924	2920	1999	1475
<b>0.2</b>	17,889	4962	1460	999	737
<b>0.5</b>	7156	1985	584	400	295
<b>1.0</b>	3578	992	292	200	147
<b>2.0</b>	1789	496	146	100	74
<b>5.0</b>	716	198	58	40	29
<b>Background Rate (%)</b>	<b>Power 90%</b>				
<b>0.1</b>	49,831	14,231	4367	3038	2273
<b>0.2</b>	24,915	7115	2184	1519	1137
<b>0.5</b>	9966	2846	873	608	455
<b>1.0</b>	4983	1423	437	304	227
<b>2.0</b>	2492	712	218	152	114
<b>5.0</b>	997	285	87	61	45

Notes: alpha = 0.05 (two-sided); Reference: Machin D, Campbell M, Fayers P, Pinol A. 1997. *Sample Size Tables for Clinical Studies*, 2nd edn, Blackwell Science: Oxford, pp. 144. (25)

As sample size calculations are based on overall cohorts, further unplanned subgroups or stratification of the data would underpower subsequent analyses.

### ***4.3.2 Sample size for general safety surveillance of events where background event rate is unknown***

For purposes of general safety surveillance (for events arising from exploratory objective (iii) Section 2.2.3) for the population of interest, it is possible to estimate a sample size necessary to detect a minimum of three cases<sup>6</sup> based on an assumed rate in that exposed sub-group and assuming the background rate is zero (i.e. the event is very rare).(26;27) For this study, a sample size of 5000 evaluable patients should allow for the detection of at least three cases of an adverse event with 85% power, if the event occurs at a rate of at least one in 1000 patients (where the background rate is unknown) (27); a sample size of 1000 evaluable patients would allow for the detection of at least three cases of an adverse event with 85% power, if the event occurs at a rate of at least one in 200, whilst a sample size of 500 evaluable patients should allow for the detection of at least three cases with a rate of at least one in 100 at 85% power. (27)

## **4.4 Data Collection**

### ***4.4.1 M-PEM Questionnaires***

For each eligible patient, at least 12 months post index date, demographic data and data on drug utilisation, relevant past medical history (see Section 4.5) and additional exposure data contained within GPs' primary care medical records for will be requested from and abstracted onto a baseline questionnaire, by the GP. Note that other than for regular monitoring of blood glucose control via assessment of HbA<sub>1C</sub> levels, undertaking other invasive laboratory tests and ECG monitoring are not current standard practice when initiating antidiabetic medication or systematically reported; therefore such specific information will not be collected on the M-PEM questionnaire. These data will be submitted to the DSRU. A proportion of GPs are likely to fail to submit these questionnaires, so they will be sent a reminder request.

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<sup>6</sup> In many situations involving rare reactions it is assumed that the frequency of the event is small, so that the occurrence of the event follows a Poisson distribution and the 95% CI calculated based on the number of events. If no events are observed in a study of X individuals then one can be 95% certain that the event occurs no more often than  $3/X$ . (26)

Data obtained from this questionnaire will include:

- date and starting dose details of first Bydureon<sup>®</sup> prescription;
- setting of initiation;
- reason for prescribing (e.g. formulary decision, patient request etc);
- date of first clinical diagnosis of diabetes
- IFCC- HbA<sub>1C</sub> levels ( within 3 months prior to index date) and date measured
- demographic characteristics (age and sex)
- general health factors (e.g. BMI and weight status closest to index date and date measured) and clinically significant changes <sup>7</sup> (ideally within 30 days of end of survey date).
- blood glucose control (IFCC HbA<sub>1C</sub> levels (mmol/mol) closest to index date (and date measured) and end of survey date (ideally within 30 days of end of survey date) as surrogate measure of compliance.
- blood pressure control (Most recent systolic blood pressure (SBP) and diastolic blood pressure (DBP) closest to index date and date measured) <sup>8</sup> (ideally within 30 days of end of survey date)
- ethnicity
- selected medical history relevant for targeted important potential and identified risks of interest (Table 2)
- treatment details of other antidiabetic drugs given as combination therapy at start of treatment and position of level of treatment of Bydureon (first-, second-, or third-line)
- prior and baseline exposure to selected medications of interest relevant for targeted important potential and identified risks of interest (e.g exenatide twice daily, warfarin)
- event reports in the first 12 months after starting treatment, with focus on selected identified risks of interest associated with starting treatment (table 2) and serious adverse event reports [classified using the International Conference on Harmonisation definitions (28)]

