Drug Safety Research Unit (DSRU)

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

Final report

December 2018

[redacted]

PASS information

Title	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
Version identifier of the final study report	Version 3 (Final)
Date of last version of the final study report	N/A
EU PAS register number	EUPAS5599
Active substance	Active substance: Exenatide ATC code: A10BJ01
Medicinal product	Bydureon 2mg powder and solvent for prolonged-release suspension for injection in pre-filled pen
Product reference	EU/1/11/696/003 4 pre-filled pens EU/1/11/696/004 3x4 pre-filled pens
Procedure number	N/A
Marketing authorisation holder(s)	AstraZeneca AB SE-151 85 Södertälje Sweden
Joint PASS	No
Research question and objectives	The overall aim was to study the utilisation and safety of exenatide once weekly (Bydureon®) to treat type 2 diabetes mellitus in new user patients (exenatide naïve) and previous Byetta® users under normal conditions of use in primary care in England. The primary objective was to quantify the cumulative incidence of acute pancreatitis in the first 12 months after starting treatment. Secondary objectives were to: (i) describe the baseline health profile of the 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; (ii) describe the risk profile of events (using incidence densities) 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 objectives included: (i) to describe the characteristics of the patient population with events of selected important identified and

	potential risks in the first 12 months after starting treatment which were: acute pancreatitis, pancreatic cancer and thyroid neoplasm (benign and malignant subtypes); (ii) where possible, quantify the incidence of other frequently and rarely reported events (including other important identified and potential risks not mentioned in the primary objective).
Country(-ies) of study	England
Author	[redacted]

Marketing authorisation holder(s)

Marketing authorisation holder(s)	AstraZeneca AB
MAH contact person	[redacted]

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1 Abstract

Title

An observational post-authorization Modified Prescription-Event Monitoring (M-PEM) safety study to monitor the safety and utilization of exenatide once weekly (Bydureon®) to treat type 2 diabetes mellitus in new user patients (exenatide naïve) and previous Byetta® users under normal conditions of use in primary care in England.

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Keywords

Bydureon- Exenatide- Observational- Cohort- Safety- Utilisation

Rationale and background

Bydureon® (exenatide) is a once weekly injection indicated for the treatment of type 2 diabetes mellitus. This post-authorisation safety study (PASS) was carried out as part of a Risk Management Plan for Bydureon®.

Research question and objectives

The primary objective was to quantify the cumulative incidence of acute pancreatitis in the first 12 months after starting treatment.

Secondary and exploratory objectives aimed to explore the baseline health profile of patients on treatment with Bydureon®, describe the risk profile of events reported in the 12-month observation period, describe characteristics of the patient population with events of selected important identified and potential risks, and where possible, quantify the incidence of other frequently and rarely reported events.

Study design

An observational cohort study using an M-PEM design.

Setting

Primary care in England.

Subjects and study size, including dropouts

The cohort was identified from dispensed Bydureon® prescriptions from January 2012- September 2016. GPs were contacted and asked to recruit patients into the study. Response rate for this study was 37.2% and the total evaluable cohort comprised of 6294 patients, 55.2% male and 44.8% female.

Variables and data sources

Information on drug utilisation, relevant past medical history and events was requested from general practitioners at ≥12 months after the first Bydureon® prescription issued for each patient.

Results

Baseline characteristics

The majority of patients were exenatide naïve (n=4556, 72.4%), while approximately one-quarter of patients (n=1629, 25.9%) were previous Byetta® users. For 109 patients (1.7%) previous exposure to exenatide (Byetta®) was not known.

Outcomes

The cumulative (12-month) incidence of acute pancreatitis was 0.2% (n=14); incidence rate was 2.5 per 1000 person-years (95% CI [1.5, 4.3]). Cumulative incidence of other targeted events was: 0.6% for gallstones, biliary colic or cholecystitis (n=38), 0.7% for hypersensitivity (type 1 reactions) (n=44), 0.5% for acute renal failure (n=29) and 3.6% for 'cardiac disorders' (n=227).

In total, 43 patients (0.7%) died during the 12-month observation period and 25 of these deaths (0.4%) occurred on treatment.

Discussion and conclusion

Bydureon® is largely being prescribed in accordance with prescribing recommendations in primary care. The estimates of risk of acute pancreatitis are generally in line with prior knowledge based on clinical trial and observational data. This study is part of a broader literature in the safety of Bydureon® and any conclusions on safety should be put into context with results from other post-marketing studies.

Marketing Authorisation Holder(s)

AstraZeneca AB, SE-151 85 Södertälje, Sweden

Names and affiliations of principal investigators

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2 List of Abbreviations

Abbreviation	Term
ACE	Angiotensin-Converting-Enzyme
ADM	Antidiabetes medication
AE	Adverse Event
AIC	Akaike Information Criteria
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BP	Blood Pressure
CHM	Commission on Human Medicines
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
DBP	Diastolic Blood Pressure
DDP-4	Dipeptidyl Peptidase-4
DM	Diabetes Mellitus
DSRU	Drug Safety Research Unit
ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drugs Administration
GGT	Gamma-Glutamyl Transpeptidase
GLP-1	Glucagon Like Peptide-1
GP	General Practitioner
HbA_{1c}	Haemoglobin A1c
HLT	Higher Level Term
ID	Incidence Density
IFCC	International Federation of Clinical Chemistry
INR	International Normalised Ratio
IQR	Interquartile Range
LFT	Liver Function Test
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 carcinoma
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NHS BSA	National Health Service Business Services Authority
NHSRxS	National Health Service Prescription Services
OTC	Over-The-Counter
ODS	Organisation Data Service
OSIRIS	Observational Research Information Management System
PEM	Prescription Event Monitoring
PT	Preferred Term
PSUR	Periodic Safety Update Report
RAIDAR	Rare and Iatrogenic Adverse Reactions
RET	Reported Event Term
RFS	Reason For Stopping

RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SGLT-2	Sodium-glucose co-transporter-2
SMQ	Standardised Medical Query
SOC	System Organ Class
SmPC	Summary of Product Characteristics
TB	Total Bilirubin
UK	United Kingdom
ULN	Upper Limit Normal
US	United States

3 Investigators

Investigator	**Appointed person(s)**
Principal investigator	[redacted] Drug Safety Research Unit
Co-investigator	[redacted] Drug Safety Research Unit
Co-investigator	[redacted], Drug Safety Research Unit

4 Other Responsible Parties

Responsible party	**Appointed person(s)**
Marketing Authorisation holder contact	[redacted] [redacted] AstraZeneca AB

5 Milestones

Milestone	**Planned Date**	**Actual Date**	**Comments**
Start of data collection	Sept 2011	Jan 2012	Prescription collection
End of data collection	Dec 2015	Sept 2016	Prescription collection stopped in Sept 2016 once sample size reached
Registration in the EU PAS register	--	Dec 2013	EUPAS5599
Annual report	May 2014	May 2014	
Interim report	Dec 2015	Dec 2015	
Final report of study results	November 2018	December 2018	

6 Rationale and Background

The aim of this study is to monitor clinically important identified and potential risks within a cohort of patients treated with prolonged release exenatide (Bydureon®) in the real-life primary care setting in England following the approval of marketing application of the license in England.

6.1 Therapeutic indication

Bydureon®, a glucagon-like peptide-1 (GLP-1) receptor agonist, was approved by the European Commission on 17th June 2011 to improve glycaemic control in combination with other glucose-lowering medicinal products including basal insulin, for adults 18 years or older with type 2 diabetes mellitus when therapy in use, together with diet and exercise, does not provide adequate glycaemic control. (1)

Bydureon® is an extended-release formulation that consists of exenatide-containing polymeric microspheres for suspension in an aqueous dilutent. Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist that exhibits several anti-hyperglycaemic actions of GLP-1, binding to and activating human GLP-1 receptor *in vitro*. It increases, on a glucose-dependent basis, the secretion of insulin from pancreatic beta cells. (1) Exenatide also suppresses glucagon secretion, which is elevated in patients with type 2 diabetes mellitus. Lower glucagon concentrations lead to decreased hepatic glucose output. Furthermore, exenatide 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. Although longer- acting extended-release exenatide has its advantages in terms of patient convenience, exenatide is also available as a short-acting GLP-agonist, known as Byetta®, which was first authorised in 2006. (2)

The recommended dose of Bydureon® is 2mg once weekly by subcutaneous injection. It is available as powder and solvent for prolonged-release suspension in a single dose vial and syringe, or in a single dose pre-filled pen. In August 2018, the European Commission approved a new pharmaceutical form of Bydureon®, prolonged-released suspension for injection in a pre-filled pen. The dose can be administered at any time of day with or without meals (1), which is in contrast to the twice daily version of exenatide (Byetta®) which must be taken within 60 minutes before the morning or evening meal. (2) After discontinuation, the effect of Bydureon® may persist as plasma levels of exenatide decline over 10 weeks. It is therefore recommended to carefully consider choice of other medicinal products and the corresponding dose as efficacy may persist and adverse reactions continue. (1)

Bydureon®-exposed populations are likely to be comprised of patients with type 2 diabetes mellitus who have not achieved adequate control with other antidiabetes treatments as well as patients switching from Byetta®. It is often prescribed in combination with metformin and sulphonylureas. (1) Initial transient alterations to blood glucose levels (hypo- and hyperglycaemic) are possible in such populations switching

from Byetta® to Bydureon®. (1) Research also suggests that prolonged-release exenatide results in significant reductions in body weight; in four comparator-controlled studies between 70%-79% of patients had both a reduction in weight and HbA1c. (1)

6.2 Efficacy, safety profile and undesirable effects

The clinical development of exenatide once weekly is based on pivotal phase III studies. These comprise the DURATION programme (Diabetes Therapy Utilization: Researching changes in HbA1c, Weight and Other Factors through Intervention with Exenatide Once Weekly). (3-10) In summary, the DURATION studies compared the efficacy and safety of exenatide 2mg once weekly in patients with poorly controlled diabetes with active controls (i.e., exenatide twice daily or other antidiabetes medications). The primary efficacy endpoint for each study was change in HbA1c; secondary endpoints included change in body weight. In addition, each study evaluated the incidence of treatment-emergent adverse events and changes in blood pressure and lipid levels.

Efficacy

The DURATION-1 was an open-label trial comparing exenatide 2mg once weekly exenatide (Bydureon®) with exenatide 10 µg twice daily (Byetta®) over 30 weeks in 295 patients with type 2 diabetes mellitus. Results demonstrated more favourable reductions in HbA1c with Bydureon® as compared to Byetta® (-1.9 [SE 0.1%] vs -1.5 [0.1%]; p=0.0023) but similar reductions in body weight (-3.7 [SE 0.5] kg vs -3.6 [0.5] kg, respectively, p=0.89). (3) Findings were similar for the 24-week DURATION-5 open-label trial, which also compared Bydureon® with Byetta®. (7)

The remaining DURATION studies compared Bydureon® with other medications used for the treatment of type 2 diabetes mellitus. In summary, the DURATION 1-6 trials have shown that exenatide once-weekly (Bydureon®) resulted in HbA1c reductions of 1.3-1.9% over 24-30 weeks and a mean weight loss of 2.0-3.7 kg. (3-8, 11) Similar improvements in glycaemic measures and weight were observed in the 28-week DURATION-7 and DURATION-8 trial. (9, 10) Furthermore, extension of the DURATION studies also showed sustained improvements in HbA1c in patients continuing on Bydureon® therapy. (11, 12)

Safety

According to the Summary of Product Characteristics (SmPC), very common adverse events (incidence >10%) include hypoglycaemia (with a sulphonylurea), nausea and diarrhoea. The risk of hypoglycaemia was increased when prolonged release exenatide was used in combination with a sulphonylurea in clinical trials (24.0% vs. 5.4%). (1) Nausea is known to be the most frequently reported adverse event with Bydureon®. However, as compared to Byetta®, patients treated with Bydureon® less frequently reported nausea; in the DURATION-1 trial, 26.4% of patients experienced nausea in the Bydureon® treatment group as compared to 34.5% of patients treated with Byetta®. (3)

Common adverse events (incidence > 1%) include hypoglycaemia (with insulin), decreased appetite, vomiting and injection site conditions such as pruritus and erythema. Clinical trial evidence suggests that injection-site reactions were generally mild and did not lead to withdrawal from studies. (1) An integrated analysis of eight randomised phase III trials (including DURATION 1-6) with 24-week and 30-week comparator controlled periods showed that injection-site reactions were more frequent with Bydureon® than Byetta® or non-GLP-1 receptor agonists (20.0% vs. 8.0% and 8.0%, respectively). (13)

Special populations for whom clinical data was limited at the time the study protocol was written includes older adults aged ≥75 years, patients with moderate renal impairment, pregnant and breastfeeding women and children/adolescents aged ≤17 years. Information on the use and safety of Bydureon® in the paediatric population still remains limited. Specific contraindications include patients who have reported previous hypersensitivity to exenatide, whilst use in individuals with type 1 diabetes mellitus, or for treatment of diabetic ketoacidosis are both listed as special warnings and precautions for use in the SmPC. Anaphylactic reactions are known to be rarely associated with Bydureon® (incidence < 1/1000). (1) Monitoring is also recommended for patients who experience rapid weight loss. Although there are significant benefits of a reduction in weight in patients with type 2 diabetes mellitus, it has been reported that weight loss can occur at a rate of >1.5 kg per week. This rate of weight loss can potentially have harmful consequences and it is recommended to monitor these patients for signs and symptoms of cholelithiasis. In addition, use of Bydureon® in severe gastrointestinal disease, end-stage renal disease and a history of acute pancreatitis, is not recommended. (1)

Although uncommon, there have been spontaneously reported cases of acute pancreatitis with Bydureon®. (1, 14, 15) Annual incidence rate of acute pancreatitis in U.S. adults is estimated at 0.7 per 1000 in the general population. (16, 17) However, patients with type 2 diabetes mellitus appear to be at nearly a three-fold greater risk than non-diabetics for developing pancreatitis and at nearly two-fold increased risk for developing biliary disease, (18) making it difficult to infer causality. In clinical studies of Bydureon®, acute pancreatitis occurred in 0.3% of patients. (1) Single cases of pancreatitis were reported in the Bydureon® treatment arms in the DURATION- 3, 5, 6 and 7 trials. (5, 7-9) Furthermore, in a randomised controlled trial investigating the effects of Bydureon® on cardiovascular outcomes in 14, 572 patients with type 2 diabetes mellitus (EXSCEL trial) with a median follow-up of 3.2 years, confirmed events of acute pancreatitis were uncommon and incidence was comparable between exenatide naïve patients and those taking placebo (0.4% vs. 0.3%, respectively). (19) Post-marketing data has also reported very rare cases of necrotising or haemorrhagic pancreatitis and/or death with Bydureon®, (1) however, it is known that necrosis or haemorrhage of the pancreas and other systemic complications occur in 15-20% of all cases of pancreatitis. (20, 21) Due to these post-marketing reports, the US FDA and the European Medicines Agency (EMA) assessed the pancreatic safety of incretin-based therapies, however, concluded that a causal relationship could not be supported by current data. (22) Nevertheless, the SmPC recommends

that Bydureon® should be discontinued if pancreatitis is suspected and if the diagnosis is confirmed, Bydureon® should not be restarted. (1)

In addition to the above, there have also been some concerns regarding the risk of pancreatic cancer with exenatide, but a causal relationship is not currently supported. (22) In an integrated analysis of eight randomised phase III trials (including DURATION 1-6) over 24-30 weeks, only one case of pancreatic neoplasm was reported for a patient taking Byetta®. (13) The estimated incidence rate for pancreatic neoplasms in the general adult population is approximately 10 cases per 100,000 persons per year. (23) Of note, patients with diabetes have approximately a two-fold increased risk of developing pancreatic neoplasm compared with patients without diabetes. In the EXSCEL trial, incidence of pancreatic cancer was comparable between the Bydureon® and placebo arm. (19)

In a two year carcinogenicity study with Bydureon® 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 then human clinical exposure to Bydureon®) compared to controls. The human relevance of these findings is currently unknown. (1, 23) 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 receptor agonists similar to exenatide have been reported to cause malignant tumours of the thyroid gland. Medullar thyroid carcinoma is rare in humans, and approximately 20% to 25% cases are familial. (24) The US FDA data suggests that the rate of reported thyroid cancer events is higher for patients taking exenatide vs. rosiglitazone (odds ratio (OR)>3.0), however, this estimate is based on spontaneous reporting. (25) In the integrated analysis of eight clinical trials, the very rare occurrences of thyroid neoplasm were all benign. The rate of thyroid neoplasm for Bydureon®, Byetta® and the comparator groups across all eight clinical trials were 0.2, 0.4, and 0.5 per 100 patient-years, respectively. (13) In EXSCEL, incidence of medullary thyroid cancer was also low (<0.1% in both Bydureon® and placebo groups). (19)

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

Cumulatively, up to 31st March 2018, the total number of patients recorded in the clinical trial database (completed and ongoing clinical trials) for exposure to exenatide include 7568 as having received Byetta® (BID), 11307 patients as having received Bydureon® SDT and DCP (QW), 579 patients as having received Bydureon® AI (QWS), and 1416 patients as having received Exenatide (QM). The cumulative global post-marketing patient exposure to exenatide, since launch to 31 March 2018, has been estimated to be approximately 1679959 patient-years for exenatide QW (20159512 packs), 7427 patient-years for exenatide QWS (autoinjector) (386208 injections), and 3238173 patient-years for exenatide BID (38858077

pens). Given these exposure estimates for exenatide BID, QW, and QWS formulations, the overall post-marketing cumulative exposure for exenatide is estimated to be 4.9 million patient-years. (26)

At the time of writing the protocol the safety specification was based on the Bydureon® RMP (revision 16). The RMP subsequently has been updated. At the time of this report, the important identified risks are pancreatitis and acute renal failure; the important potential risks are pancreatic cancer and thyroid neoplasms (v7 Exenatide core RMP). 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 Bydureon®.

6.3 Background to antidiabetes medication prescribing in the UK

In the UK, antidiabetes medication initiation and ongoing prescribing to patients for type 2 diabetes mellitus takes place in a range of primary care and secondary care settings, including in-patient and outpatient (hospital based and led by a medical consultant or a nurse specialist; community clinic based usually led by a nurse specialist). According to data from the Quality and Outcomes Framework, 6.4% of people aged 17 years+ and registered with a GP in England have diabetes, of whom type 2 diabetes accounts for 89%. (27) Prescriptions for medicines to treat diabetes make up one in every 22 items dispensed and the volume and cost of these medications has increased by >80% over the past decade. Excluding the most commonly prescribed metformin and sulphonylureas, the GLP-1 receptor agonists are the third largest group of other antidiabetes medications prescribed after the DPP-4 inhibitors and thiazolidinediones; exenatide is also the second most commonly prescribed GLP-1 agonist, accounting for 30% of volume and 26% of cost of all GLP-1 receptor agonists. (27)

7 Research Question and Objectives

7.1 Overall aim

To study the utilisation and safety of exenatide once-weekly (Bydureon®) to treat type 2 diabetes mellitus in new user patients (exenatide naïve) and previous Byetta® users under normal conditions of use in primary care in England.

7.2 Specific objectives

7.2.1 The primary objective

The purpose of the primary objective was to:

(i) Quantify the cumulative incidence of acute pancreatitis in the first 12 months after starting treatment with Bydureon®.

7.2.2 Secondary objectives

These are given below. Their purpose was to:

(i) 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;

(ii) Describe the risk profile of events (using incidence densities) 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).

7.2.3 Exploratory objectives

The specific objectives that follow are all exploratory. The purposes of these objectives were to:

(i) Describe the characteristics of the patient population with events of selected important identified and potential risks on the first 12 months after starting treatment with Bydureon®, which were:

- Acute pancreatitis
- Pancreatic cancer[1]
- Thyroid neoplasm (benign and malignant sub-types)[1]

(ii) 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 7.2.1)

8 Amendments and Updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	November 2014	All	Amendment	Revision of text in accordance with GVP module VIII general guidance
2	June 2018	Protocol version, dates, contacts	Update	Updated to Version 3.3, June 2018, correspondence updated
2	June 2018	Executive summary	Amendment	Minor modification of text relating to CHMP and EMA
3	June 2018	1.4.2 Synopsis of safety data	Amendment	Minor modification of text relating to 'results from an observational study'

[1] It is important to note that this M-PEM study only characterises any cases of thyroid neoplasm and pancreatic cancer that are reported during the 12-month observation period. This study cannot give any inference on the incidence of these neoplasms in the M-PEM cohort, as the study length and size has not been designed for this.

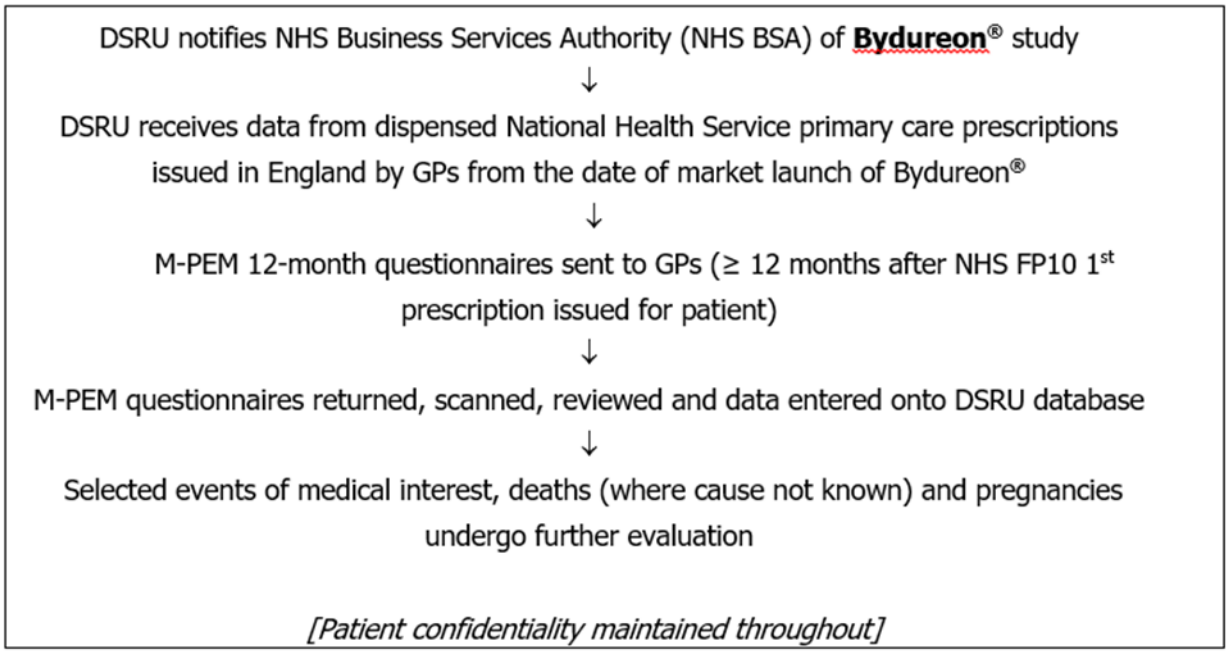
Number	Date	Section of study protocol	Amendment or update	Reason
4	June 2018	Drug-relatedness assessments (all)	Amendment	Text relating to drug-relatedness assessments removed/amended in accordance with recommendations from AstraZeneca. It was agreed that case series tables at aggregate level will be provided but without individual case-level relatedness.
5	June 2018	Reference to specific protocol sections, company name, protocol references	Update	Change of marketing authorisation holder

9 Research Methods

9.1 Study Design

This observational cohort study was conducted in England, using the technique of Modified Prescription-Event Monitoring (M-PEM). (28) Figure 1 outlines the methodology used in this study.

Figure 1. M-PEM study process for Bydureon®



Further information on study design and strengths of M-PEM can be found in Sections 4.1 and 5.1 of the study protocol (Appendix 1).

9.2 Setting

The study was conducted in the primary care setting in England in the immediate post-marketing period of Bydureon®. This report includes patients with evaluable data prescribed Bydureon® in primary care in England identified from dispensed prescription data collected between January 2012 and September 2016.

Twelve-month questionnaires were sent for patients identified from prescriptions dated up to and including September 2016. As a result of reaching the threshold ceiling count of new user patients, prescription collection was suspended from September 2016 onwards. Twelve-month questionnaires were only sent for patients when the 12-month observation period after the date of the first Bydureon® prescription had been reached.

9.3 Subjects

9.3.1 Inclusion Criteria

Patients were identified by means of data extracted from dispensed National Health Service (NHS) primary care prescriptions for Bydureon®, written by GPs in England (irrespective of past participation within PEM studies) and supplied in confidence to the DSRU by the NHS BSA for England. Patients identified from the NHS BSA were first time users of Bydureon®, however, may have had previous exenatide use (e.g. Byetta®). Modified-PEM questionnaires were sent according to the chronological order of prescription issue date (January 2012-September 2016) to those GPs who prescribed the newly marketed medicine until the target sample size was achieved. A maximum of four questionnaires per month per GP were sent. Questionnaires were not sent to GPs who had requested to be excluded from studies or to non-GP prescribers. The intention as per the study aim was to recruit a cohort of patients prescribed Bydureon®. Thus, since this is an observational cohort study conducted in a naturalistic setting, open patient entry criteria was applied to maximise external validity.

9.3.2 Exclusion Criteria

Patients were excluded from the evaluable study cohort if one of the following criteria applied:

- The GP reported that the patient was no longer registered with the practice or was not known to the GP and no further information was provided. Where information was available up to a specific date prior to deregistration that data was included, providing the 12-month questionnaire had analysable data beyond Q5 (Bydureon® start date).
- If the 12-month questionnaire was blank from Q5 (Bydureon® start date) onwards.
- The GP reported that the patient did not take or was never prescribed Bydureon®.
- The information on the 12-month questionnaire related to another antidiabetes medication (e.g. Dulaglutide®)

- The GP only reported an indication for prescribing Bydureon® other than type 2 diabetes mellitus. Note: These patients were considered to be inappropriate to analyse alongside those with type 2 diabetes mellitus, but were summarised separately in an appendix.
- The reported date of diagnosis of type 2 diabetes mellitus was after the specified Bydureon® index date.
- The patient was reported to have died, however, no further analysable information was provided[2].
- The 12-month questionnaire was returned after the study data-lock date (28th February 2018).

9.3.3 Evaluable patients

In summary, evaluable patients included those for whom a 12-month questionnaire was returned with analysable data beyond Q5, and were considered to have taken Bydureon® for an indication of type 2 diabetes mellitus diagnosed before the reported Bydureon® index date.

9.3.4 Cohort definitions

9.3.4.1 Cohort entry and exit

9.3.4.1.1 Cohort entry

Cohort entry for each patient was defined according to the date of their first Bydureon® dispensation (i.e. 'index date') if all inclusion criteria were fulfilled and exclusion criteria were not met.

9.3.4.1.2 Cohort exit

Cohort exit for each patient was defined according to the end of study period (12 months) or at point of censoring, whichever was the earliest.

A continuous variable representing total period of treatment with Bydureon® for each patient was derived from primary data on cohort entry and exit dates. Each patient was regarded as being treated between index date and last known date of treatment. For event analyses, the period has been restricted to where cohort exit was defined according to the first of the following dates:

- End of 12-month study treatment period
- Censoring

9.3.4.1.3 Censoring

Censoring has been defined as the following in this study:

- Loss to follow up
- Death

[2] In total, 17 patients met this exclusion criteria. For one patient the GP had confirmed Bydureon® use (Q5), however, no further information was provided beyond Q5. The GP reported that the patient died from 'hypoglycaemic injury'. For the remaining 16 patients, Bydureon® use was not specified (Q5); a cause of death was provided for only one patient (myocardial infarction).

- First report of stopping treatment (+ 10 weeks to account for drug elimination, hereafter referred to as a washout period)
- First report of outcome of interest[3]
- Date left practice (if patient had moved)

9.4 Variables

Data obtained from the 12-month questionnaire included:

- Date and starting dose details of first Bydureon® prescription;
- Setting of initiation;
- Reason for prescribing (e.g. formulary decision, patient request etc.);
- Date of first clinical diagnosis of diabetes;
- International Federation of Clinical Chemistry (IFCC) Haemoglobin A1c (HbA_{1C}) levels (within three months prior to index date) and date measured;
- Demographic characteristics (age and sex);
- General health factors (e.g. body mass index (BMI) and weight status closest to index date and date measured) and clinically significant changes[4];
- Blood glucose control (IFCC HbA_{1C} levels (mmol/mol) closest to index date (and date measured) and 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)[5];
- Ethnicity;
- Selected medical history relevant for targeted important potential and identified risks of interest;
- Treatment details of other antidiabetes drugs given as combination therapy at start of treatment (monotherapy, dual therapy, triple therapy);
- Prior and baseline exposure to selected medications of interest relevant for targeted important potential and identified risks of interest (e.g. Byetta®, warfarin);
- Event reports in the first 12 months after starting treatment, with focus on selected identified risks of interest associated with starting treatment and serious adverse event reports (classified using the International Conference on Harmonisation definitions) (29);
- 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 three months after stopping treatment if stopped;

[3] Censoring at first outcome applies to each individual event. Where there are multiple episodes of the same event, only the first event is reported. However the same patient can still contribute person time (if patient is still exposed to the drug) to allow for the reporting of other (different) events.

[4] Clinically significant weight loss is regarded as ≥ 3% change from index measure; clinically significant BMI change is regarded as ≥1 kg/m^2 change from index measure.

[5] Clinically significant SBP change gain is regarded as >=5 mmHg change from index measure.

- Date and causes of death (if died);
- Use during pregnancy[6].

9.5 Data Sources and Measurement

9.5.1 Patient identification

Patients prescribed Bydureon® in primary care in England were identified from dispensed prescription data provided by the NHS BSA.

9.5.2 Exposure/outcome data collection

Modified-PEM data is derived through secondary use of medical charts as abstracted onto study specific questionnaires by GPs in England. At least 12 months after the date the NHS BSA provided as the date of the first GP-issued Bydureon® prescription for each individual patient, the prescribing doctor was sent a M-PEM questionnaire which gathered information on baseline characteristics of the patient, drug utilisation and information on clinical events of medical interest and serious adverse event reports [serious defined according to the International Conference on Harmonisation definitions]. (28, 30) All information requested on this study specific questionnaire is summarised in Section 9.4 and copies of the 12-month questionnaires are provided as Appendix 2. Single reminder questionnaires were sent to those GPs who had not responded to the 12-month questionnaire within a given time period. Supplementary questionnaires were sent for selected events if additional information was required to characterise the event and patient (listed in protocol, Appendix 1). These included all Rare and Iatrogenic Adverse Reactions (RAIDAR) events compiled by the DSRU (listed in the protocol, Appendix 1). All returned initial questionnaires were reviewed by a DSRU research fellow.

9.5.3 Data coding

Following review by a research fellow, all information on the 12-month and supplementary questionnaires was entered onto the DSRU database including events collected as free-text which were coded onto the database using the MedDRA dictionary, as detailed in the protocol (Appendix 1).

9.6 Bias

Bias in epidemiological studies occurs when there is a systematic difference in the likelihood of or accuracy of response based on specific participant characteristics.

In a M-PEM study prescribers and patients are identified from prescription data (Figure 1, Section 9.1). General practitioners are requested to participate in the study by means of responding to a questionnaire on the identified patient based on medical records review.

[6] All reported pregnancies were followed up post-estimated delivery date to capture additional information on outcomes relevant to the birth.

A M-PEM study recruits patients defined on a specific exposure characteristic and follows them for outcome events. It is therefore an epidemiological cohort study by design. In cohort studies an association between drug and an outcome is usually more likely to be causal than one demonstrated by other epidemiological methods such as the 'case-control', as patients are recruited on the basis of exposure or non-exposure to a drug and their subsequent event course examines temporal relationships. (31) However, in any cohort study, there is still a potential for bias and in a M-PEM study, bias may arise from a number of data collection points.

The first consideration is the impact of GP non-response to requests for participation and non-responses to questionnaires as non-responding GPs may be different to responding GPs. Whilst we examine the geographical distribution of participating GPs we do not consider any other possible characteristics such as the size of the practice or quality measures.

A second consideration is that if patients included by GPs are systematically different to patients not included, selection bias will occur. (28) Patient inclusion in this study is based on the information available to GPs at 12 months post treatment initiation, and it is possible that GPs might enrol patients who had outcome events preferentially to uneventful patients, which would result in an over-estimate of the frequency and incidence of outcome events. On the other hand it is also possible that GPs may under-report on the patients who have outcome events, leading to underestimates of the frequency of these outcomes. There is also a possibility that patients report some events of interest to other doctors or health organisations without informing their GP. This bias is not quantifiable without information on non-participating patients.

An important point to consider in studies designed to follow patients or monitor patient health records over time is information bias whereby under- and mis-reporting of outcomes can be possible based on the available information. For example, GPs' notes may be incomplete with regard to medical history and outcomes associated with current treatment especially if these have resulted in hospitalisation. It is possible that in M-PEM serious adverse reactions including those with fatal outcomes may be under reported. For analyses that consider exposure, inaccurate ascertainment of exposure is possible as this is based on prescription data with no verification of compliance.

Potential for bias is discussed further in Section 5.3 of the study protocol (Appendix 1) and the possible impact of these biases on the study results is discussed in Section 11.2 of this report.

9.7 Study Size

For this M-PEM study, a sample size of 5000 evaluable patients was chosen to detect a two-fold increase (at the 5% significance level and with a power of 80%) in the primary event of interest (acute pancreatitis)

assuming the hypothesised background rate is uncommon (0.2%). For further information on sample size can be found in Section 4.3 of the protocol (Appendix 1).

9.8 Data Transformation

There were very few data transformations performed. Some quantitative continuous variables such as age were grouped for some of the tables, but in those cases means (standard deviations (SD)) and medians (Interquartile Range (IQR)) are also provided. Age groupings were introduced using ten-year age bands as this gave sufficient numbers in each band but also allowed for good discrimination between different age groups.

Patients were grouped into two mutually exclusive groups for the analysis, based on prior use of exenatide reported by the GP. The groups were 'exenatide naïve' which included patients without a record of prior use of Byetta® and 'previous Byetta® users' which included patients for whom the GP had reported prior Byetta® use. Stratification of the cohort between exenatide naïve and past users has been performed throughout the report. Where prior use of Byetta® was not specified, these patients have contributed to the total cohort column only[7]; a separate grouping for these patients did not seem to be warranted based on the relatively small number of patients for whom prior exenatide use was unknown. Further information on these exposure groups can be found in the results, Section 10.2.1.

9.9 Statistical Methods

A full description of the main statistical summary measures and main statistical methods for this final report is provided in the study statistical analysis plan (SAP) (Appendix 3). There are four main analysis sections in the report as follows; (1) Demographic information and baseline health characteristics of the patient cohort, (2) Outcome assessment for the primary, secondary and exploratory endpoints, (3) Hazard over time for acute pancreatitis events, (4) and Incidence density analysis for other targeted outcomes. The sections below provide information on each of the four analysis sections in the report.

9.9.1 Main Summary Measures

A full description of the main statistical summary measures and main statistical methods for this final report is provided in the study SAP (Appendix 3).

9.9.1.1 Demographics

Demographic information is tabulated and provided as counts and percentages for categorical variables. In some instances, where this is meaningful, medians and IQR are also provided for categorical variables. Continuous variables are provided as means with standard deviations, and as medians with IQR.

[7] Total cohort column includes patients who were exenatide naïve, previous Byetta® users and where prior use of exenatide was not specified. Therefore the number of patients in total cohort is more than the sum of the number of patients in the exenatide naïve and previous Byetta® user groups.

9.9.1.2 Primary, secondary and exploratory outcome assessments

The primary, secondary and some exploratory outcome measures are presented as unadjusted cumulative incidence estimates. For the primary outcome of acute pancreatitis, incidence rate has also been calculated.

The following definitions/rules apply to all outcome analyses:

Incidence

Cumulative incidence or incidence refers to a risk. This is calculated as the number of events divided by the number of people at risk. The unit of analysis is a percentage (%).

Incidence rate

Incidence rate refers to a rate. This is calculated as the number of events divided by person time at risk. The unit of analysis is events per person time.

New event

A new event has been defined as first report of the event after starting the drug (including index date) irrespective of prior history. Only the first reported event (incident events) has been included in the analyses.

Events on drug

An event occurring on drug has been defined as the last known date[8] plus 10-weeks in order to account for drug elimination. This definition has been applied to all events reported in the main report.