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<sup>7</sup> Clinically significant weight loss is regarded as  $\geq 3\%$  change from index measure; clinically significant BMI change is regarded as  $\geq 1 \text{ kg/m}^2$  change from index measure

<sup>8</sup> Clinically significant SBP change gain is regarded as  $\geq 5 \text{ mmHg}$  change from index measure

- GP awareness of non-compliance to administration requirements after starting treatment;
- GP awareness of general adherence problems after starting treatment
- date and reasons for stopping (if stopped);
- event reports in the first 3 months after stopping treatment if stopped.
- date and causes of death (if died)
- use during pregnancy<sup>9</sup>

Patient data to be captured for this study is summarised in Figure 1.

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<sup>9</sup> All reported pregnancies are followed up post estimated delivery date to capture additional information on outcomes relevant to the birth. Information on lactation is obtained through routine event reports.



Figure 1 M-PEM study of Bydureon®

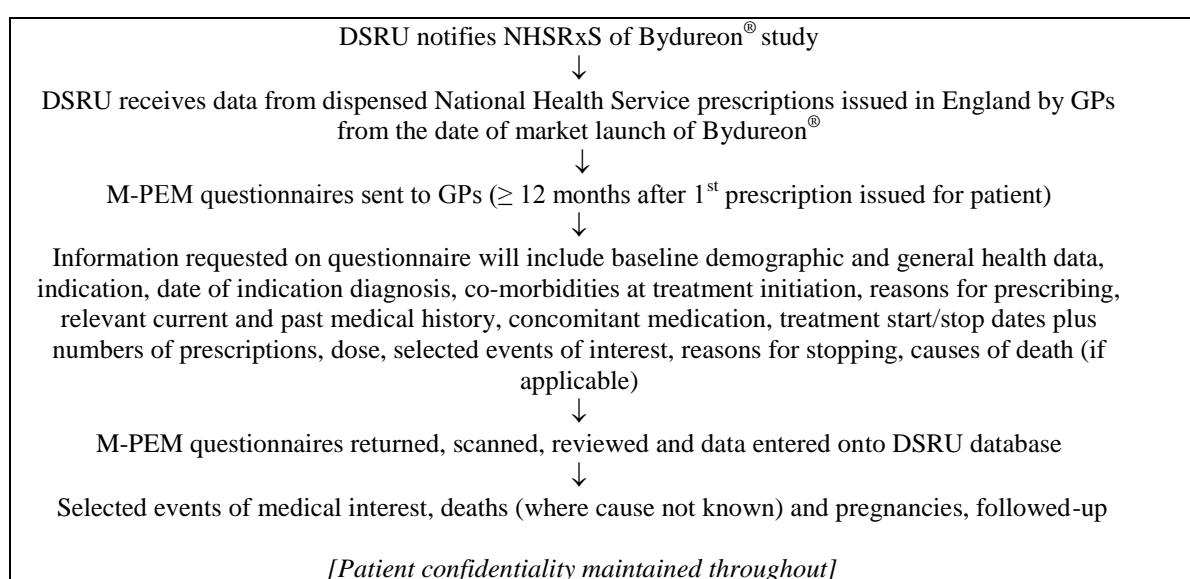


Table 2 Selected events of interest requiring further evaluation

Risk/Missing Information	Proposed data capture	Comment
<b>IDENTIFIED AND POTENTIAL RISKS for targeted data collection on M-PEM questionnaires</b>		
<b>Acute pancreatitis and associated events</b>	Targeted outcome questions	Selected risk factors collected on M-PEM questionnaire. Further data on severity, management and risk factors to be collected via follow-up.
<b>Pancreatic neoplasm</b>	Targeted outcome question	Further data on severity, management and risk factors to be collected via follow-up
<b>Thyroid neoplasm</b>	Targeted outcome questions	Further data on symptoms, severity, management and risk factors to be collected via follow-up.
<b>Rapid weight loss<sup>1</sup></b>	Targeted outcome question on weight and BMI	Further data may be collected via follow-up.
<b>IDENTIFIED AND POTENTIAL RISKS for general surveillance</b>		
<b>Acute renal failure</b>	General event report	Further data may be collected via follow-up.
<b>Allergic reactions (type 1 hypersensitivity)</b>	General event report	Further data may be collected via follow-up.
<b>Cardiac events</b>	General event report	Further data may be collected via follow-up
<b>IMPORTANT MISSING INFORMATION for targeted data collection on M-PEM questionnaires</b>		
<b>Use in patients concomitantly using TZDs</b>	Targeted question on concomitant medications	Further data may be collected via follow-up to ascertain exposure details
<b>Use in patients with severe gastrointestinal disease</b>	Targeted question on past and baseline medical history	Not for follow up
<b>Use in patients with hepatic impairment</b>	Targeted question on past and baseline medical history	Not for follow up
<b>Use in patients with impaired renal function</b>	Targeted question on past and baseline medical history	Not for follow up
<b>IMPORTANT MISSING INFORMATION for general surveillance</b>		
<b>Use during pregnancy and lactation</b>	General event report	Further data to be collected via follow-up
<b>Use in the elderly ≥ 75 years</b>	Age is standard variable on M-PEM questionnaire	Not for follow up
<b>Use in adolescents<sup>2</sup></b>		