Further sensitivity analyses have been performed for each of the event analyses for events occurring on treatment excluding the washout period (i.e., defined as reported stop date or last reported prescription date plus one month). The results of these have been provided in appendices.

Events occurring outside the 12-month observation period

For the outcomes analyses, events are included in the primary analyses if they occurred on or after the index date and all patients were censored at 12 months (as described in Section 9.3.4).

Events reported to occur outside the 12-month observation period have been summarised in appendices as counts[9], providing they occurred on drug as defined by the inclusion of the 10-week washout period. No further stratification excluding the 10-week washout period has been performed for these events.

[8] Last known use date is either the reported stop date on the 12-month questionnaire or the last reported prescription date. Where only the last known prescription date has been provided, one month has been added to this to define the stop date.

9 Events occurring outside the 12-month observation period have not be stratified according to including or excluding the 10-week washout period; event analyses were performed including the 10-week washout period only.

Events with a missing event date

For events where an event date has not been provided for particular questions on the 12-month questionnaire, it has not been possible to infer that the event occurred within the 12-month observation period. Thus, these events have not contributed to the primary analyses of this report but have been reported as counts in appendices. The only exception for this is for events reported as a reason for stopping (Q11 on the 12-month questionnaire) without a stop date; as this question specifies 12 months it has been inferred that events with a missing date occurred within the 12-month observation period and have contributed to the primary analyses.

Events reported on multiple sections of the 12-month questionnaire

For events reported in multiple sections of the 12-month questionnaire (e.g. same event in Q11 'reason for stopping' and Q25 'other events'), these events have been reported in the corresponding tables (e.g. reason for stopping table and cumulative incidence tables), however, the first reported date has been taken as the event date.

Use of supplementary questionnaires

Information on supplementary questionnaires (where available) has been used to update the 12-month questionnaire data (e.g. where the GP reports the patient did not have the event, drug cessation conflicts).

Events provided as cause of deaths

Events reported as the immediate cause of death (COD) on the 12-month questionnaire and COD supplementary questionnaire has contributed to targeted/RAIDAR outcome primary analyses incidence estimates. However, this information has not contribute to the general event analyses. Events reported as an underlying cause/condition for deaths have not contributed to the primary event analyses but have been reported in the underlying cause/condition tables in the mortality section only.

MedDRA reporting of events

Data on events may have been recorded in response to specific tick-box questions on the 12-month questionnaire. Events may also have been reported as free text in response to open questions; such data were coded using MedDRA and in this report have been presented according to MedDRA Preferred Terms (PTs), unless where otherwise specified.

9.9.1.3 Hazard over time analyses

The risk of acute pancreatitis has been explored by estimating the hazard rates of this event over time (i.e., probability to have an event "in the next instant", given that no event occurred so far). Further information on hazard over time analyses can be found in Section 9.9.2.3 of this report and in Section 7.4.1.2 of the SAP (Appendix 3).

9.9.1.4 Incidence density event analyses

For this analysis, incidence densities for other targeted outcomes have been calculated for each two-month treatment period of the 12-month study period (ID_{0-2}, $_{2-4}$ etc.) and all 12 months combined (ID_A). Incidence densities refers to a rate; they are a calculation of rate of an event within a specific time period (e.g. month 0-2) and the unit of analysis is number of events per patient months in a specific time period. (32) Incidence density calculations have been described in Section 9.9.2.4 below and in the SAP Section 7.4.2.2 (Appendix 3).

9.9.2 Main Statistical Methods

The following main statistical methods were applied.

9.9.2.1 Demographics

Descriptive statistics were applied to the demographic data, no formal statistical testing was conducted.

9.9.2.2 Primary, secondary and exploratory outcome assessments

Analyses of acute pancreatitis events identified within the primary objective were explored for the total cohort and by prior exenatide use using unadjusted cumulative incidence and incidence rate estimates with 95% Binomial exact CI. Analyses of other events identified within the secondary and exploratory objectives were evaluated for the total cohort and prior exenatide use using unadjusted cumulative incidence estimates (+ 95% Binomial exact CI). For these event analyses, right censoring at the end of the 12 months observation was undertaken. Where events were reported but with no supporting event date and/or treatment exit date, these patients were excluded from numerator and denominator of this primary analysis.

9.9.2.3 Hazard over time analyses

Time-to-first acute pancreatitis analyses has been performed for the total cohort and by prior exenatide use to explore the risk of having an event over time by calculating the risk function (probability of first event before time point t) based on the estimated cumulative hazard over time. Such method accounts for censoring; for this analysis the exposure time has been censored at the time of the first event. Smoothed hazard plots describe how this hazard changes over time, in particular if the hazard of acute pancreatitis increases or decreases with time. A constant hazard over time may be consistent with a constant background event hazard (not caused by the drug), whereas a non-constant hazard over time may be an indicator of a drug-event relationship. The null hypothesis that the hazard function of acute pancreatitis in patients prescribed Bydureon® (naïve or previous Byetta® users) is constant during the 12-month exposure period following the start of treatment has been 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. At least ten reports of an event were deemed necessary for modelling purposes. Further information on hazard over time analyses can be found in Section 7.4.1.2 of the SAP (Appendix 3).

9.9.2.4 Incidence density event analyses

Calculating and ranking crude incidence densities (IDs) is one of a number of standard quantitative evaluations used in event monitoring methodology for descriptive analysis of multiple events as part of initial inspection of all event data for general safety surveillance. (33) For purposes of this analysis, IDs were calculated for other targeted events evaluated as part of the secondary objectives:

- Gallstones, biliary colic or cholecystitis
- Acute renal failure
- Allergic reactions (type 1 hypersensitivity)
- Cardiac events

The numerator was the first report of events reported as occurring on or after the index date and during treatment[10]. This analysis excluded events with a missing event date[11] and/or where treatment exit date is missing. The time at risk used in calculating IDs was in accordance with the definitions provided in Section 9.3.4 of this report and it was assumed that the pattern of use was continuous. Incidence densities were calculated, for each given time period (t), for events reported in patients who continued to take Bydureon® for a given time period, or for whom the date of stopping was known. Only the first report (in chronological date order) of an event in an individual patient, irrespective of whether there were further recurrent episodes, was used in the calculation of IDs and these have been expressed as the number of first reports of an event per 1000 patient-months. For this study, IDs were calculated for each event for each two month period 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,

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

[10] 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 does not initially include censoring at the time of event. If an elevated crude ID was identified in this monitoring analysis, a subsequent analysis with appropriately censored denominator has been performed for that outcome.

[11] Excluding events reported in reason for stopping with a missing stop date. These will be included in the event analysis as the question specifies within the 12-month observation period.

Incidence densities were also calculated for all 12-months during treatment combined (ID_A). In addition, the arithmetic differences between two time periods for each reported event (e.g. ID_{0-2} and ID_{2-4}) with a 95% confidence interval (CI) were calculated to examine the null hypothesis that the rate for the event was not increasing or decreasing between the two time periods. Further information on the calculation of incidence densities and incidence density differences can be found in Section 7.4.2.2 and Section 7.4.2.3 of the SAP (Appendix 3).

9.9.3 Missing Values

9.9.3.1 Demographics

All evaluable patients with data for a specific variable were included in the demographic tabulations. Patients with missing demographic data were excluded from the analysis for that specific variable.

9.9.3.2 Primary, secondary and exploratory outcome assessments

Cumulative incidence estimates and incidence rate estimates included all patients with an event date and a treatment exit date. No imputation for missing data on explanatory variables was conducted.

9.9.3.3 Hazard over time analyses

All evaluable patients with an event date of acute pancreatitis and treatment exit date were included. No imputation for missing data on explanatory variables was conducted.

9.9.3.4 Incidence density event analyses

All evaluable patients with an event date and treatment exit date were included. No imputation for missing data on explanatory variables was conducted.

9.9.4 Sensitivity Analyses

A sensitivity analysis was performed to examine the impact on cumulative incidence estimates of the Bydureon® 10-week washout period. The main analyses includes all events reported to occur on drug (i.e., defined as reported stop date or last reported prescription date plus one month) and within the 10-week washout period. The sensitivity analyses includes all events reported to occur on drug only (excluding the 10-week washout period). In summary, this sensitivity analyses includes in the numerator events reported to occur on drug only, and reduces the denominator by 10 weeks as compared to the main analyses.

In addition, a sensitivity analyses was performed which included events that occurred with missing event dates or the treatment exit date was unknown and for events reported outside the 12-month observation period (not stratified by plus/minus the 10-week washout period).

9.9.5 Amendments to the Statistical Analysis Plan

None.

9.10 Quality Control

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

- 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 entry and 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
- Random reviews of M-PEM questionnaires 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

10 Results

10.1 Participants

A total of 24760 unique patients were identified from 283523[12] Bydureon® prescriptions issued by primary care General Practitioners (GPs) between January 2012 and September 2016 (Table 1, Figure 2). This gives an approximate average accrual rate of 551 patients per month.

Twelve-month questionnaires were sent for 20860 patients (84.2% of unique patients) identified from prescriptions dated up to and including September 2016 for Bydureon®. The required sample size for this study was 5000 patients. A maximum of four questionnaires per month per GP were sent; once the threshold ceiling count of new user patients was achieved, prescription collection was suspended and no further questionnaires were sent.

[12] Includes all prescriptions (first and repeat)

Of the 20860 eligible patients for whom a 12-month questionnaire was sent to prescribing GPs, 7752 patients (37.2% of 12-month questionnaires sent) had a 12-month questionnaire returned; 7742 of these 12-month questionnaires were returned up to and including the data-lock date (28th February 2018) and 10 were returned post data-lock. Only the 12-month questionnaires returned prior to or on the data-lock date were eligible for inclusion in the analyses of this report. The 10 patients for whom the 12-month questionnaire was returned post data-lock have not contributed to the primary analyses of the report, however, have been summarised in Appendix 4[13].

Of the 7742 12-month questionnaires which were returned by the time of data-lock, 1448 12-month questionnaires (18.7% of 12-month questionnaires returned prior to data-lock; 6.9% of 12-month questionnaires sent) were subsequently excluded from the evaluable cohort. The reasons for exclusion have been summarised in Table 2 with the most common reason for exclusion provided as 'patient not registered with the practice' (n=586; 40.5% of all exclusion reasons, 7.6% of 12-month questionnaires returned prior to data-lock). For 16 patients (1.1% of all exclusion reasons, 0.2% of 12-month questionnaires returned prior to data-lock), an off-label indication was provided as the indication (i.e., type 1 diabetes mellitus). These patients were excluded from the evaluable cohort as it was considered inappropriate to analyse them alongside patients with type 2 diabetes mellitus, but they have been summarised in Appendix 5.

Therefore, the final evaluable cohort comprised of 6294 patients (81.3% of 12-month questionnaires returned prior to data-lock; 30.2% of 12-month questionnaires sent). All of these patients were considered to be taking Bydureon® for an indication of type 2 diabetes mellitus, which was diagnosed prior to or at the time of starting Bydureon®. Thus, all subsequent tables from Section 10.2 onwards in the report (unless otherwise specified) will exclude patients with only an off-label indication reported and for whom the type 2 diabetes mellitus diagnosis was reported after index. The evaluable cohort for the primary analyses has been defined as the number of patients taking Bydureon® for the licensed indication of type 2 diabetes mellitus at index.

Table 1. Recruitment

Cohort data	n	%
Number of Bydureon® prescriptions reconciled from NHS BSA data	283523	--
Number of unique eligible patients identified with at least one Bydureon® prescription on database	24760	--
Number of unique patients for whom a 12-month questionnaire was sent to prescribing GPs (% of unique eligible patients identified)	20860	84.2
Number of unique patients for whom a 12-month questionnaire was returned from prescribing GPs (% of 12-month questionnaires sent)	7752	37.2

[13] One patient had an event of acute pancreatitis on treatment with Bydureon®, which has been summarised in Appendix 4.

Number of questionnaires returned prior to data-lock[a] (% of 12-month questionnaires sent)	7742	37.1
Number of questionnaires returned post data-lock[a] (% of 12-month questionnaires sent)	10	0.0
Cohort data	**n**	**%**
Number of 12-month questionnaires not returned (% of 12-month questionnaires sent)	13108	62.8
Number of 12-month questionnaires returned prior to data-lock[a] but where the exclusion criteria apply (% of 12-month questionnaires returned prior to data-lock[a]; % of 12-month questionnaires sent)	1448	18.7; 6.9
Number of patients with an off-label indication only[b] (% of 12-month questionnaires returned prior to data-lock[a] but where exclusion criteria apply; % of 12-month questionnaires returned prior to data-lock[a])	16	1.1; 0.2
Number of 12-month questionnaires returned prior to data-lock[a] with evaluable data and a licensed indication of type 2 diabetes mellitus reported prior to or at index[c] (% of 12-month questionnaires returned prior to data-lock[a]; % of 12-month questionnaires sent)	**6294**	81.3; 30.2

[a] Data-lock 28th February 2018. In addition, as presented in the table above, ten 12-month questionnaires were returned after this data-lock date. These patients have not contributed to the primary analysis of the report however have been summarised in Appendix 4.

[b] Patients with off-label indications were not be included in the primary analysis of the report, however, are summarised in Appendix 5.

[c] Only these patients have been included in the primary analysis for the report. This is the denominator for the evaluable cohort for the primary analysis. Patients with a type 2 diabetes mellitus date of diagnosis reported after the index date were excluded from the evaluable cohort but have been summarised in Appendix 6.

Table 2. Reasons for exclusion of 12-month questionnaires returned prior to data-lock[a]

Reason for exclusion	n	%
Patient not registered with the practice	586	40.5
Patient did not start study drug	191	13.2
Reporter declined to complete questionnaire	150	10.4
Blank questionnaire returned	128	8.8
Patient not prescribed study drug	122	8.4
Patient not known to reporter	76	5.2
Reporter moved	46	3.2
No clinical information on questionnaire	28	1.9
Study drug not taken	24	1.7
Reporter too busy	20	1.4
Patients diagnosed with type 1 diabetes mellitus	16	1.1
Reporter no longer completes study questionnaire	13	0.9
Reporter retired	11	0.8
Patients with type 2 diabetes mellitus diagnosis date post index date[c]	8	0.6
No record of patient taking the study drug	7	0.5
No patient consent given[b]	5	0.3
Practice no longer operating	5	0.3
Reporter requesting too high a payment	4	0.3
Data not related to underlying questionnaire evaluation	3	0.2
Duplicate patient	1	0.1
Questionnaire filled out incorrectly	1	0.1
Medical records unavailable	1	0.1

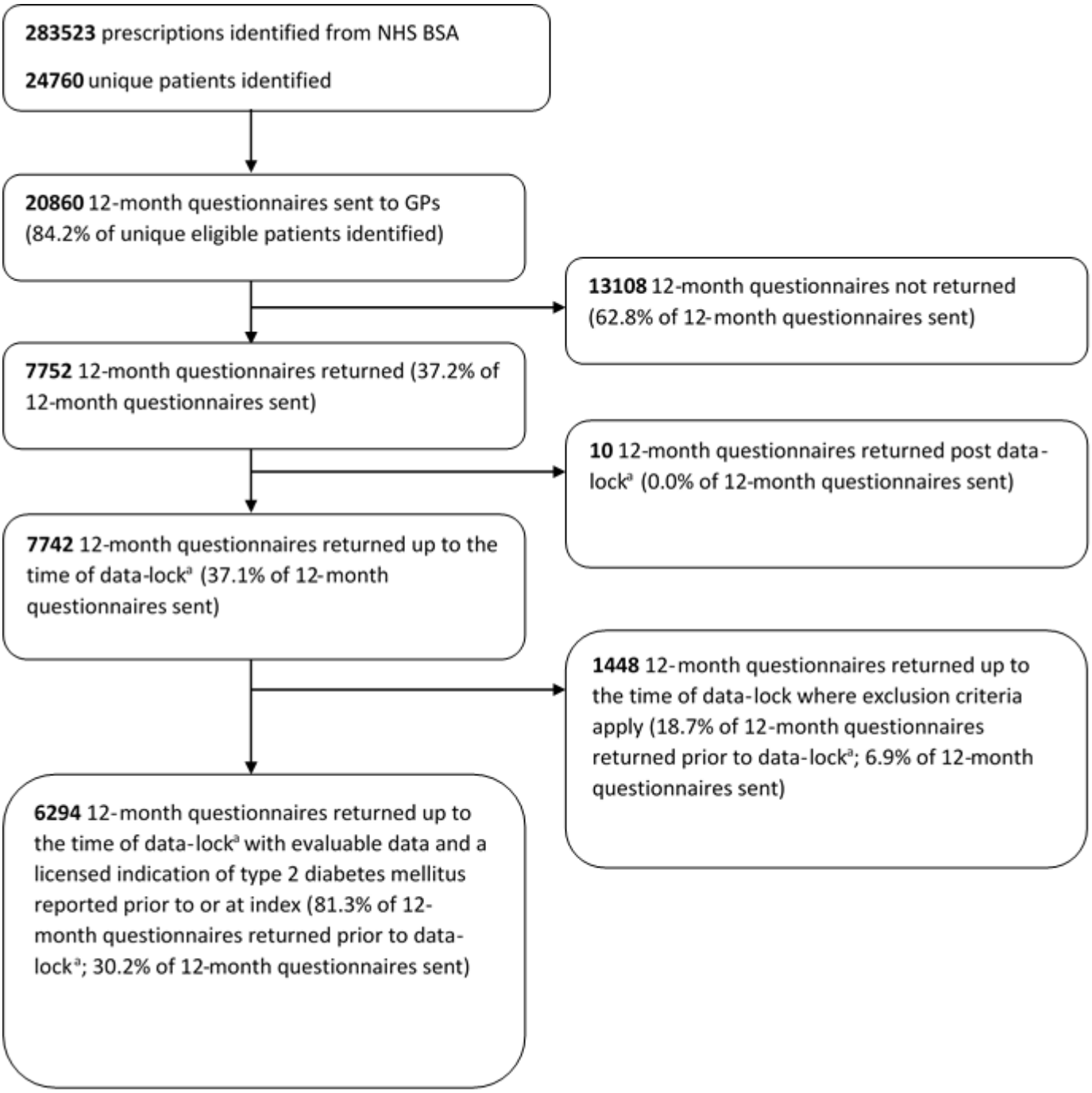
Reason for exclusion	n	%
Reporter not certain if study drug prescribed	1	0.1
Temporary patient	1	0.1
Total (N)	1448	100.0

[a] Data-lock date 28th February 2018

[b] Patient consent is not required to participate in this study but some GPs may choose not to participate without explicit patient consent

[c] Patients with a type 2 diabetes mellitus date of diagnosis reported after the index date have been summarised in Appendix 6

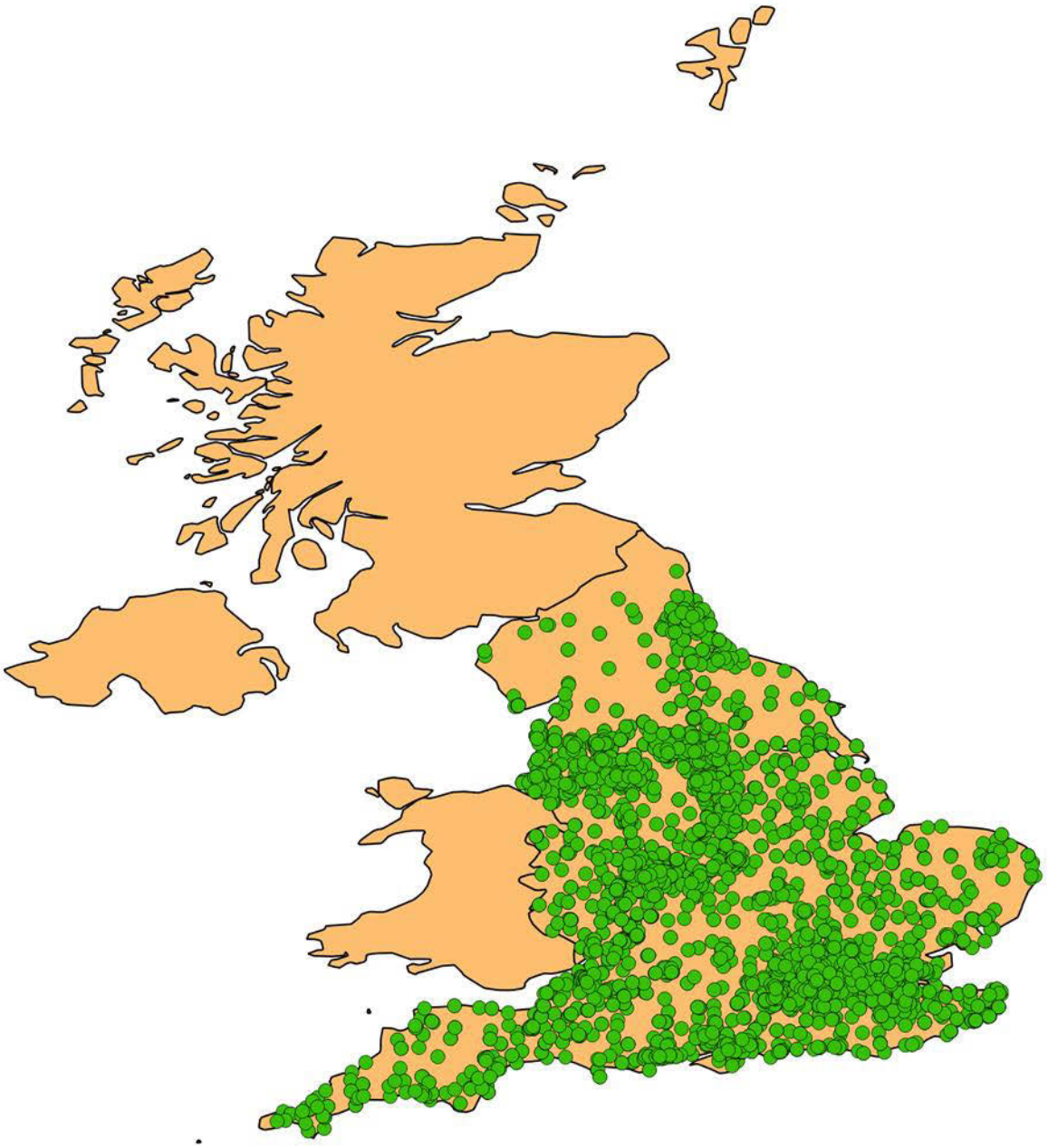
Figure 2. STROBE flow chart defining the evaluable cohort



[a] Data-lock date: 28th February 2018

The geographical distribution of all GP practices with 12-month questionnaires returned in this M-PEM study is presented in Figure 3. By using dispensed Bydureon® prescription data from the NHS BSA to identify eligible patients for inclusion in the study, and the resultant large cohort of evaluable patients, there is no reason to believe that the M-PEM evaluable patient cohort is likely to be unrepresentative of the accessible Bydureon® treated population in England.

Figure 3. Geographical distribution of GP practices who returned a 12-month questionnaire



10.2 Descriptive Data

10.2.1 Prior use of Byetta®

The 12-month questionnaire asked GPs to confirm whether the patient had previous exposure to exenatide twice daily (Byetta®). Using this information, stratification of the cohort between naïve and past users has been performed throughout the report. This allows for the safety and utilisation information of Bydureon®, such as incidence of acute pancreatitis, to be compared between naïve and past-users of exenatide. Patients for whom prior use of Byetta® was not known (non-response in Table 3) have contributed to the total cohort column only in all tables of this report[14].

For some patients there was conflicting information on whether specific questions were completed for Byetta® or Bydureon®. Examples of this include where the GP had provided a Byetta® start dose in response to the question on treatment regimen details for Bydureon®. For these patients it is possible that the GP may have misinterpreted the difference between Byetta® and Bydureon®, however, because the DSRU has received FP10 prescription data on Bydureon® for these patients they have remained in the evaluable cohort. In order to account for these potential conflicts a systematic and non-biased method using the following rules were applied to the data:

- If the GP reported that the Bydureon® index date was prior to the marketing authorisation date (17th June 2011) and provided a Byetta® start dose at index (Q6) and/or stopping (Q11), the patient was allocated to the previous Byetta® user group irrespective of what the GP specified in response to the question on previous Byetta® use (Q7). Information on the specific doses reported have been provided in Section 10.2.3.3.1. The Bydureon® index date for these patients has remained as the FP10 date obtained from the NHS BSA.

- If the GP reported that the Bydureon® index date was more than or equal to the marketing authorisation date (17th June 2011) and provided a Byetta® start dose at index (Q6) and/or stopping (Q11), the patient was allocated to the unknown prior exenatide use group if the GP had ticked 'no' or not specified a response to the question on previous Byetta® use (Q7) due to conflicting information. Information on the specific doses reported have been provided in Section 10.2.3.3.1.

- If the GP reported that the Bydureon® index date was more than or equal to the marketing authorisation date (17th June 2011) and reported a Byetta® start dose at index (Q6) and/or stopping (Q11), the patient was allocated to the previous Byetta® user group if the GP had ticked 'yes' as a

[14] The total cohort column includes patients who were exenatide naïve, previous Byetta® users or for whom previous use of exenatide was not specified. Therefore, the number of patients in the total cohort is equal to more than the sum of the number of patients in the exenatide naïve and the previous Byetta® user group.

response to the question on previous Byetta® use (Q7). Information on the specific doses reported have been provided in Section 10.2.3.3.1.

- In all other circumstances, allocation of patients to the exenatide naïve, previous Byetta® user or not known group was made according to the GP response provided to the question on previous Byetta® use (Q7).

Results show that the majority of patients did not have previous exposure to Byetta® (n=4556, 72.4% of cohort) and were therefore classified as 'exenatide naïve'. Approximately one-quarter of patients (n=1629, 25.9% of cohort) did however have prior exenatide use and therefore contributed to the 'previous Byetta® user' group. For 109 patients (1.7% of cohort) previous exposure to exenatide (Byetta®) was not known from the information available. Using this information, stratification of the cohort between exenatide naïve and past users has been performed throughout the report.

Table 3. Previous exposure to exenatide twice daily (Byetta®)

Previous exposure to Byetta®	n	%
Yes[a]	1629	25.9
No[b]	4556	72.4
Non-response[c]	109	1.7
Total (N)	6294	100.0

[a] Defined as the 'previous Byetta® user' group throughout the report
[b] Defined as the 'exenatide naïve' group throughout the report
[c] Accounts for patients for whom the GP did not specify a response to Q7 or with the scenario of conflicting information described in the section above. These patients contribute to the total cohort column only throughout the report.

Of the 1629 patients (25.9% of cohort) who were previously on Byetta® prior to starting Bydureon®, information on duration of Byetta® therapy was available for 1376 patients (84.5% of previous Byetta® users) (Table 4). The majority of these patients had taken Byetta® for less than one year (n=563, 34.6% of previous Byetta® users, 40.9% where duration specified). There is evidence of a decrease in the number of patients within each increasing duration of therapy category; only two patients (0.1% of previous Byetta® users, 0.1% where duration specified) had taken Byetta® for more than 10 years.

Table 4. Duration of therapy with Byetta®

Years	n	%
<1	563	34.6
1, <2	309	19.0
2, <3	213	13.1
3, <4	138	8.5
4, <5	87	5.3
5, <10	64	3.9
≥10	2	0.1
Not calculable[a]	253	15.5

Total (N)	1629	100.0

[a] Not calculable=number of patients for whom start and/or stop date of Byetta® was not provided

For those patients who were previously on Byetta®, the time elapsed between stopping Byetta® and starting Bydureon® was calculated (Table 5). Duration between discontinuation of Byetta® and commencement of Bydureon® was available for 1397 patients (85.8% of previous Byetta® users). Where duration was calculated, the majority of patients had less than six months between stopping Byetta® and starting Bydureon® (n=807, 49.5% of previous Byetta® users, 57.8% where duration specified). This was followed by 15.1% of patients (n=246, 17.6% where duration specified) starting Bydureon® more than or equal to 30 months after stopping Byetta®. There were similar proportion of patients within the remaining time periods between discontinuation of Byetta® and commencement of Bydureon®.

Table 5. Duration between discontinuation of Byetta® and commencement of Bydureon®

Months between stopping Byetta® and starting Bydureon®	n	%
<6	807	49.5
6, <12	117	7.2
12, <18	89	5.5
18, <24	68	4.2
24, <30	70	4.3
≥30	246	15.1
Not calculable[a]	232	14.2
Total (N)	1629	100.0

[a]Not calculable=number of patients for whom date of stopping Byetta® and/or starting Bydureon® was not provided

10.2.2 Cohort baseline characteristics

10.2.2.1 Patient demography

Table 6 below provides information on patient age and sex. Information on age and sex was derived from NHS BSA data and GPs were asked to either confirm or correct this data on the 12-month questionnaire. Thus, age and sex is known for all patients in the evaluable cohort (as displayed in Table 6 and Figure 4). In the overall evaluable cohort, there were 3475 (55.2% of cohort) males and 2819 (44.8% of cohort) females. The mean age (SD) of the overall evaluable cohort was 56.9 (10.9) years; for males the mean (SD) age was 57.4 (10.3) years and for females the mean age was 56.3 (11.5) years. The corresponding median (IQR) age was 58 (51-65) years for males and 56 (49-65) years for females. On average patients were slightly older in the previous Byetta® user group as compared to the exenatide naïve group; the median (IQR) age was 58 (51-65) years for previous Byetta® users and 57 (49-65) years for patients who were exenatide naive. In addition, there was a marginally higher proportion of females in the previous Byetta® user group as compared to exenatide naïve patients (46.3% vs. 44.2%, respectively). There were also two female patients aged <18 years, which constitutes off-label prescribing; one patient was aged 15

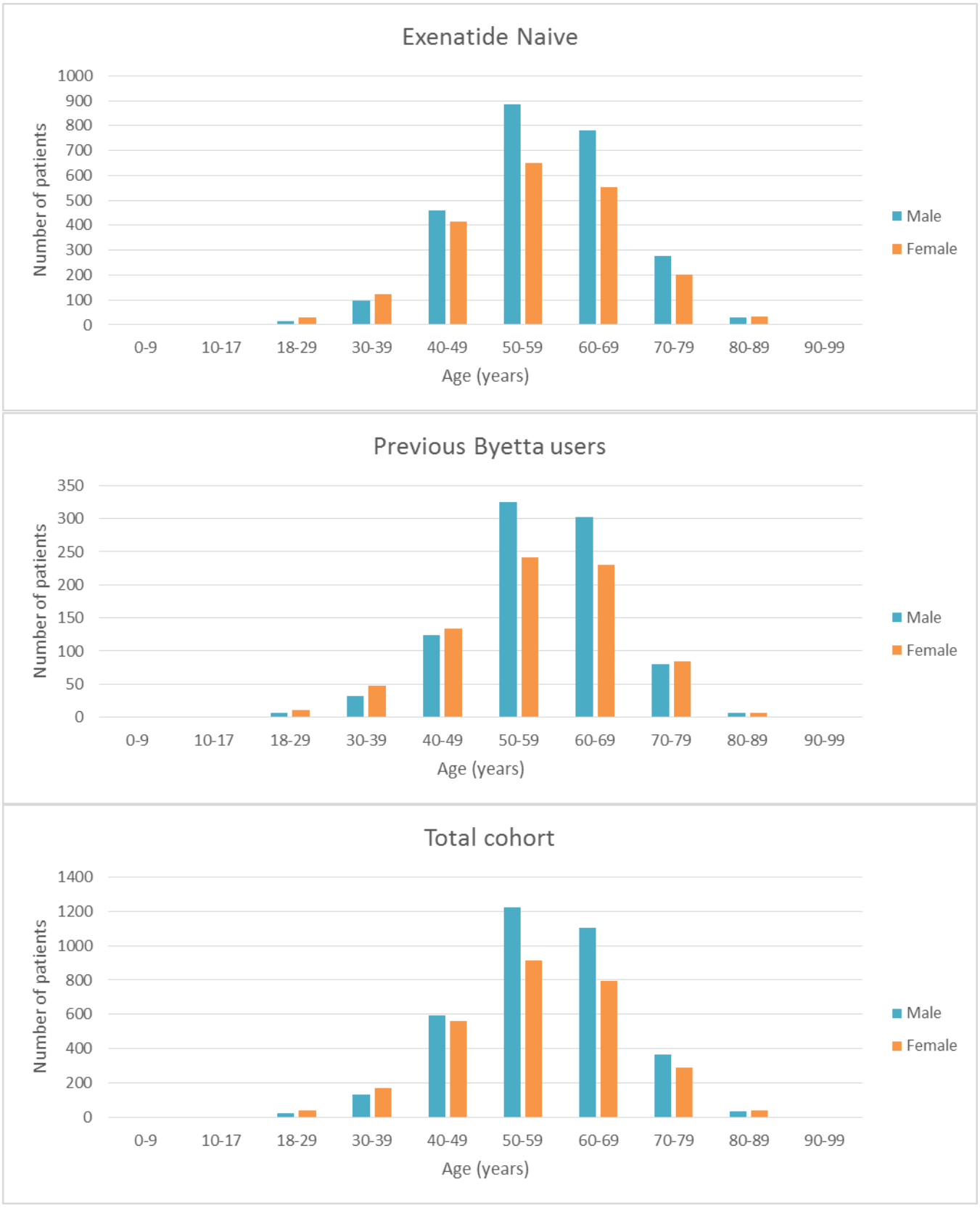
years and the other patient was 16 years of age. In contrast, there were three patients aged 90 years+; all were female and the maximum age reported was 93 years.

Table 6. Age distribution and sex of patients

Age Range (years)	Exenatide naïve (N=4556)						Previous Byetta® user (N=1629)						Total cohort (N=6294)					
	Male		Female		Total		Male		Female		Total		Male		Female		Total	
	n	%	n	%	n	%	n	%	N	%	n	%	n	%	n	%	n	%
0-9	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
10-17	0	0.0	1	0.0	1	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	0.0	2[a]	0.0
18-29	16	0.4	30	0.7	46	1.0	6	0.4	11	0.7	17	1.0	23	0.4	41	0.7	64	1.0
30-39	96	2.1	122	2.7	218	4.8	32	2.0	47	2.9	79	4.8	132	2.1	173	2.7	305	4.8
40-49	460	10.1	416	9.1	876	19.2	124	7.6	134	8.2	258	15.8	592	9.4	559	8.9	1151	18.3
50-59	885	19.4	651	14.3	1536	33.7	325	20.0	241	14.8	566	34.7	1222	19.4	915	14.5	2137	34.0
60-69	782	17.2	554	12.2	1336	29.3	302	18.5	230	14.1	532	32.7	1105	17.6	793	12.6	1898	30.2
70-79	275	6.0	203	4.5	478	10.5	80	4.9	85	5.2	165	10.1	365	5.8	293	4.7	658	10.5
80-89	29	0.6	33	0.7	62	1.4	6	0.4	6	0.4	12	0.7	36	0.6	40	0.6	76	1.2
90-99	0	0.0	3	0.1	3	0.1	0	0.0	0	0.0	0	0.0	0	0.0	3	0.0	3	0.0
Total	2543	55.8	2013	44.2	4556	100.0	875	53.7	754	46.3	1629	100.0	3475	55.2	2819	44.8	6294	100.0
Mean (SD)	57.3 (10.5)		56.1 (11.6)		56.8 (11.0)		57.6 (9.7)		56.7 (11.2)		57.2 (10.4)		57.4 (10.3)		56.3 (11.5)		56.9 (10.9)	
Median (IQR)	57 (50-65)		56 (48-64)		57 (49-65)		58 (52-64)		57 (49-65)		58 (51-65)		58 (51-65)		56 (49-65)		57 (50-65)	
Maximum	89		93		93		87		85		87		89		93		93	
Minimum	18		15		15		18		21		18		18		15		15	

[a] n=1 Exenatide naïve group, 15-year-old female; n=1 previous Byetta® use not specified, 16-year-old female

Figure 4. Age and sex distribution of patients for exenatide naïve, previous Byetta® users and the total cohort



Information regarding the race/ethnicity of patients was collected in order to determine prescribing of Bydureon® across different ethnic groups (Table 7). In total, a response to information on race/ethnicity was provided for 5999 patients (95.3% of cohort). The most frequently reported race was 'Caucasian' (n=5347, 85.0% of cohort, 89.1% where response provided). The second most frequently reported ethnicity was 'Asian (Indian sub-cont)', which comprised of 408 patients (6.5% of cohort, 6.8% where response provided). Very few patients were reported to be within the other pre-specified race/ethnicity groups (Table 7) and the proportion of patients within each race/ethnicity group appeared to be similar for exenatide naïve and previous Byetta® users. Where the GP had ticked 'other' (n=104, 1.7% of cohort, 1.7% where response provided), the GP was requested to specify the patients' race/ethnicity. Where possible any free text reports of race/ethnicity have been re-allocated to the appropriate pre-specified race/ethnicity group. For the remainder, race/ethnicity as specified by the GP has been listed in Appendix 7. This includes patients for whom the GP had ticked 'other' race/ethnicity, however, had either not specified the other race/ethnicity (missing) or specifically reported that it was not known/not clear to them.