Notes: <sup>1</sup> Rapid weight loss was defined as a rate of weight loss >1.5kg/week. <sup>2</sup> Adolescence was defined as male or female patients of 10 to 17 years of age.

#### **4.4.2 Follow-up of Selected Events**

During the course of the study, selected outcomes of interest (arising from Section 2.2) may undergo further evaluation to inform on any unusual features/manifestations, relevant risk factors, clinical course and behaviours. Where necessary, a supplementary follow-up questionnaire which is bespoke to the outcome of interest may be sent to gather additional relevant information. These events will be assessed for drug-relatedness by at least two trained DSRU research staff (of which at least one will be a medical physician).(29)

With the exception of these enquiries for additional information on selected events, no further monitoring of patients for purposes of data collection will occur post the survey period. In accordance with Good Pharmacovigilance Practice (GVP) Sections VI.C.1.2.1 and VI.C.2.2.2, (30) data will be analysed at aggregate level partially at the time of compiling the interim report (because not all information may be available then) and at study completion. Such aggregate analyses can help formulate possible hypotheses which then require further analytic study. Because of the epidemiological nature of the design of this cohort study, any conclusions on drug-relatedness will be made on aggregate basis at study milestones, i.e. when the interim and final reports are written (see Section 5.0 on Communications).

If any other safety issues become apparent during the conduct of this study, additional events and/or event categories may be added to the list of events for follow up and this will be documented accordingly.

Specific outcomes of interest for further evaluation are:

1. Pregnancies: All reported pregnancies will be specifically followed-up using a supplementary questionnaire to ascertain the outcome of pregnancy.
2. Deaths: All reported deaths will be followed-up to try to establish the cause of death.
3. Prescribing: If on concomitant medications of interest (see Section 4.4.1.1), number of prescriptions (date and dose) and duration (start/stop dates)

4. Events: Selected events of interest as defined in Table 2 may be followed-up for additional information on relevant risk factors.
5. Adverse events: Other adverse events deemed of medical importance by the DSRU which are considered to be possible safety signals (either arising from literature reports post marketing, or subsequent to interim data analysis) may also be followed-up for additional information on relevant risk factors for signal strengthening purposes.
6. Adverse events: Events within the list of Rare and Iatrogenic Adverse Reactions (RAIDAR) events compiled by the DSRU (Appendix 1) will be automatically followed up if a more likely alternative explanation for their occurrence is not given.

#### ***4.4.3 Methods to Maximise Questionnaire Response Rate***

##### ***4.4.3.1 M-PEM questionnaires***

A proportion of GPs are likely to fail to respond to these questionnaires at this monitoring stage. Single reminder questionnaires are sent by post to those GPs who have not responded within one month of the date the initial questionnaire was sent.

##### ***4.4.3.2 Specific event follow-up questionnaires***

A duplicate event follow-up questionnaire will be sent to GPs for the specific patient(s) for whom they have not responded to the initial follow-up questionnaire; within six weeks of the date the initial event follow-up questionnaire was sent. GPs will be offered remuneration for each follow-up questionnaire that is completed and returned to the DSRU.

#### **4.5 Data processing**

GP and patient identifiable information will be stored within the DSRU PEM database. All original documents, individual correspondence from health care professionals will be stored for 15 years at the DSRU, with considerable care taken to preserve patient confidentiality (see below).