Table 7. Race/ethnicity

Race/Ethnicity	Exenatide naïve (N=4556)		Previous Byetta® users (N=1629)		Total cohort (N=6294)	
	n	%	n	%	n	%
Caucasian	3870	84.9	1402	86.1	5347	85.0
Asian (Indian sub-cont)	314	6.9	90	5.5	408	6.5
Black- Caribbean	53	1.2	19	1.2	74	1.2
Black- African	34	0.7	8	0.5	42	0.7
Asian (China/Japan)	20	0.4	4	0.2	24	0.4
Other[a]	76	1.7	26	1.6	104	1.7
Non-response[b]	189	4.1	80	4.9	295	4.7
Total (N)	4556	100.0	1629	100.0	6294	100.0

[a] All other specified ethnicities have been listed in Appendix 7. This includes patients for whom the GP had ticked 'other' race/ethnicity, however, had either not specified the other race/ethnicity (missing) or specifically reported that it was not known/not clear to them.
[b] Number of patients for whom the GP did not provide a response to Q27

10.2.2.2 Baseline cohort characteristics

Information on prior medical history has been gathered from the 12-month questionnaire through pre-specified tick-box responses and free text information. GPs were requested to provide information through pre-specified tick-box responses on the presence of specific disorders prior to or present at the start of Bydureon®. The specific questions which requested information on prior medical history (as listed in Table 8 below) were Q9 and Q22. 'Acute pancreatitis' and 'gallstones, biliary colic or cholecystitis' were tick-box categories in Q9; the remainder were tick-box and corresponding free text fields in Q22.

Where GPs had ticked one of the pre-specified disorder categories in Q22 they were further requested to specify the type of condition and provide a date of first diagnosis. These conditions have been reported as listed in Q22 by the GP unless there was clear evidence to suggest reallocation to one of the other

categories. In addition to clinical diagnoses, some GPs may have provided a list of all relevant signs, symptoms and investigations. These have not been removed from prior events or reallocated to a different category unless there was clear evidence to suggest this was appropriate.

In addition, free text events reported in other sections of the 12-month questionnaire (e.g. Q25, Q26) with a date prior to index have been reallocated to the specific prior disorders categories in Table 8 below, where applicable. All other non-specific events reported on the 12-month questionnaire, other than in Q22, with a date prior to index have been listed in Appendix 8b.

Table 8 provides the number of patients with a prior history of the pre-specified events (according to the rule base defined above). A patient may have had more than one prior event, so these counts are not mutually exclusive.

For the total cohort, the most frequently reported disorder at the time of starting Bydureon® was 'gastrointestinal disorder' (n=932, 14.8% of cohort, 15.4% where 'gastrointestinal disorder' specified). 'Hepatic disorder' was reported in 353 patients (5.6% of cohort, 5.9% where 'hepatic disorder' specified). A similar number of patients fulfilled the prior disorder category of 'gallstones, biliary colic or cholecystitis' (n=333, 5.3% of cohort, 5.4% where 'gallstones, biliary colic or cholecystitis' specified). 'Renal disorder' history was reported for 7.1% of the cohort (n=444, 7.4% where 'renal disorder' specified) and 'neoplasms' prior to or at index were present for 3.8% of the cohort (n=239, 4.0% where 'neoplasms' specified). The prevalence of 'acute pancreatitis' and 'pancreatic disorders' was low; 'acute pancreatitis' was reported in 0.6% of the cohort (n=38, 0.6% where 'acute pancreatitis' specified) and 0.4% of the cohort were observed to have a prior history of a 'pancreatic disorder' (n=25, 0.4% where 'pancreatic disorder' specified').

After stratifying by previous exenatide use, the proportion of patients within each event/disorder category were fairly similar between exenatide naïve and previous Byetta® users. Prevalence was slightly higher for 'gallstones, biliary colic or cholecystitis', 'gastrointestinal disorder', 'hepatic disorder', 'renal disorders' and 'neoplasms' in the previous Byetta® user group as compared to exenatide naïve patients. The reverse was true for 'pancreatic disorders', however, the difference was minimal between the two groups; the prevalence of 'acute pancreatitis' was identical.

Table 8. Events reported prior to or present at start of treatment with Bydureon®

Event[a]	Exenatide Naïve (N=4556)						Previous Byetta® users (N=1629)						Total Cohort (N=6294)					
	Yes		No		Non-response		Yes		No		Non-response		Yes		No		Non-response	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Acute pancreatitis[b]	27	0.6	4461	97.9	68	1.5	9	0.6	1590	97.6	30	1.8	38	0.6	6133	97.4	123	2.0
Gallstones, biliary colic or cholecystitis[c]	230	5.1	4255	93.4	71	1.6	100	6.1	1497	91.9	32	2.0	333	5.3	5831	92.6	130	2.1
Gastrointest-inal disorder	669	14.7	3724	81.7	163	3.6	247	15.2	1316	80.8	66	4.1	932	14.8	5107	81.1	255	4.1
Hepatic disorder[c]	250	5.5	4122	90.5	184	4.0	93	5.7	1461	89.7	75	4.6	353	5.6	5656	89.9	285	4.5
Renal disorder	299	6.6	4074	89.4	183	4.0	140	8.6	1417	87.0	72	4.4	444	7.1	5567	88.5	283	4.5
Pancreatic disorder[b]	18	0.4	4353	95.5	185	4.1	4	0.3	1551	95.2	74	4.5	25	0.4	5983	95.1	286	4.5
Neoplasms	165	3.6	4215	92.5	176	3.9	69	4.2	1491	91.5	69	4.2	239	3.8	5783	91.9	272	4.3

[a] Counts potentially include a list of all events (clinical diagnoses, signs, symptoms, investigations) as reported by the GP in Q22
[b] Potential duplication of pancreatitis events in 'acute pancreatitis' and 'pancreatic disorders' category
[c] Potential duplication of gallstone, biliary colic or cholecystitis events in 'gallstone, biliary colic or cholecystitis' and 'hepatic disorders' category

As described above, where GPs had ticked one of the pre-specified prior disorder categories in Q22 they were further requested to specify the condition. Table 9 below provides the ten most frequently reported conditions within each prior disorder category. A patient may have had more than one event within each disorder category and/or in different disorder categories, so these counts are not mutually exclusive. Note, the list of conditions potentially includes all signs, symptoms and investigations reported by the GP in addition to clinical diagnoses. The list of prior events in Table 9 also includes free text events reported in other sections of the 12-month questionnaire considered to be prior to index and which fulfilled the specific disorder category definition. A list of all specified events within each disorder category are provided in Appendix 8a.

Within the total cohort, gastrointestinal disorders were specified for 654 patients (70.2% of patients for whom 'gastrointestinal disorder' was ticked). The most frequently reported event was 'gastro-oesophageal reflux disease' (n=118, 1.9% of cohort, 12.7% where 'gastrointestinal disorder' ticked). Use of Bydureon® has not been studied in patients with severe gastrointestinal disease, including gastroparesis. (1) In this study, there were three patients with a prior history of 'impaired gastric emptying' and one patient with 'diabetic gastroparesis' (Appendix 8a).

A 'hepatic disorder' was specified for 283 patients within the total cohort (80.1% of patients for whom 'hepatic disorder' was ticked). 'Hepatic steatosis' was the most prevalent prior disorder (n=108, 1.7% of cohort, 30.6% of patients for whom 'hepatic disorder' was ticked).

According to the SmPC, Bydureon® is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance < 30 ml/min) and due to limited clinical experience, it is also not recommended in patients with moderate renal impairment (creatinine clearance 30 to 50 ml/min). (1) In this M-PEM study, 'chronic kidney disease' was the most common prior 'renal disorder' specified for the total cohort (n=169, 2.7% of cohort, 44.2% of patients for whom 'renal disorder' was ticked), however, the stage of chronic kidney disease was not specified. A prior history of 'acute kidney injury' was much lower (n=11; 0.2% of cohort, 2.9% of patients for whom 'renal disorder' was ticked).

A 'pancreatic disorder' was specified for 18 patients (72.0% of patients for whom 'pancreatic disorder' was ticked). Of these, events relating to pancreatitis were most frequently reported ('pancreatitis' n=5, 'pancreatitis acute' n=4, 'pancreatitis chronic' n=2, 'obstructive pancreatitis' n=1). However, counts were overall low and in keeping with the SmPC recommendations of caution for use in patients with a history of pancreatitis. (1)

A neoplasm was specified for 171 patients (71.5% of patients for whom 'neoplasm' was ticked). 'Breast cancer' was the most prevalent neoplasm reported prior to index for the total cohort (n=30; 0.5% of cohort,

12.6% of patients for whom 'neoplasm' was ticked). Of note, a prior history of 'thyroid cancer' was also reported in one patient (Appendix 8a).

Stratification of prior history events by previous exenatide use (as presented in Table 9 and Appendix 8a) shows no evidence of any significant differences between the two user groups.

Table 9. Ten[a] most frequently reported disorders (specified as free text) prior to or present at start of treatment with Bydureon®

Ten most frequent disorders (MedDRA Preferred Term) within each category	n	%
Exenatide naïve (N=4556)		
Gastrointestinal disorder		
Gastro-oesophageal reflux disease	81	1.8
Irritable bowel syndrome	57	1.3
Diverticulum	54	1.2
Dyspepsia	53	1.2
Hiatus hernia	40	0.9
Diarrhoea	36	0.8
Gastritis	34	0.7
Nausea	29	0.6
Oesophagitis	20	0.4
Duodenitis	18	0.4
Total number of events	593	n/a
Non-response[b]	210	n/a
Hepatic disorder		
Hepatic steatosis	80	1.8
Non-alcoholic fatty liver	40	0.9
Cholecystectomy	16	0.4
Cholelithiasis	15	0.3
Liver function test abnormal	13	0.3
Non-alcoholic steatohepatitis	11	0.2
Hepatic cirrhosis	9	0.2
Alanine aminotransferase increased	8	0.2
Cholecystitis	7	0.2
Cirrhosis alcoholic	5	0.1
Total number of events	253	n/a
Non-response[b]	52	n/a
Renal disorder		
Chronic kidney disease	113	2.5
Nephrolithiasis	33	0.7
Renal colic	18	0.4
Microalbuminuria	14	0.3
Glomerular filtration rate abnormal	13	0.3
Proteinuria	11	0.2
Acute kidney injury	9	0.2

Ten most frequent disorders (MedDRA Preferred Term) within each category	n	%
Nephrectomy	7	0.2
Glomerular filtration rate decreased	6	0.1
Haematuria	5	0.1
Total number of events	287	n/a
Non-response[b]	62	n/a
Pancreatic disorder		
Pancreatitis	5	0.1
Pancreatitis acute	3	0.1
Pancreatic failure	2	0.0
Pancreatitis chronic	2	0.0
Abdominal pain	1	0.0
Alcohol use	1	0.0
Obstructive pancreatitis	1	0.0
Pancreatic disorder	1	0.0
Pancreatic operation	1	0.0
Type 2 diabetes mellitus	1	0.0
Total number of events	18	n/a
Non-response[b]	3	n/a
Neoplasms		
Breast cancer	21	0.5
Prostate cancer	17	0.4
Rectal cancer	8	0.2
Basal cell carcinoma	7	0.2
Colon cancer	6	0.1
Bladder cancer	5	0.1
Bladder neoplasm	5	0.1
Renal cancer	5	0.1
Renal cell carcinoma	5	0.1
Endometrial cancer	4	0.1
Total number of events	141	n/a
Non-response[b]	48	n/a
Previous Byetta® users (N=1629)		
Gastrointestinal disorder		
Gastro-oesophageal reflux disease	34	2.1
Dyspepsia	22	1.4
Irritable bowel syndrome	22	1.4
Diarrhoea	19	1.2
Diverticulum	18	1.1
Hiatus hernia	17	1.0
Nausea	13	0.8
Abdominal pain	12	0.7
Oesophagitis	11	0.7
Barrett's oesophagus	9	0.6
Total number of events	255	n/a
Non-response[b]	61	n/a

Ten most frequent disorders (MedDRA Preferred Term) within each category	n	%
Hepatic disorder		
Hepatic steatosis	25	1.5
Non-alcoholic fatty liver	14	0.9
Cholecystectomy	12	0.7
Alanine aminotransferase increased	10	0.6
Liver function test abnormal	10	0.6
Cholelithiasis	7	0.4
Hepatic cirrhosis	7	0.4
Aspartate aminotransferase increased	3	0.2
Non-alcoholic steatohepatitis	3	0.2
Alanine aminotransferase abnormal	2	0.1
Total number of events	105	n/a
Non-response[b]	15	n/a
Renal disorder		
Chronic kidney disease	54	3.3
Nephrolithiasis	15	0.9
Glomerular filtration rate abnormal	13	0.8
Microalbuminuria	6	0.4
Proteinuria	5	0.3
Renal colic	5	0.3
Glomerular filtration rate decreased	4	0.2
Renal impairment	4	0.2
Haematuria	3	0.2
Pyelonephritis acute	3	0.2
Total number of events	141	n/a
Non-response[b]	23	n/a
Pancreatic disorder		
Pancreatic atrophy	3	0.2
Diabetes mellitus	1	0.1
Pancreatic pseudocyst drainage	1	0.1
Pancreatitis acute	1	0.1
Total number of events	6	n/a
Non-response[b]	1	n/a
Neoplasms		
Breast cancer	8	0.5
Colon cancer	8	0.5
Prostate cancer	6	0.4
Bladder cancer	4	0.2
Endometrial cancer	4	0.2
Gastrointestinal carcinoma	4	0.2
Malignant melanoma	4	0.2
Bladder transitional cell carcinoma	2	0.1
Breast neoplasm	2	0.1
Craniopharyngioma	2	0.1
Total number of events	65	n/a

Ten most frequent disorders (MedDRA Preferred Term) within each category	n	%
Non-response[b]	17	n/a
Total cohort (N=6294)		
Gastrointestinal disorder		
Gastro-oesophageal reflux disease	118	1.9
Irritable bowel syndrome	79	1.3
Dyspepsia	76	1.2
Diverticulum	73	1.2
Hiatus hernia	59	0.9
Diarrhoea	56	0.9
Gastritis	43	0.7
Nausea	43	0.7
Oesophagitis	31	0.5
Duodenitis	24	0.4
Total number of events	861	n/a
Non-response[b]	278	n/a
Hepatic disorder		
Hepatic steatosis	108	1.7
Non-alcoholic fatty liver	56	0.9
Cholecystectomy	28	0.4
Liver function test abnormal	24	0.4
Cholelithiasis	23	0.4
Alanine aminotransferase increased	18	0.3
Hepatic cirrhosis	16	0.3
Non-alcoholic steatohepatitis	14	0.2
Cholecystitis	8	0.1
Cirrhosis alcoholic	6	0.1
Total number of events	368	n/a
Non-response[b]	70	n/a
Renal disorder		
Chronic kidney disease	169	2.7
Nephrolithiasis	48	0.8
Glomerular filtration rate abnormal	26	0.4
Renal colic	23	0.4
Microalbuminuria	20	0.3
Proteinuria	16	0.3
Acute kidney injury	11	0.2
Glomerular filtration rate decreased	10	0.2
Haematuria	8	0.1
Nephrectomy	8	0.1
Total number of events	431	n/a
Non-response[b]	87	n/a
Pancreatic disorder		
Pancreatitis	5	0.1
Pancreatitis acute	4	0.1
Pancreatic atrophy	3	0.0

Ten most frequent disorders (MedDRA Preferred Term) within each category	n	%
Pancreatic failure	2	0.0
Pancreatitis chronic	2	0.0
Abdominal pain	1	0.0
Alcohol use	1	0.0
Diabetes mellitus	1	0.0
Obstructive pancreatitis	1	0.0
Pancreatic disorder	1	0.0
Total number of events	24	n/a
Non-response[b]	7	n/a
Neoplasms		
Breast cancer	30	0.5
Prostate cancer	23	0.4
Colon cancer	14	0.2
Bladder cancer	9	0.1
Endometrial cancer	8	0.1
Malignant melanoma	8	0.1
Rectal cancer	8	0.1
Basal cell carcinoma	7	0.1
Renal cancer	7	0.1
Bladder neoplasm	6	0.1
Total number of events	208	n/a
Non-response[b]	68	n/a

[a] All specified events have been listed in Appendix 8a
[b] Number of patients for whom the GP had ticked 'yes' to the specific disorder but did not specify the condition in free text

In addition, any other events prior to starting Bydureon® reported on the 12-month questionnaire (other than in Q22), which did not meet the disorder categories specified in Table 8 and 9, have been listed in Appendix 8b.

10.2.3 Drug Utilisation

10.2.3.1 Indications characteristics

Bydureon® is recommended by the National Institute for Health and Care Excellence (NICE) for the treatment of type 2 diabetes mellitus as third line co-therapy in combination with metformin and sulphonylurea for patients with inadequate glycaemic control (HbA1c≥7.5%). (34) On the 12-month questionnaire, GPs were requested to provide the date the patient was first diagnosed with type 2 diabetes mellitus. As reported in Table 1 and Table 2 (Section 10.1), for 16 patients the GP had categorically stated type 1 diabetes mellitus as the indication for prescribing; these patients have therefore been excluded from the evaluable cohort and have not contributed to any of the analyses in this report. However, information on these patients has been provided in Appendix 5. In addition, there were eight patients for whom the diagnosis date of type 2 diabetes mellitus was provided after their respective Bydureon® index date. These patients have also been excluded from the evaluable cohort but further information can be found in Appendix 6. Thus, Table 10 below (and all tables in this report, unless otherwise specified) provides

information on patients who have a diagnosis of type 2 diabetes mellitus and for whom the date of diagnosis is after index.