#### ***4.5.1 Review of data***

All returned questionnaires with clinical data will be reviewed by a DSRU research fellow and coded onto the study database. Section 4.2.2 outlines the reasons for not including questionnaires in the evaluable study cohort. Medically important adverse events that have been selected for follow-up will be coded as a priority. There will be regular monthly review of both the number of patients identified and study questionnaires returned, processed, and classified as void. This will assist in determining the point at which the final cohort size will be achieved. Aggregate data will be reviewed at interim and end of study milestones.

#### ***4.5.2 Coding of data***

Data on indications, exposure, relevant medical history and medication use plus events of interest will be coded directly from targeted closed format questions on the questionnaire using the Medical Dictionary for Regulatory Activities (MedDRA) terminology (31) and coded onto the DSRU PEM database (PEMBase).

Study specific coding procedures will facilitate consistency in coding the data. An SOP will be created upon development of the study specific PEM database region and will be maintained within the DSRU. Regular meetings of DSRU staff will be held to discuss study questionnaires that are difficult to code. A consensus opinion would be reached by medically qualified staff.

Methods to handle issues of missing or conflicting data, will be summarised within the detailed study specific Statistical Analysis Plan (SAP) which will be constructed to assist database development.

#### ***4.5.3 Confidentiality procedures***

All DSRU staff sign confidentiality agreements and the DSRU is registered with the office of the Data Protection Registrar (Registration No. Z5438861).

DSRU information security policies are in place to preserve the confidentiality, integrity and availability of the organisation's systems and data. These include ensuring the premises provides suitable physical and environmental security, all

DSRU equipment is secure and protected against malicious software, the network can only be accessed by authorised DSRU staff, telecommunication lines to the DSRU premises are protected from interception by being routed overhead or underground and personnel receive training regarding security awareness.

All original documents, individual correspondence from health care professionals, will be stored for 15 years at the DSRU, with considerable care taken to preserve the confidentiality of data. The DSRU databases are well protected. To ensure patient anonymity, the names and addresses of patients will be deleted from the DSRU database after two years from receipt by NHSRxS, as per current policy (see Section 3.0). Until this time, only appointed staff would have access to such data.

#### **4.6 Quality Assurance**

Good clinical data management is a high priority at the DSRU. A number of strategies exist to minimise biased PEM study results. The DSRU has a set of rules and processes associated with the conduct of pharmacoepidemiological studies. Data quality is assured through a number of methods based on error-prevention, data monitoring, data cleaning and documentation. These include:

- Operator training;
- Vigilance of operators at the various stages of processing,
- On screen validation during data entry,
- Adoption of and adherence to study-specific data coding conventions,
- Coding review meetings,
- Code list and algorithms
- Double entry (random sample of 10% of M-PEM questionnaires), error reporting and correction of discrepancies between the entries by quality assurance staff
- Coding of M-PEM questionnaires are randomly reviewed by a quality assurance assessor.
- Routine data cleaning to screen for errors, missing values and extreme values and diagnose their cause; this being supported by bespoke software with objective, standardised logical checks and undertaken by the DSRU data manager or allocated staff.
- Relevant maintenance of reference tables, e.g., Event Dictionary

- Pilot testing of study documentation

## 4.7 Data Analysis

### ***4.7.1 To quantify the incidence of the important identified risk of acute pancreatitis in the first 12 months after starting treatment among type 2 diabetes mellitus patients treated with exenatide once weekly***

The following relates to Section 2.2.1 (primary objective). The incidence rate of acute pancreatitis will be explored in exenatide naïve and switcher patients by estimating the hazard rate of this event over time. Such methods account for censoring; for these analyses the exposure time would be censored at the time of the first event. Smoothed hazard plots will be used to describe how the baseline risk of an event changes over time. Estimates of the hazard function will also be modelled to determine whether the baseline hazard (risk) of the event increases or decreases with time. A constant hazard over time may be consistent with a background (not caused by the drug) event rate, whereas a non-constant hazard over time may be an indicator of a drug-event relationship. The null hypothesis that the hazard rate of acute pancreatitis in patients prescribed Bydureon<sup>®</sup> (naïve or switcher) will be constant during the 12 month exposure period following the start of treatment will be tested by fitting parametric time to event models (e.g. Weibull). Such models have a shape parameter that indicates whether the hazard is significantly increasing or decreasing over time. Several parametric models will be fitted; the Akaike's information criterion (AIC) and model fit will be assessed. At least five reports of an event are deemed necessary for modelling purposes.\*

\*When the shape parameter (p) for the Weibull model is equal to one, the hazard is estimated to be constant over time, if p is greater than one the hazard is increasing, if p is less than one the hazard is decreasing. The hazard function will be determined as non-constant if the 95% CI excludes the value one.

***4.7.2 To describe the baseline health profile of patients on treatment with Bydureon® in the primary care setting and the treatment they received (and by whom), to advance the understanding of the Bydureon® patient population in actual clinical practice***

The following relates to Section 2.2.2 (secondary objective i). Data on prescriber and valid cohort response rates will be presented, as will data on prescriber type and setting. These data will be used to inform on cohort accrual and study timelines to target sample size. Pooled evaluable cohort demography (age, gender and ethnicity) will be presented, as reported at baseline. Other baseline general health factors [e.g. BMI, HbA<sub>1C</sub> level, BP] and indication-related characteristics [date of first diagnosis]; treatment initiation programme (first initiated by specialist or in primary care, details of combination therapy and level (first-, second-, third-line) and prescribing reasons as reported on the M-PEM questionnaire will be described. A synopsis of prior and baseline morbidities and medication use will also be provided.

Patient subgroups defined by whether exenatide naïve or past user, or other subgroups of special interest [Table 2] will be characterised in order to inform on missing information regarding use of exenatide. Where possible, these groups will be compared in terms of demographic factors and other study variables. Further stratification by calendar period *may* also be undertaken to identify any cohort effects or trends that may be emerging.

***4.7.3 To describe the risk profile of events reported in the 12 month observation period in the overall cohort and in special populations (arising from contraindications and those for which: precautions for use are recommended; appropriate clinical monitoring is recommended; and limited information is available).***

The following also relates to Section 2.2.2 secondary objective (ii). PEM methodology provides a numerator (the number of reports of an event) and a denominator (the number of patient-months at risk), both collected within a known time frame. This allows for the calculation of risk (percent of total valid cohort exposed) and incidence densities (ID; person-time incidence rates) for each event. Such analyses will be performed using ‘Higher-level’ event terms from the MedDRA dictionary. The risk profile of the overall cohort and sub-group of interest (based on

characteristics defined at baseline, including whether exenatide naïve or past user) will be described by presenting summary tabulations (by rank) of counts and incidence risk of reported events, and crude event rates (IDs).

Crude Incidence Densities (ID)<sup>10</sup> can be calculated by month in order quantify rates of events. IDs will be calculated, for each given time period (t), for all events reported in patients who continue to use exenatide for a given time period, or for whom the date of stopping is known. Only the first report of an event in an individual patient is used in the calculation of IDs. They are usually expressed as the number of first reports of an event per 1000 patient-months. This assumes pattern of use is continuous. The numerator will be the first reports of events reporting as occurring after the index date and during treatment.<sup>11</sup> For this study, IDs will be calculated for each event as for each month as follows:

$$ID_t = \frac{\text{Number of first reports of an event during treatment for period } t \times 1000}{\text{Number of patient-months of treatment for period } t}$$

$$\text{Thus, } ID_t = \frac{N_t \times 1000}{D_t}$$

where:  $N_t$  = Number of first reports of an event during treatment for period t,

$$\text{and } D_t = \frac{\text{Number of patient-days of treatment for period } t}{30}$$

IDs will also be calculated for all 12 months during treatment combined ( $ID_A$ ) and the first month after stopping ( $ID_{S1}$ ) if patient stopped (and where patients are recorded as remaining on treatment for at least four weeks) after index date.

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<sup>10</sup> It should be noted such quantification of rate does not only reflect the rate attributable to the drug but also reflects the background rate in the general population and rate attributable to other factors such as age or other disease risk factors

<sup>11</sup> Ideally, the exposure time would be censored at the time of the first event. However, since there are a large number of health outcomes of interest and the censoring would be different for each outcome, the denominator for the crude ID will not initially include censoring. If an elevated crude ID is identified in this monitoring analysis, a subsequent analysis with appropriately censored denominator will be performed for that outcome.