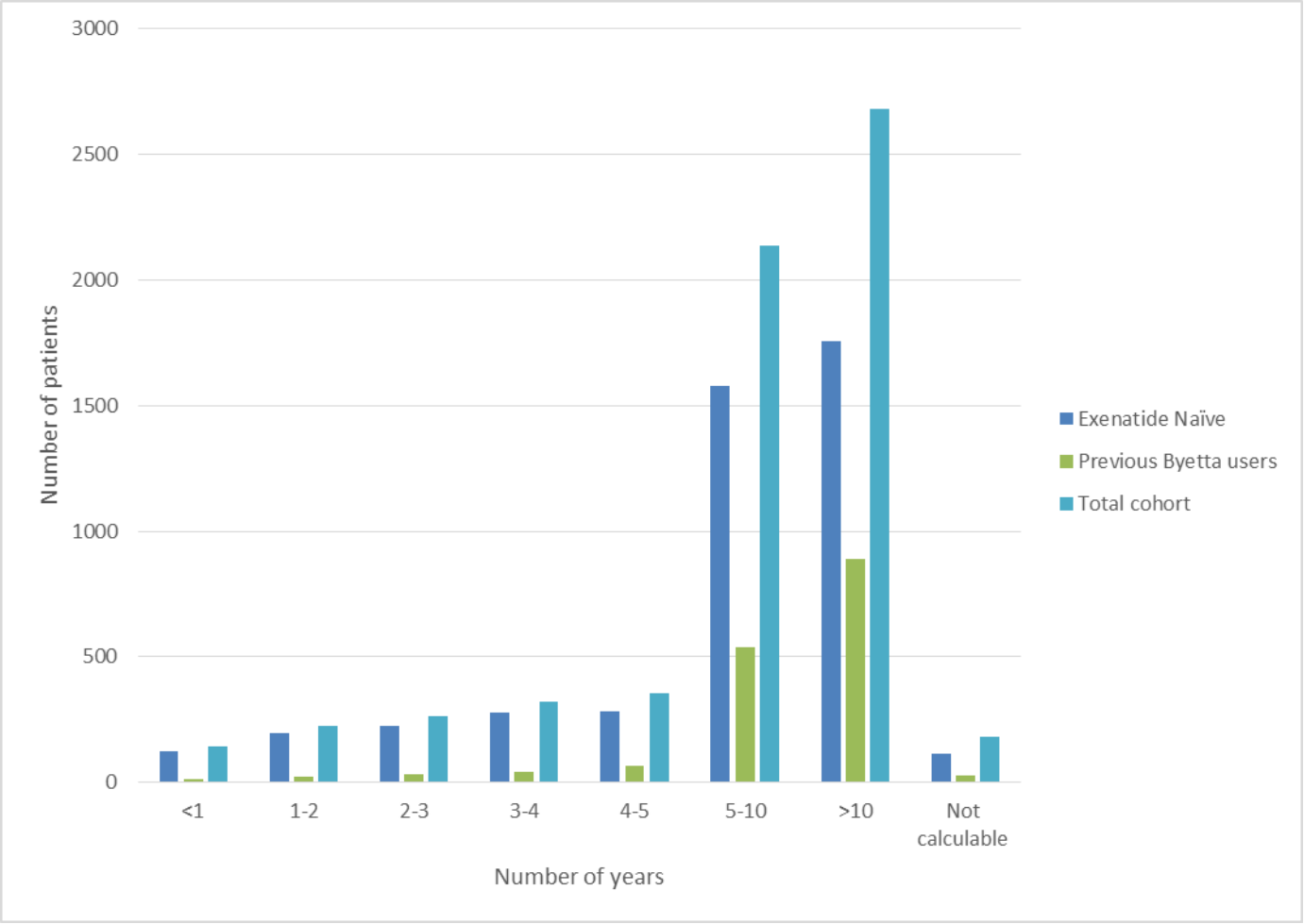
Information on the date of type 2 diabetes mellitus diagnosis was provided for 6114 patients (97.1% of cohort). In the total cohort, the highest proportion of patients (n=2681, 42.6% of cohort, 43.9% where diagnosis date specified) were diagnosed with type 2 diabetes mellitus >10 years prior to starting treatment with Bydureon®. This was followed by approximately one-third of patients (n=2136, 33.9% of cohort, 34.9% where diagnosis date specified) having a diagnosis of type 2 diabetes mellitus between 5-10 years prior to index. In contrast, only 141 patients (2.2% of cohort, 2.3% where diagnosis date specified) were diagnosed within one year prior to starting Bydureon®. When comparing exenatide naïve to previous Byetta® users, the proportion of patients who had type 2 diabetes mellitus ≥10 years prior to starting Bydureon® was higher in the previous Byetta® user group than for exenatide naïve patients (54.6% vs. 38.6%, respectively); overall the exenatide naïve group had higher proportions of patients with shorter duration of prior disease (<10 years). These results are summarised in Table 10 and illustrated graphically in Figure 5.

Table 10. Duration of type 2 diabetes mellitus indication prior to treatment

Years prior to starting Bydureon®	Exenatide Naïve (N=4556)		Previous Byetta® users (N=1629)		Total cohort (N=6294)	
	n	%	n	%	n	%
<1	125	2.7	14	0.9	141	2.2
1-2	196	4.3	24	1.5	222	3.5
2-3	226	5.0	33	2.0	262	4.2
3-4	275	6.0	41	2.5	319	5.1
4-5	283	6.2	65	4.0	353	5.6
5-10	1580	34.7	536	32.9	2136	33.9
>10	1758	38.6	890	54.6	2681	42.6
Not calculable[a]	113	2.5	26	1.6	180	2.9
Total (N)	4556	100.0	1629	100.0	6294	100.0

[a] Not calculable= patients for whom a date of type 2 diabetes mellitus diagnosis was not provided

Figure 5. Time interval (years) from date of diagnosis to start date of Bydureon® for exenatide naïve, previous Byetta® users and the total cohort



10.2.3.2 Setting for initiation of therapy and supporting reasons for prescribing

To further inform on determinants of prescribing, it was of interest to have insight into the prescribing arrangements between primary and secondary care. The 12-month questionnaire requested information on the setting in which Bydureon® was first initiated/recommended (Table 11).

The prescribing setting was specified for 6160 patients (97.9% of cohort). As reflected in Table 11, the most frequently reported setting was primary care (n=3269, 51.9% of cohort, 53.1% where setting specified), followed by secondary care reported for 2441 patients (38.8% of cohort, 39.6% where setting specified). In comparison, intermediate care was provided as the setting for prescribing for only a small proportion of the cohort (n=233, 3.7% of cohort, 3.8% where setting specified). For 217 patients (3.4% of cohort, 3.5% where specified) the GP had ticked 'other' setting and was further requested to specify the setting; a complete list of 'other' settings reported verbatim can be found in Appendix 9. When comparing the two user groups, a higher proportion previous Byetta® users were prescribed Bydureon® in secondary care as compared to exenatide naïve patients (50.2% vs. 34.8%, respectively). The majority of exenatide naïve patients had Bydureon® initiated in primary care (n=2556, 56.1% of exenatide naïve patients). Intermediate care and 'other' settings were reported in similar proportions for both user groups.

Table 11. Setting for initiation of Bydureon®

	Exenatide naïve (N=4556)		Prior Byetta® users (N=1629)		Total cohort (N=6294)	
Setting	**n**	**%**	**n**	**%**	**n**	**%**
Primary care	2556	56.1	677	41.6	3269	51.9
Secondary care	1584	34.8	818	50.2	2441	38.8
Intermediate care[a]	173	3.8	58	3.6	233	3.7
Other[b]	158	3.5	54	3.3	217	3.4
Non-response	85	1.9	22	1.4	134	2.1
Total (N)	4556	100.0	1629	100.0	6294	100.0

[a]Intermediate care clinics for diabetes (ICCD) were first introduced in the NHS in 2004 and fit between primary care management and secondary care services. Through use of multidisciplinary teams of secondary care specialist health care practitioners linked to general practices, the aim of ICCDs are to improve the provision of care and outcomes for patients with diabetes within the community.
[b] All 'other' specified settings are listed in Appendix 9.

On the 12-month questionnaire GPs were also requested to provide supporting reasons for prescribing Bydureon®. Table 12 provides the reasons for prescribing associated with external forces and/or non-medical patient factors. More than one reason for prescribing could be reported, so counts are not mutually exclusive. In total, 6305 supporting reasons for prescribing were provided for 6159 patients (97.9% of cohort); supporting reasons for prescribing were missing for 135 patients (2.1% of cohort). Specialist decision was the overwhelming reason for prescribing for the total cohort (n=3113, 49.5% of cohort, 50.5% where supporting reason specified) and when stratified by previous exenatide use, however, this was more frequently reported for previous Byetta® users as compared to exenatide naïve patients (59.9% vs. 45.9%, respectively). GP clinical decision was the second most common reason for prescribing within the total cohort (n=2655, 42.2% of cohort, 43.1% where supporting reason specified) and was more frequently reported for exenatide naïve patients than previous Byetta® users (46.1% vs. 32.5%, respectively). Patient preference (n=464, 7.4% of cohort, 7.5% where supporting reason specified) was also a common reason for starting Bydureon®; the proportion of GPs reporting this was higher for previous Byetta® users than for exenatide naïve patients (9.1% vs. 6.9%, respectively). Hospital formulary was reported in similar but low proportions for both user groups. For 769 patients (12.2% of cohort, 12.5% where supporting reason specified) the GP had specified 'other' as a supporting reason; 775 counts of other reasons were provided by the GP and these have been listed verbatim in Appendix 10.

Table 12. Supporting reasons for prescribing Bydureon®

Supporting reason	Exenatide naïve (N=4556)		Previous Byetta® users (N=1629)		Total cohort (N=6294)	
	n	%	n	%	n	%
GP clinical decision	2100	46.1	529	32.5	2655	42.2
Specialist decision	2089	45.9	975	59.9	3113	49.5
Hospital formulary	48	1.1	24	1.5	73	1.2
Patient preference	313	6.9	149	9.1	464	7.4
Other[a]	576	12.6	182	11.2	769	12.2
Non-response	82	1.8	23	1.4	135	2.1

[a] Where specified, other supporting reasons for prescribing have been listed verbatim in Appendix 10

10.2.3.3 Therapy Plan- treatment initiation

10.2.3.3.1 Dose and frequency at index

Starting dose, frequency and presentation of Bydureon® was requested through tick-box responses on the 12-month questionnaire. Results are provided in Table 13. Dosing regimen was specified for 6075 patients (96.5% of cohort). The majority of patients (n=5948, 94.5% of cohort, 97.9% where dose/frequency specified) were initiated on Bydureon® as a 2mg once weekly subcutaneous injection. Of these, more patients were taking Bydureon® via the pre-filled pen (n=1878) as compared to the vial and syringe (n=1463); for 2607 patients the method of administration was not known. For both user groups, similar proportion of patients were prescribed Bydureon® 2mg once weekly and the pre-filled pen was more commonly the method of administration than the vial and syringe.

For 127 patients (2.0% of cohort, 2.1% where dose/frequency specified) the GP had ticked 'other'. All other doses and frequencies as reported by the GP have been summarised in Appendix 11. Of note, as reflected in Appendix 11, there are a number of reports of off-label prescribing with respect to the Bydureon® recommended dose/frequency. For some patients the GP reported a Byetta® start dose (e.g. 5 or 10 micrograms) at index with an index date either prior to or after the Bydureon® marketing authorisation date. For these patients it is possible that the GP may have misinterpreted the difference between Byetta® and Bydureon®, however, because the DSRU has received FP10 data on Bydureon® prescriptions for these patients they have remained in the evaluable cohort. The rule base described in Section 10.2.1 was used to allocate these patients to the either the previous Byetta® user or unknown prior exenatide use group.

Table 13. Dosage and Frequency of Bydureon®

	Exenatide naïve (N=4556)		Previous Byetta® user (N=1629)		Total cohort (N=6294)	
Dosage/frequency	**n**	**%**	**n**	**%**	**n**	**%**
2mg once weekly	4329	95.0	1546	94.9	5948	94.5
Vial & syringe 2mg once weekly	1120	24.6	324	19.9	1463	23.2
Prefilled pen 2mg once weekly	1480	32.5	370	22.7	1878	29.8
Unspecified 2mg once weekly[a]	1729	37.9	852	52.3	2607	41.4
Other[b]	91	2.0	31	1.9	127	2.0
Non-response	136	3.0	52	3.2	219	3.5
Total (N)	4556	100.0	1629	100.0	6294	100.0

[a] The sub-question on presentation (pen or vial) was added during the study. Thus, for some patients only dose/frequency was collected and there is no information on presentation.
[b] All other doses as specified by the GP have been listed in Appendix 11.

10.2.3.3.2 Treatment regimen

On the 12-month questionnaire GPs were requested to indicate whether Bydureon® was initiated as monotherapy or add-on therapy, and if initiated as co-therapy to provide the name of the concomitant antidiabetes medication (ADM) at index. Table 14 summarises the reported treatment regimen at index.

Patients were allocated to mutually exclusive treatment groups of 'monotherapy', 'dual therapy', 'triple therapy' or 'more than triple therapy' depending on the specified tick-box in Q14 and the number of concomitant ADMs reported in Q15. All reported antidiabetes medications were analysed according to the Anatomical Therapeutic Chemical (ATC) classification and name. Fixed-dose combination products were separated out into their separate active ingredients and allocated to their respective ATC class. Where there was conflicting data between the type of co-therapy and the number of ADMs reported in Q15, the number of reported ADMs has been used to allocate the patient to the correct line of therapy. Patients with one alternative ADM reported were allocated to the 'dual therapy' group, patients with two alternative ADMs reported were allocated to the 'triple therapy' group and if more than two alternative ADMs were reported, these patients contributed to the 'more than triple therapy' group. Note, insulin based therapy (i.e., more than one type of insulin reported) has contributed as one type of ADM; if only insulin was reported without other alternative oral ADMs the patient has been allocated to the 'dual therapy' group. Where the GP had specified the type of co-therapy in Q14 but no medications were provided in Q15, these patients have remained allocated to the GP specified co-therapy group.

Table 14 reveals that the line of antidiabetes therapy for which Bydureon® was prescribed was specified for 5983 patients (95.1% of cohort). The majority of patients started Bydureon® as 'triple therapy' (n=3876, 61.6% of cohort, 64.8% where line of therapy specified). Approximately one-third of patients (n=1936, 30.8% of cohort, 32.4% where line of therapy specified) were prescribed Bydureon® as 'dual therapy'. In contrast, only a small minority of patients had 'monotherapy' use of Bydureon® (n=161, 2.6% of cohort, 2.7% where line of therapy specified) or 'more than triple therapy' reported (n=10, 0.2% of cohort, 0.2%

where line of therapy specified). After stratifying by prior exenatide use, a similar proportion of patients in both user groups were observed have started Bydureon® within each of the line of therapy categories.

Table 14. Treatment regimen of Bydureon®

	Exenatide naïve (N=4556)		Previous Byetta® user (N=1629)		Total cohort (N=6294)	
Treatment Regimen	**N**	**%**	**n**	**%**	**n**	**%**
First-line monotherapy	119	2.6	39	2.4	161	2.6
Second-line dual therapy	1435	31.5	481	29.5	1936	30.8
Third-line triple therapy	2786	61.2	1032	63.4	3876	61.6
More than triple therapy	8	0.2	1	0.1	10	0.2
Non-response	208	4.6	76	4.7	311	4.9
Total (N)	4556	100.0	1629	100.0	6294	100.0

10.2.3.3.3 Prior antidiabetes medications

Information regarding prior use of antidiabetes medication and date the medication was first started was requested from GPs on the 12-month questionnaire. Results are presented in Table 17 below according to Anatomical Therapeutic Chemical (ATC) classification and name. A patient may have had more than one prior medication reported within each ATC class and/or may have been taking more than one medication from different ATC classes simultaneously, therefore counts are not mutually exclusive. As described above, fixed-dose combination products were classified according to their separate active ingredients and de-duplication was performed. For example, if metformin was reported twice for an individual patient (i.e., once in a fixed combination product and once alone as metformin in Q18) the metformin has only been reported once and the earliest date of the two has been used to calculate median duration of therapy from index date. In circumstances where only one date has been provided for a medication that has been reported twice, the specified date has been used to calculate the median duration of therapy. Thus, there is a possibility that the patient may have been on the particular antidiabetes medication for a longer duration and using the only reported date could potentially lead to an under-estimation of prior antidiabetes medication exposure time. However, it was considered appropriate to use the provided date in favour of having missing information. In addition, where the GP provided multiple prior medications within the same ATC class with different start dates (e.g. two insulins with two different dates), only the earliest prescribed medication was analysed (and presented in Table 15 below) to provide an estimate of exposure of that particular class of antidiabetes medication. However, if the GP reported multiple prior medications within the same ATC class but only provided one date (e.g. two different insulins with one date specified), both medications have been presented in Table 15 below as it was not possible to infer which was started first from the available information.

Table 15 reveals that the majority of patients had previously been on metformin either alone or in combination with other antidiabetes medications (n=4988, 79.3% of cohort). The second most frequently reported prior medications were sulphonylureas; 3934 patients (62.5% of cohort) had taken at least one sulphonylurea prior to starting Bydureon® (62.5% of cohort). Prior exposure to at least one insulin (n=1563,

24.8% of cohort), thiazolidinediones (n=1407, 22.4% of cohort) or DPP-4 inhibitors (n=1924, 30.6% of cohort) was also common. After stratifying by previous exenatide use, prior exposure to insulins, sulphonylureas, thiazolidinediones, glucagon-like peptide-1 (GLP-1) analogues and other glucose lowering drugs was more common for previous Byetta® users as compared to exenatide naïve patients. In contrast, exenatide naïve patients were more likely to have been prescribed dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose co-transporter 2 (SGLT-2) inhibitors than previous Byetta® users. Prior use of metformin and alpha glucosidase inhibitors was similar between the both groups of patients. Where duration of previous exposure was specified[15], the median (IQR) duration of exposure for the total cohort was the longest for alpha glucosidase inhibitors at 11.5 (4.6, 13.9) years. This was followed by metformin for which the median (IQR) duration of exposure was 6.3 (3.6, 9.8) years. As expected, the shortest median (IQR) duration of exposure was for SGLT-2 inhibitors (0.7 (0.3, 1.2) years). Median duration of exposure was only marginally different between exenatide naïve patients and previous Byetta users; for nearly all ATC classes, patients were on the respective antidiabetes medications for slightly longer in the previous Byetta® user group as compared to exenatide naïve patients.