***4.7.3 To describe the characteristics of selected important identified and potential risks in the first 12 months after starting treatment, which are: acute pancreatitis (plus signs and symptoms); pancreatic neoplasm and thyroid neoplasms<sup>12</sup>***

The following relates to Section 2.2.3 (exploratory objective i). A qualitative assessment of the summary characteristics of patients reported with these outcomes. This will include evaluation of treatment details, the detection and clinical features and management of events of interest, resolution, relevant investigations prior to and during therapy, the patient's relevant medical history and concurrent medication and any sequelae. Data will be derived from the M-PEM and follow up questionnaires sent to gather other relevant essential information for construction of a case-series summary descriptive table.

***4.7.4 Where possible, to quantify the incidence of other frequently and rarely reported events (including other important identified and potential risks not mentioned in Objective 2.2.1)***

The following relates to Section 2.2.3 exploratory objective (ii). Analysis of event data for purposes of signal detection includes calculating the difference (or ratio) between selected time periods, and also examining time to onset profiles for selected events.

The initial approach for generating signals will be to calculate the arithmetic difference and ratio between two time periods for each reported event (e.g. ID<sub>t1</sub> and ID<sub>t2</sub>) with a 95% confidence interval (CI) in order to examine the null hypothesis that the rate for the event is not increasing or decreasing between the two time periods.(32) This assumes that there is no difference in reporting between the two periods. ID differences and ratios can be used to identify events that occur significantly more frequently soon after starting treatment – e.g., if looking at the first three months of observation, where the ID<sub>1</sub>-ID<sub>2-3</sub> value for an event is positive, and the 95% confidence interval does not include zero, or where ID<sub>1</sub>/ID<sub>2-3</sub> is greater than one and the 95% confidence interval does not include the value one, then the rate of events in

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<sup>12</sup> It is important to note that this M-PEM study will only characterise any cases of thyroid neoplasm and pancreatic neoplasm that are reported during the twelve month observation period. This study cannot give any inference on the incidence of these cancers in the M-PEM cohort, as the study length and size has not been designed for this.

month one is significantly greater than the rate of events in months two to twelve. This result is considered to be a signal for an event occurring shortly after starting treatment with exenatide once weekly. Similarly, ID differences and ID ratios can be used to identify events that have a delayed-onset where the ID differences or ratio statistic is negative and the 95% confidence intervals exclude the value zero or one respectively, then the rate of events is significantly lower during month one than subsequent months. This result is considered to be a signal for a delayed-onset event.

As IDs for the overall cohort may sometimes mask significant signals in specific risk groups, the subgroups defined by specific characteristics (e.g. previous/baseline use of selected medications, exenatide naïve or past user) will have IDs calculated and compared according to strata for relevant events, where appropriate.

It is acknowledged that the generalised approach to segregation of time periods may not be appropriate for all events with respect to their most relevant time periods of excess. It is possible to explore the time taken for an event of interest using parametric time to event models (e.g. Weibull) as described previously, thus providing an additional tool for signal generation purposes. This approach will be explored for events of interest, where counts  $\geq 5$ . If undertaken, a sensitivity analysis will be performed to include in the numerator events reported within 30 days of stopping, and extend the denominator by 30 days.

#### ***4.7.5 Multiple comparison adjustments***

The methods of signal surveillance require a large number of multiple comparisons on adverse events, which involve inferring statistical significance on multiple  $p$ -values. To control for an excess of false positive signals, suitable multiple comparison adjustments will be made with the false discovery rate (FDR) approach.(33) The Simes method (34;35) in addition to the double FDR method (33) will be implemented to maintain the false discovery rate at the acceptable 10% level for all statistical tests. Such approaches would allow for a balance between false positive and false negative signals.

#### 4.8 Aggregate assessment of drug-relatedness of selected events

As described previously (Section 4.4.2.2) selected events of interest (Table 1) that require further characterisation and evaluation may be followed-up via a questionnaire sent to the patient's GP seeking further information, if the relevant information is not provided on the M-PEM questionnaire. This information received at follow-up for events of medical significance or those which require further clarification will be used in conjunction with other available information to facilitate further evaluation at the aggregate level, including assessment of drug-relatedness, by experienced research staff at the DSRU. A drug-relatedness assessment will occur once all requested information (i.e. 12 month questionnaire and follow-up questionnaire if applicable) have been received. In the process of aggregate assessment of event data, the application of elements of the Austin Bradford Hill criteria, when the necessary information is available and the use of the method is considered appropriate, will be used.<sup>(36)</sup> This assessment takes into consideration of the points (see Box 1).<sup>(37)</sup>

##### Box 1. Points for consideration in evaluation of reported events

- *the temporal relationship (time to onset);*
- *the clinical and pathological characteristics of the event;*
- *the pharmacological plausibility based on previous knowledge of the drug and the therapeutic class if appropriate;*
- *whether the event was previously reported as an adverse reaction in clinical trials or postmarketing in the UK or in other countries;*
- *any possible role of concomitant medications or medications taken prior to the event;*
- *the role of the underlying or concurrent illnesses;*
- *the effect of de-challenge or dose reduction;*
- *the effect of re-challenge or dose increase;*
- *patient's characteristics, including previous medical history, such as history of drug allergies, presence of renal or hepatic impairment, etc.;*
- *the possibility of drug interactions.*

The following four categories are used to classify relatedness of events that are assessed as: probable, possible, unlikely or not assessable.<sup>(37)</sup>

Events are assessed as ‘probable’ if the event is well defined clinically and pathologically, if there is a reasonable time sequence, if it is more likely to be attributed to the study drug rather than to a concurrent disease or concomitant medication, if there is a positive dechallenge, rechallenge or response to dose increase, and if there are other supporting criteria (e.g. on the basis of lab tests or histological findings).

Events are assessed as ‘possible’ if the event has a reasonable clinical and pathological definition, if there is a reasonable time sequence, if it could also be explained by concurrent disease or concomitant medication, but dechallenge, rechallenge and confirmatory investigations are inconclusive or not fully available. Medical judgement will be necessary in some cases.

Events are assessed as unlikely if the event had a temporal relationship to the study drug administration that made a causal relationship improbable, or if concurrent disease or concomitant medication provided a far more plausible explanation.

Events are unassessable if insufficient information about the event has been provided and an appropriate evaluation is therefore not possible.

## **4.9 Data Monitoring**

### ***4.9.1 Communications***

If requested, a cohort accrual progress report can be produced from study start (date of prescription collected for first eligible patient) in time for inclusion in the scheduled Periodic Safety Update Reports (PSUR) for the product or regular updates of the RMP for as long as the study continues.

Examination of aggregate event data will be limited to one interim report on a study cohort of 2500 evaluable patients or on the evaluable cohort achieved at approximately 18 months after study start, whichever is the sooner. A detailed final report based on a study cohort of 5000 evaluable patients or on the evaluable cohort achieved at approximately 36 months, whichever is the sooner (unless an extension to study period is required).

#### 4.9.2 Reporting

The DSRU shall on an ongoing basis notify the MAH when they consider, based on their evaluation, that any issues or matters of interest relating to the Study or its outcomes are of importance and shall provide the MAH with related results of the study and analyses thereof. The DSRU shall deliver interim and final reports in accordance with the Protocol and with content sufficient for the MAH to meet its obligations under Volume 9A, Section 7.4.3.

Since the clinicians are prescribing a licensed product, they will be reminded in the study documentation that it is their responsibility to report any suspected adverse reactions (including serious<sup>13</sup> adverse drug reactions) to the company and/or to the MHRA (using Yellow Cards) as they would normally do in their practice in support of routine pharmacovigilance. In cases where the DSRU receives, by mistake, such reports it will forward them to the MHRA and/or the MAH as appropriate.

## 5.0 STRENGTHS, LIMITATIONS AND POSSIBLE SOURCES OF BIAS

### 5.1 Strengths

- All patients who are dispensed Bydureon® in primary care are identifiable and will be eligible for inclusion. There are no exclusion criteria based on indication, dose, age or past medical history.
- The observational non-interventional nature of PEM study design is maintained; prescribing of relevant pharmacological therapy should not be affected because of participation in this study.

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<sup>13</sup> **Definition of Serious Adverse Event** "Serious Adverse Event means an adverse event which is fatal or life-threatening, results in persistent or significant disability, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, or is a congenital anomaly, cancer, the result of an overdose or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered a Serious Adverse Event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

- Data is collected on large numbers of Bydureon<sup>®</sup> users in conditions of routine clinical practice.
- Special populations can be characterised.
- Time-dependent effects can be examined.

## **5.2 Limitations**

- Possible delay in new user cohort accrual if adoption by primary care physicians is low.
- PEM prescription data will only identify those initiated in primary care.
- Only GP prescribers are identifiable from Organisation Data Service (ODS; which relate to General Medical Practitioner Codes and GP Practice Codes) data – hospital prescribers are not identifiable in PEM despite FP10 HP prescription data supplied by NHSRxS.
- There is no comparator cohort, however where appropriate, within cohort comparisons will be considered.
- Design may preclude obtaining information on patients who have died, or have newly registered with UK primary care services from abroad and have limited information on past medical history.