[15] Calculated from date antidiabetes medication first started to Bydureon® index date

Table 15. Prior antidiabetes medication exposure

Prior antidiabetes medication (ATC class)	Prior antidiabetes medication (ATC name)	Exenatide naïve (N=4556)			Previous Byetta user (N=1629)			Total cohort (N=6294)		
		n	%	Median (IQR) duration (years) from start of therapy prior to starting Bydureon®	n	%	Median (IQR) duration (years) from start of therapy prior to starting Bydureon®	n	%	Median (IQR) duration (years) from start of therapy prior to starting Bydureon®
Biguanides	**Metformin**	3615	79.3	5.8 (3.1, 9.2)	1310	80.4	7.8 (5.0, 11.5)	4988	79.3	6.3 (3.6, 9.8)
Sulphonylureas	**Number of patients with at least one sulphonylurea**	2779	61.0	4.3 (2.1, 7.6)	1112	68.3	6.5 (3.7, 10.3)	3934	62.5	4.9 (2.4, 8.5)
	Chlorpropamide	1	0.0		0	0.0		1	0.0	
	Glibenclamide	46	1.0		30	1.8		76	1.2	
	Gliclazide	1461	32.1		565	34.7		2052	32.6	
	Glimepride	190	4.2		95	5.8		286	4.5	
	Glipizide	42	0.9		20	1.2		62	1.0	
	Tolbutamide	12	0.3		4	0.2		16	0.3	
	Not specified	1057	23.2		416	25.5		1489	23.7	
Insulin	**Number of patients with at least one insulin**	940	20.6	4.0 (1.5, 7.4)	600	36.8	4.4 (1.8, 7.9)	1563	24.8	4.2 (1.7, 7.8)
Insulins and analogues	**At least one**	25	0.5	2.8 (1.4, 6.5)	15	0.9	4.6 (1.3, 11.0)	40	0.6	2.8 (1.3, 6.5)
	Insulin (human)	13	0.3		11	0.7		24	0.4	
	Insulins and analogues (NOS)	14	0.3		4	0.2		18	0.3	
Insulins and analogues for injection, fast-acting	**At least one**	134	2.9	4.7 (1.6, 7.3)	79	4.8	6.0 (2.1, 9.3)	218	3.5	5.1 (1.7, 8.0)
	Insulin (human)	12	0.3		8	0.5		20	0.3	
	Insulin aspart	70	1.5		44	2.7		118	1.9	

Prior antidiabetes medication (ATC class)	Prior antidiabetes medication (ATC name)	Exenatide naïve (N=4556)			Previous Byetta user (N=1629)			Total cohort (N=6294)		
		n	%	Median (IQR) duration (years) from start of therapy prior to starting Bydureon®	n	%	Median (IQR) duration (years) from start of therapy prior to starting Bydureon®	n	%	Median (IQR) duration (years) from start of therapy prior to starting Bydureon®
	Insulin glulisine	7	0.2		3	0.2		10	0.2	
	Insulin lispro	49	1.1		25	1.5		75	1.2	
Insulins and analogues for injection, intermediate-acting	At least one	76	1.7	3.0 (1.1, 8.0)	53	3.3	5.5 (1.7, 9.7)	132	2.1	4.4 (1.3, 9.0)
	Insulin (human)	77	1.7		54	3.3		134	2.1	
Insulins and analogues for injection, intermediate-or long-acting combined with fast-acting	At least one	199	4.4	4.5 (2.0, 9.2)	125	7.7	4.6 (2.3, 8.6)	330	5.2	4.5 (2.1, 9.1)
	Insulin (human)	79	1.7		40	2.5		121	1.9	
	Insulin aspart	85	1.9		70	4.3		158	2.5	
	Insulin lispro	45	1.0		23	1.4		69	1.1	
Insulins and analogues for injection, long-acting	At least one	211	4.6	4.3 (2.2, 7.2)	156	9.6	4.1 (2.0, 6.7)	372	5.9	4.2 (2.1, 7.0)
	Insulin degludec	1	0.0		1	0.1		3	0.0	
	Insulin detemir	68	1.5		56	3.4		125	2.0	
	Insulin glargine	156	3.4		106	6.5		265	4.2	
Not specified		420	9.2		251	15.4		680	10.8	
Thiazolidinediones	Number of patients with at least one thiazolidinedione	947	20.8	5.3 (2.9, 7.7)	446	27.4	6.0 (3.9, 8.3)	1407	22.4	5.5 (3.2, 8.0)

Prior antidiabetes medication (ATC class)	Prior antidiabetes medication (ATC name)	Exenatide naïve (N=4556)			Previous Byetta user (N=1629)			Total cohort (N=6294)		
		n	%	Median (IQR) duration (years) from start of therapy prior to starting Bydureon®	n	%	Median (IQR) duration (years) from start of therapy prior to starting Bydureon®	n	%	Median (IQR) duration (years) from start of therapy prior to starting Bydureon®
	Pioglitazone	522	11.5		227	13.9		757	12.0	
	Rosiglitazone	240	5.3		121	7.4		365	5.8	
	Not specified	217	4.8		107	6.6		327	5.2	
Liraglutide		459	10.1	1.7 (0.7, 2.8)	235	14.4	2.0 (1.1, 2.7)	700	11.1	1.8 (0.8, 2.8)
Dipeptidyl peptidase 4 (DPP-4) inhibitors	Number of patients with at least one DPP-4 inhibitor	1562	34.3	1.8 (0.9, 3.2)	340	20.9	2.6 (1.6, 4.0)	1924	30.6	1.9 (1.0, 3.4)
	Alogliptin	14	0.3		1	0.1		15	0.2	
	Linagliptin	97	2.1		14	0.9		111	1.8	
	Saxagliptin	132	2.9		18	1.1		150	2.4	
	Sitagliptin	956	21.0		214	13.1		1184	18.8	
	Vildagliptin	53	1.2		12	0.7		68	1.1	
	Not specified	319	7.0		85	5.2		409	6.5	
Other Glucagon-like peptide-1 (GLP-1) analogues (not including Liraglutide)	At least one GLP-1 analogue (not Liraglutide)	78	1.7	0.6 (0.3, 1.3)	120	7.4	2.1 (0.9, 3.2)	202	3.2	1.4 (0.4, 2.6)
	Dulaglutide	3	0.1		0	0.0		3	0.0	
	Exenatide	7	0.2		105	6.4		113	1.8	
	Lixisenatide	69	1.5		17	1.0		89	1.4	
	Not specified	0	0.0		0	0.0		0	0.0	
Sodium-glucose co-transporter 2 (SGLT2) inhibitors	At least one SGLT-2 inhibitor	241	5.3	0.8 (0.3, 1.2)	41	2.5	0.6 (0.2, 1.2)	283	4.5	0.7 (0.3, 1.2)

Prior antidiabetes medication (ATC class)	Prior antidiabetes medication (ATC name)	Exenatide naïve (N=4556)			Previous Byetta user (N=1629)			Total cohort (N=6294)		
		n	%	Median (IQR) duration (years) from start of therapy prior to starting Bydureon®	n	%	Median (IQR) duration (years) from start of therapy prior to starting Bydureon®	n	%	Median (IQR) duration (years) from start of therapy prior to starting Bydureon®
	Canagliflozin	39	0.9		3	0.2		42	0.7	
	Dapagliflozin	194	4.3		37	2.3		232	3.7	
	Empagliflozin	9	0.2		2	0.1		11	0.2	
	Not specified	0	0.0		0	0.0		0	0.0	
Alpha glucosidase inhibitors	At least one alpha glucosidase inhibitor	18	0.4	8.5 (2.5, 14.2)	20	1.2	12.4 (8.2, 13.9)	38	0.6	11.5 (4.6, 13.9)
	Acarbose	18	0.4		20	1.2		38	0.6	
Other blood glucose lowering drugs, excl. insulins	At least one other blood glucose lowering drug	36	0.8	5.3 (3.1, 8.2)	37	2.3	7.2 (3.8, 11.1)	76	1.2	5.9 (3.2, 9.8)
	Netaglinide	5	0.1		6	0.4		12	0.2	
	Repaglinide	31	0.7		31	1.9		64	1.0	
Not specified		1	0.0		3	0.2		4	0.1	

10.2.3.3.4 Concomitant antidiabetes medication at index

As described above, where GPs had reported co-therapy at index, the GP was requested to specify details of the antidiabetes medications that were co-prescribed with Bydureon®. Results are presented in Table 16 below according to Anatomical Therapeutic Chemical (ATC) classification and name. Fixed dose combination products have been separated out into the active ingredients for this purpose and de-duplication was performed. Similar to Table 15 above, a patient may have had more than one concomitant medication reported within each ATC class and/or may have been taking more than one medication from different ATC classes simultaneously, therefore counts are not mutually exclusive. Of note, although where more than one type of insulin reported has contributed to only one type of antidiabetes medication for the purposes of categorising patients into the line of therapy (as reported in Table 14), for Table 16 all reported insulins have been provided for completeness.

For the total cohort, a type of co-therapy was reported for 5822 patients (92.5% of cohort) (Table 16). The type of concomitant antidiabetes medications were specified for nearly all patients (n=5753, 98.8% of patients with co-therapy reported). The vast majority of patients were prescribed Bydureon® with metformin (n=5130, 81.5% of cohort, 89.2% of patients with co-therapy reported). The proportion of patients prescribed metformin was similar for exenatide naïve patients and previous Byetta® users. Sulphonylureas were also commonly prescribed with Bydureon®; 2832 patients (45.0% of cohort, 49.2% of patients with co-therapy reported) had at least one sulphonylurea prescribed. Gliclazide was reported in 1498 patients (23.8% of cohort, 26.0% of patients with co-therapy reported) and for 1103 patients (17.5% of cohort, 19.2% of patients with co-therapy reported) the GP had specified 'sulphonylurea' but not provided the specific drug name. Use of sulphonylureas was similar between patients who were exenatide naïve and those who had previously taken Byetta®. Furthermore, a number of patients were also prescribed Bydureon® with insulin (n=1528, 24.3% of cohort, 26.6% of patients with co-therapy reported). Concomitant use of at least one insulin was more prevalent for previous Byetta® users than exenatide naïve patients (34.6% vs. 20.6%, respectively). Few patients, however, were concomitantly prescribed Bydureon® with thiazolidinediones (n=428, 6.8% of cohort, 7.4% of patients with co-therapy reported) and prescribing prevalence was fairly similar between the stratified prior exenatide use groups. Finally, at least one 'other' antidiabetes medication was prescribed with Bydureon® in 11.9% of the cohort (n=750, 13.0% of patients with co-therapy reported); these medications were more commonly prescribed for exenatide naïve patients as compared to previous Byetta® users (12.8% vs. 9.3%, respectively). The most common other antidiabetes medication reported was sitagliptin (n=298, 4.7% of cohort, 5.2% of patients with co-therapy reported). Of note, 'exenatide' was reported in five patients (0.1% of cohort, 0.1% where co-therapy reported); this potentially could be because of misreporting by the GP on the 12-month questionnaire or a true prescribing error (i.e., concomitant use of Byetta®). Figure 6 illustrates concomitant antidiabetes medications presented by ATC class.

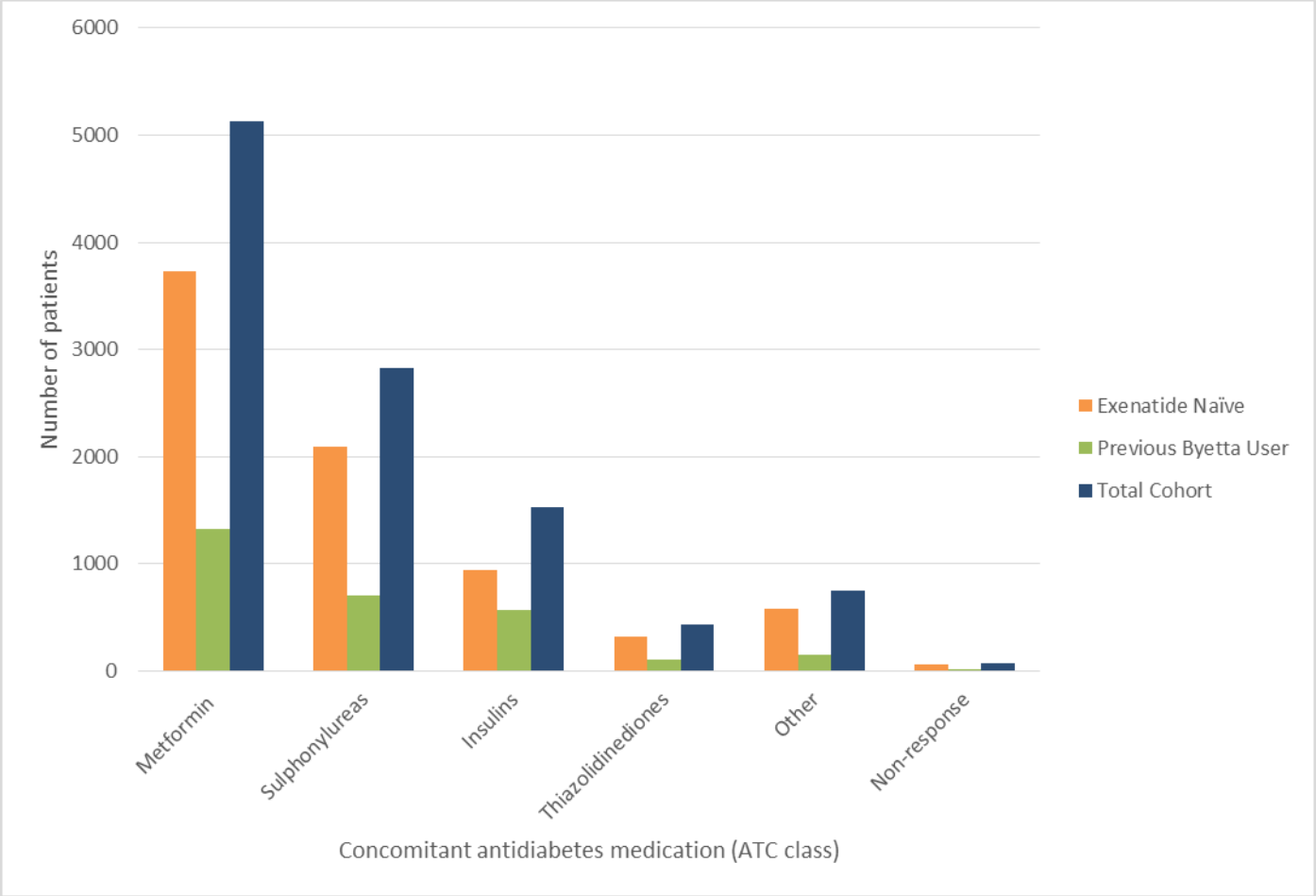
Table 16. Types of antidiabetes medications co-prescribed with Bydureon® at index

Concomitant antidiabetes medication at index[a] (ATC class)	Concomitant antidiabetes medication at index[b] (ATC name)	Exenatide naïve (N=4556)		Previous Byetta® user (N=1629)		Total cohort (N=6294)	
		n	%	n	%	n	%
Biguanides	Metformin	3731	81.9	1324	81.3	5130	81.5
Sulphonylureas	Number of patients with at least one sulphonylurea	2093	45.9	700	43.0	2832	45.0
	Glibenclamide	12	0.3	2	0.1	14	0.2
	Gliclazide	1107	24.3	373	22.9	1498	23.8
	Glimepride	135	3.0	53	3.3	189	3.0
	Glipizide	20	0.4	12	0.7	32	0.5
	Tolbutamide	3	0.1	0	0.0	3	0.0
	Not specified[c]	823	18.1	260	16.0	1103	17.5
Insulins	Number of patients with at least one insulin	937	20.6	563	34.6	1528	24.3
Insulins and analogues	Insulin (human)	14	0.3	6	0.4	20	0.3
	Insulins and analogues (NOS)	11	0.2	5	0.3	16	0.3
Insulins and analogues for injection, fast-acting	Insulin (human)	6	0.1	1	0.1	7	0.1
	Insulin aspart	77	1.7	51	3.1	132	2.1
	Insulin glulisine	9	0.2	8	0.5	17	0.3
	Insulin lispro	41	0.9	22	1.4	65	1.0
Insulins and analogues for injection, intermediate-acting	Insulin (human)	72	1.6	50	3.1	123	2.0
Insulins and analogues for injection, intermediate-or long-acting combined with fast-acting	Insulin (human)	63	1.4	24	1.5	89	1.4
	Insulin aspart	89	2.0	68	4.2	160	2.5
	Insulin lispro	45	1.0	30	1.8	75	1.2
Insulins and analogues for injection, long-acting	Insulin degludec	2	0.0	3	0.2	6	0.1
	Insulin detemir	65	1.4	52	3.2	118	1.9
	Insulin glargine	138	3.0	85	5.2	228	3.6
Not specified[c]		425	9.3	242	14.9	682	10.8
Thiazolidinediones	Number of patients with at least one thiazolidinedione	325	7.1	101	6.2	428	6.8
	Pioglitazone	203	4.5	67	4.1	270	4.3
	Rosiglitazone	7	0.2	1	0.1	8	0.1
	Not specified[c]	119	2.6	33	2.0	154	2.4
Other	Number of patients with at least one other ADM	583	12.8	152	9.3	750	11.9
Dipeptidyl peptidase 4 (DPP-4) inhibitors	Alogliptin	18	0.4	2	0.1	21	0.3
	Linagliptin	39	0.9	6	0.4	45	0.7
	Saxagliptin	23	0.5	3	0.2	26	0.4

Concomitant antidiabetes medication at index[a] (ATC class)	Concomitant antidiabetes medication at index[b] (ATC name)	Exenatide naïve (N=4556)		Previous Byetta® user (N=1629)		Total cohort (N=6294)	
		n	%	n	%	n	%
Glucagon-like peptide-1 (GLP-1) analogues	Sitagliptin	241	5.3	47	2.9	298	4.7
	Vildagliptin	18	0.4	3	0.2	21	0.3
	Not specified	11	0.2	1	0.1	12	0.2
	Dulaglutide	2	0.0	1	0.1	3	0.0
	Exenatide	0	0.0	5	0.3	5	0.1
	Liraglutide	19	0.4	7	0.4	26	0.4
	Lixisenatide	2	0.0	0	0.0	3	0.0
	Not specified[c]	0	0.0	1	0.1	1	0.0
Sodium-glucose co-transporter 2 (SGLT2) inhibitors	Canagliflozin	31	0.7	13	0.8	45	0.7
	Dapagliflozin	157	3.4	51	3.1	209	3.3
	Empagliflozin	31	0.7	6	0.4	38	0.6
	Not specified[c]	0	0.0	0	0.0	0	0.0
Alpha glucosidase inhibitors	Acarbose	6	0.1	4	0.2	10	0.2
Other blood glucose lowering drugs, excl. insulins	Netaglinide	1	0.0	1	0.1	2	0.0
	Repaglinide	13	0.3	7	0.4	21	0.3
Not specified[c]		0	0.0	0	0.0	0	0.0
Non-response[d]		55	1.2	12	0.7	69	1.1
Number of patients with co-therapy reported[e]		4229	92.8	1514	92.9	5822	92.5

[a] More than one ATC class of antidiabetes medication could be specified per patient, so counts are not mutually exclusive
[b] More than one antidiabetes medication within each ATC class may have been provided by the GP, so counts are not mutually exclusive
[c] Number of patients for whom the GP had ticked/specified the class of antidiabetes medication but not reported the particular drug name
[d] Co-therapy specified in Q14 but concomitant antidiabetes medication not specified in Q15
[e] Number of patients with co-therapy reported as provided in Table 14

Figure 6. Number of patients with at least one antidiabetes medication co-prescribed at index within each ATC class



10.2.3.3.5 Concomitant medications whilst on Bydureon® (including antidiabetes medication reported after index)

The GP was also requested to report all other medications (including antidiabetes medications) prescribed for the patient whilst on Bydureon®. Table 17 provides the ten most frequently reported concomitant medications during treatment with Bydureon®. All medications have been presented according to the Anatomical Therapeutic Chemical (ATC) classification and name. Fixed dose combination products have been separated out into the active ingredients for this purpose and de-duplication was performed. Similar to Table 15 and Table 16 above, a patient may have had more than one concomitant medication reported within each ATC class and/or may have been taking more than one medication from different ATC classes simultaneously, so counts are not mutually exclusive.