## **5.3 Potential for bias**

- Confounding by indication is a form of selection bias where the disease that forms the indication being treated (irrespective of severity) is not only associated with treatment but also an independent risk factor for selected outcomes (events of interest) in patients not exposed to antidiabetics. This is likely and needs to be examined since such channelling may result in apparent association of increased risk of such events in this population. It may be introduced through prescribing of treatment based on certain characteristics of a patient. For this study, patients for whom prior alternative treatment was poorly tolerated or ineffective may be selectively prescribed the new treatment.
- Confounding by severity is possible, as is treatment switching of multiple-drug therapy, and needs to be accounted for.

- Patients started and stopped in hospital will not be identified. Exclusion of this subset will introduce selection bias in that patients who may have more severe disease will not be included.
- Immeasurable time bias in terms of inaccurate measurement of exposure is likely as a result of unidentified hospitalisation
- With this patient population, patient attrition and loss to follow-up is possible which may introduce selection bias.
- Non-response bias as a result of GPs being unwilling to complete a complex questionnaire with multiple outcomes is possible, however, this will be addressed by a) payment to cover administrative costs of completing a more complex questionnaire (response rate for M-PEM studies is approximately 64%, which is similar to average GP response rate to postal surveys in general)(38) and b) sending single reminder questionnaires by post to those GPs who have not responded within one month of the sent date of the initial questionnaire.
- Under-reporting, including that of serious or fatal events, is possible in PEM, as for any other observational study. However, a ten fold difference in reporting of serious events between PEM and the Yellow card spontaneous reporting system has been identified, in favour of PEM.(39)
- Given the M-PEM questionnaires prompts prescribers to report on selected and often serious outcomes of interest through use of specific questionnaires, differential over-recording (and reporting) of serious to non-serious events is possible.
- Misclassification bias of outcomes may occur which is of particular importance for rare outcomes, however, it will be minimised by follow-up of medically important events. Patients with events of interest will be followed-up with regard to co-prescribed medicines and concurrent illness. Events that represent features of the respective indications will be taken into account when signals are investigated (i.e. confounding by indication).
- Time bias may also become an issue if the study collection period, and thus the observation period, is extended because of low prescribing rates.
- Furthermore unidentified poor adherence may also lead to misclassification of exposure. In PEM, exposure is based on dispensed prescription data. These data are more accurate than exposure data based solely on written

prescriptions, e.g. GPRD. However, as with many observational studies, the degree of patient compliance in taking the prescribed medication cannot be ascertained. While it is not possible to be sure the patient used the medication, it is almost certain that the patient received it. Repeat prescriptions would indicate that a patient continued to obtain the medication, whilst GP awareness of adherence would inform on pattern of dosing.

## **6.0 STUDY SPONSORSHIP**

This study is being undertaken by the DSRU as part of the Risk Management Plan for the product at the request of the Committee for Medicinal Products for Human Use (CHMP). The Drug Safety Research Trust is a registered independent charity (No, 327206) operating in association with the University of Portsmouth and is sponsor of the study. The DSRU is the academic sponsor and receives an unconditional grant from Eli Lilly and Company.



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**Appendix 1. DSRU Rare and Iatrogenic Adverse Events (RAIDAR) list**

Agranulocytosis  
Alveolitis  
Anaemia aplastic  
Anaphylaxis  
Angioneurotic oedema  
Arrhythmia  
Bone marrow abnormal  
Congenital abnormality  
Dermatitis exfoliative  
Disseminated intravascular coagulation  
Erythema multiforme  
Erythroderma  
Guillain-Barre syndrome  
Hepatic failure  
Hepatitis  
Jaundice  
Leucopenia  
Multiorgan failure  
Nephritis  
Nephrotic syndrome  
Neuroleptic malignant syndrome  
Neutropenia  
Pancreatitis  
Pancytopenia  
Pseudomembranous colitis  
Renal failure acute  
Retroperitoneal fibrosis  
Rhabdomyolysis  
Stevens Johnson syndrome  
Sudden Unexpected Death  
Thrombocytopenia  
Torsades de pointe  
Toxic epidermal necrolysis

Any event for which there is a positive rechallenge