A total of 42531 counts of concomitant medications were reported. The most frequently reported medication taken concomitantly with Bydureon® was metformin (n=2977, 47.3% of cohort). Sulphonylureas were the second most commonly prescribed concomitant antidiabetes medication (n=1266, 20.1% of cohort). The most frequently prescribed non-antidiabetes medication was atorvastatin (n= 2085, 33.1% of cohort). In addition, as expected for patients with type 2 diabetes mellitus, other commonly prescribed

medications reported in the top ten included antihypertensives (ACE inhibitors, dihydropyridine derivatives) and antiplatelets. A list of all concomitant antidiabetes medications and non-antidiabetes medications are provided in Appendix 12.

Table 17. Ten[a] most frequently reported concomitant medications whilst on Bydureon® (including antidiabetes medication reported after index)

Concomitant medications whilst taking Bydureon® (ATC class)	Concomitant medications whilst taking Bydureon® (ATC name)	n	%
Exenatide naïve (N=4556)			
Biguanides	Metformin	2140	47.0
HMG CoA reductase inhibitors	Atorvastatin	1501	32.9
HMG CoA reductase inhibitors	Simvastatin	1357	29.8
ACE inhibitors, plain	Ramipril	1190	26.1
Platelet aggregation inhibitors excl. heparin	Acetylsalicylic acid	1058	23.2
Sulphonylureas	Gliclazide	941	20.7
Proton pump inhibitors	Omeprazole	776	17.0
Dihydropyridine derivatives	Amlodipine	770	16.9
Selective beta-2-adrenoreceptor agonists	Salbutamol	558	12.2
Proton pump inhibitors	Lansoprazole	518	11.4
Previous Byetta® user (N=1629)			
Biguanides	Metformin	787	48.3
HMG CoA reductase inhibitors	Atorvastatin	552	33.9
HMG CoA reductase inhibitors	Simvastatin	487	29.9
Platelet aggregation inhibitors excl. heparin	Acetylsalicylic acid	451	27.7
ACE inhibitors, plain	Ramipril	395	24.2
Proton pump inhibitors	Omeprazole	313	19.2
Sulfonylureas	Gliclazide	305	18.7
Dihydropyridine derivatives	Amlodipine	276	16.9
Proton pump inhibitors	Lansoprazole	228	14.0
Selective beta-2-adrenoreceptor agonists	Salbutamol	228	14.0
Total cohort (N=6294)			
Biguanides	Metformin	2977	47.3
HMG CoA reductase inhibitors	Atorvastatin	2085	33.1
HMG CoA reductase inhibitors	Simvastatin	1868	29.7
ACE inhibitors, plain	Ramipril	1608	25.5
Platelet aggregation inhibitors excl. heparin	Acetylsalicylic acid	1529	24.3
Sulfonylureas	Gliclazide	1266	20.1
Proton pump inhibitors	Omeprazole	1109	17.6
Dihydropyridine derivatives	Amlodipine	1067	17.0
Selective beta-2-adrenoreceptor agonists	Salbutamol	798	12.7
Proton pump inhibitors	Lansoprazole	753	12.0

10.2.3.3.6 Concomitant use of warfarin

Concomitant use of warfarin with Bydureon® is a special warning and precaution for use resulting from an interaction between the two medications increasing the INR (International Normalised Ratio), which has sometimes been associated with bleeding. (1) GPs were requested to specify whether the patient had

been prescribed warfarin prior to starting Bydureon® or during its use. Table 27 below shows that use of warfarin one week prior to or whilst taking Bydureon® was reported in a total of 265 patients (4.2% of cohort, 5.0% where warfarin use specified). After stratifying by prior exenatide use, results show that warfarin was prescribed slightly more frequently for exenatide naïve patients (4.3%) as compared to previous Byetta® users (3.8%).

Table 18. Use of warfarin one week prior to starting or during Bydureon® treatment

	Exenatide naïve (N=4556)						Previous Byetta® user (N=1629)						Total cohort (N=6294)					
	Yes		No		Non-response		Yes		No		Non-response		Yes		No		Non-response	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Warfarin use one week prior to starting or during Bydureon® treatment	198	4.3	3651	80.1	707	15.5	62	3.8	1359	83.4	208	12.8	265	4.2	5073	80.6	956	15.2

10.2.3.4 Treatment cessation and cohort exposure

10.2.3.4.1 Frequency of treatment cessation

Information on whether treatment with Bydureon® was stopped was requested on the 12-month questionnaire (Table 19). Note, if the GP reported that the patient had stopped Bydureon® but not provided a stop date it was inferred that the patient had stopped Bydureon® during the 12-month observation period due to the nature of the question on the 12-month questionnaire. Thus, events reported as reasons for stopping have contributed to the 12-month event analyses for this report.

A total of 1881 patients (29.9% of cohort) were reported to have stopped Bydureon® during the 12-month observation period. For 86 patients (1.4% of cohort) it was not known whether the patient stopped treatment or not. The proportion of patients stopping Bydureon® treatment was slightly higher in the exenatide naïve group as compared to previous Byetta® users (31.1% vs. 26.6%, respectively).

Table 19. Number of patients stopping treatment with Bydureon® during the 12-month observation period

Treatment stopped	Exenatide Naïve (N=4556)		Previous Byetta® users (N=1629)		Total cohort (N=6294)	
	n	%	n	%	n	%
Yes	1417	31.1	434	26.6	1881	29.9
No	3097	68.0	1174	72.1	4327	68.7
Non-response	42	0.9	21	1.3	86	1.4
Total (N)	4556	100.0	1629	100.0	6294	100.0

10.2.3.4.2 Reasons for stopping

Where patients were reported to have stopped Bydureon® (n=1881, 29.9% of cohort) the GP was requested to further specify the reason for stopping. More than one reason for stopping could be provided for each patient, so counts are not mutually exclusive. A total of 2682 reasons for stopping were provided; all reported reasons have been listed in Appendix 13, stratified by prior exenatide use[16]. A total of 143 patients (7.7% of patients who were reported to have stopped Bydureon®) had no reason for stopping treatment specified.

For the total cohort, the three most frequently reported reasons for stopping were 'drug ineffective', 'therapy change', and 'nausea'. Other reasons were those related patient compliance (i.e., 'refusal of treatment by patient' and 'treatment non-compliance') and to poor efficacy (i.e., 'glycosylated haemoglobin increased' and 'diabetes mellitus control inadequate control'). Similar reasons for stopping were observed after stratifying by prior exenatide use groups. Of note, 'pancreatitis', 'acute pancreatitis' or 'obstructive pancreatitis' was reported in eight patients, 'acute kidney injury' in four patients and 'weight decreased' in 33 patients; these cases are analysed further in Section 10.4.1, 10.4.2.2 and 10.5.1.5.2, respectively. All

[16] Reasons for stopping have been reported according to MedDRA Preferred Terms. Where MedDRA terms are not applicable, the reasons have been reported according to the DSRU drug utilisation dictionary preferred terms or the reported event term (RET) for unevaluable events.

reasons for stopping reported within 12-month observation period are provided in Appendix 13a. All reasons for stopping reported after the 12-month observation period are provided in Appendix 13b.

Table 20. Ten most frequently reported reasons for stopping treatment during the 12-month observation period

Reasons for stopping[a]	n	% of patients who stopped treatment
Exenatide naïve (N=1417)[b]		
Drug ineffective	237	16.7
Therapy change	143	10.1
Nausea	126	8.9
Refusal of treatment by patient	115	8.1
Glycosylated haemoglobin increased	102	7.2
Diabetes mellitus inadequate control	74	5.2
Diarrhoea	71	5.0
Treatment non-compliance	69	4.9
Unevaluable event[c]	62	4.4
Vomiting	54	3.8
Non-response[d]	107	7.6
Previous Byetta® user (N=434)[b]		
Drug ineffective	76	17.5
Therapy change	40	9.2
Refusal of treatment by patient	36	8.3
Nausea	30	6.9
Diabetes mellitus inadequate control	29	6.7
Glycosylated haemoglobin increased	22	5.1
Unevaluable event[c]	22	5.1
Secondary care advice, formulary or guidelines	19	4.4
Diarrhoea	17	3.9
Drug intolerance	17	3.9
Non-response[d]	28	6.5
Total cohort (N=1881)[b]		
Drug ineffective	318	16.9
Therapy change	186	9.9
Nausea	157	8.3
Refusal of treatment by patient	154	8.2
Glycosylated haemoglobin increased	126	6.7
Diabetes mellitus inadequate control	103	5.5
Diarrhoea	90	4.8
Unevaluable event[c]	85	4.5
Treatment noncompliance	84	4.5
Vomiting	71	3.8
Non-response[d]	143	7.6

[a]All reasons for stopping have been listed in Appendix 13

[b] Number of patients who stopped Bydureon® treatment

[c] Unevaluable events refers to events which are not possible to code to MedDRA or the DSRU drug utilisation dictionary. These have been listed as the reported event term in Appendix 13.

[d] Non-response refers to the number of patients who were reported to have stopped treatment but the GP did not provide a reason for stopping.

10.2.3.4.3 Dose and frequency on stopping

Where patients were reported to have stopped treatment, information on dose and frequency on stopping treatment was requested. Table 21 presents results on the Bydureon® dose and frequency reported at the time of stopping. Percentages have been derived from the number of patients who stopped Bydureon®.

Dose and/or frequency on stopping was specified for 1778 patients (94.5% of patients who stopped Bydureon®). In the total cohort, the majority of patients (n=1752, 93.1% of patients who stopped Bydureon®) were reported to be on Bydureon® 2mg once weekly at the time of stopping. Of these, slightly more patients were taking Bydureon® via the pre-filled pen (n=506) as compared to the vial and syringe (n=466); for 780 patients the presentation is not known. After stratifying by previous exenatide use, more patients were taking Bydureon® vial and syringe as compared to the pre-filled pen in the previous Byetta® user group; the opposite was true for exenatide naïve patients. For 26 patients in total (1.4% of patients who stopped Bydureon®), an 'other' dose/frequency was specified; these have all been summarised as reported by the GP in Appendix 14. Of note, as reflected in Appendix 14, there are a number of reports of off-label prescribing with respect to the recommended dose/frequency. For some patients the GP reported a Byetta® dose (e.g. 5 or 10 micrograms) at stopping. For these patients it is possible that the GP may have misinterpreted the difference between Byetta® and Bydureon®, however, because the DSRU has received FP10 prescription data on Bydureon® for these patients they have remained in the evaluable cohort. The rule base described in Section 10.2.1 was used to allocate these patients to either the previous Byetta® user or unknown prior exenatide use group.

Table 21. Dose and frequency of Bydureon® upon stopping

	Exenatide naïve		Previous Byetta® users		Total cohort	
Stop dose/frequency	**n**	**% of patients who stopped treatment**	**n**	**% of patients who stopped treatment**	**n**	**% of patients who stopped treatment**
2mg once weekly injection	1329	93.8	404	93.1	1752	93.1
Pre-filled pen 2mg once weekly	431	30.4	71	16.4	506	26.9
Vial & syringe 2mg once weekly	367	25.9	96	22.1	466	24.8
Unspecified 2mg once weekly[a]	531	37.5	237	54.6	780	41.5
Other[b]	20	1.4	4	0.9	26	1.4
Non-response	68	4.8	26	6.0	103	5.5
Total (N)	1417	100.0	434	100.0	1881	100.0

[a] The sub-question on presentation (pre-filled pen or vial) was added during the study. Therefore, for some patients only dose/frequency was collected and there is no information on presentation.
[b] All other doses as specified by the GP have been listed in Appendix 14.

10.2.3.4.4 Time to treatment cessation

Data on duration of treatment exposure to Bydureon® has been derived from the following where patient exposure was censored according to:

- stop date (if stopped)
- end of observation date (365 days after index date if not stopped)

- date of death (if died)
- or date left practice (if patient moved)

Data on cohort exposure has been presented in Table 22 below and a graphical presentation of time to treatment cessation has been provided in Figures 7a-7c. Note that it is assumed that drug use is continuous between index and stop date. In addition, for this analysis treatment cessation excludes the 10-week washout period in order to reflect the true current use of Bydureon®.

In summary, the majority of patients continued to take Bydureon® until weeks 43-52 (n=4594, 73.0% of cohort). The mean (SD) duration of treatment for the total cohort was 308.2 (121.0) days and the median (IQR) duration of treatment was 365 (273-365) days. In the overall cohort, similar proportion of patients stopped treatment in each of the categories up to 43 weeks. After stratifying by previous exenatide use, the proportion of patients taking Bydureon® at 43-52 weeks was only slightly higher for previous Byetta® users as compared to exenatide naïve patients (75.6% vs. 72.1%, respectively). The mean (SD) treatment duration was 305.9 (121.9) days for exenatide naïve patients and 314.6 (119.4) days for previous Byetta® users.

Table 22. Count and percent of number of weeks on treatment[a] with Bydureon®

	Exenatide naïve (N=4556)		Previous Byetta® users (N=1629)		Total cohort (N=6294)	
Number of weeks on treatment	**n**	**%**	**n**	**%**	**n**	**%**
<8	262	5.8	88	5.4	355	5.6
8-17	293	6.4	83	5.1	381	6.1
17-26	260	5.7	83	5.1	352	5.6
26-34	210	4.6	81	5.0	297	4.7
34-43	248	5.4	62	3.8	315	5.0
43-52	3283	72.1	1232	75.6	4594	73.0
Total (N)	4556	100.0	1629	100.0	6294	100.0
Mean (SD) days	305.9 (121.9)		314.6 (119.4)		308.2 (121.0)	
Median (IQR) days	365 (266-365)		365 (320-365)		365 (273-365)	

[a] Number of days on treatment calculated from entry date to stop date (either reported stop date or last known prescription date plus one month)

Figure 7a. Time to treatment cessation within the 12-month observation period for the total cohort

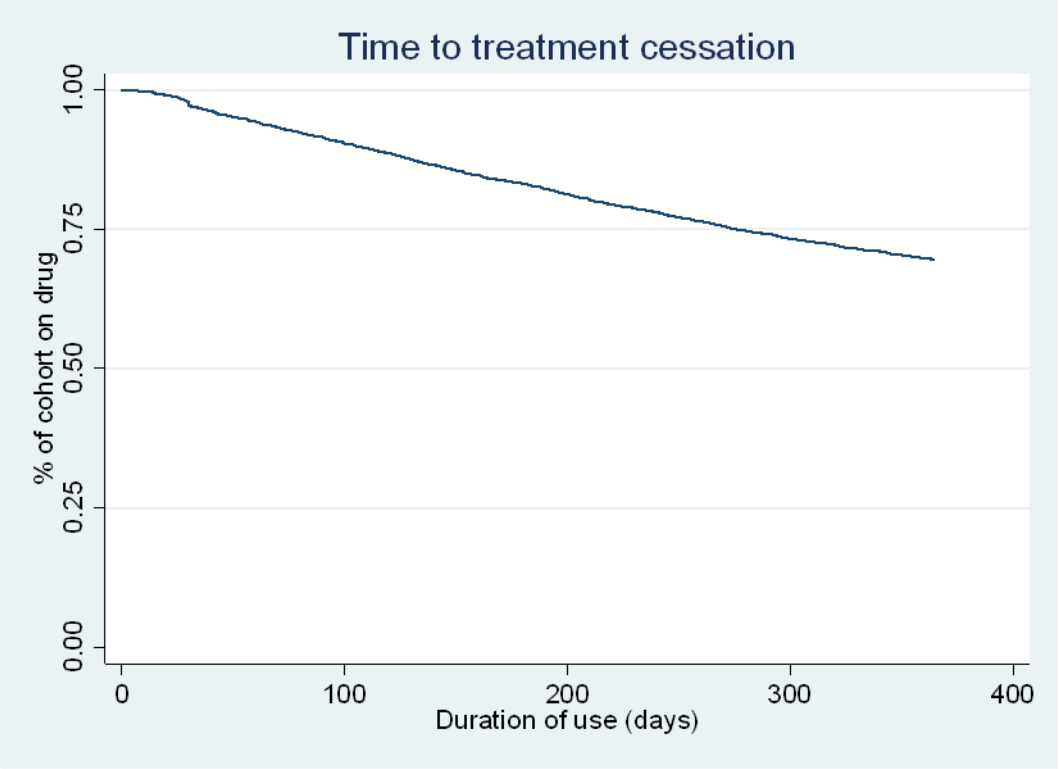


Figure 7b. Time to treatment cessation within the 12-month observation period for patients who were exenatide naïve

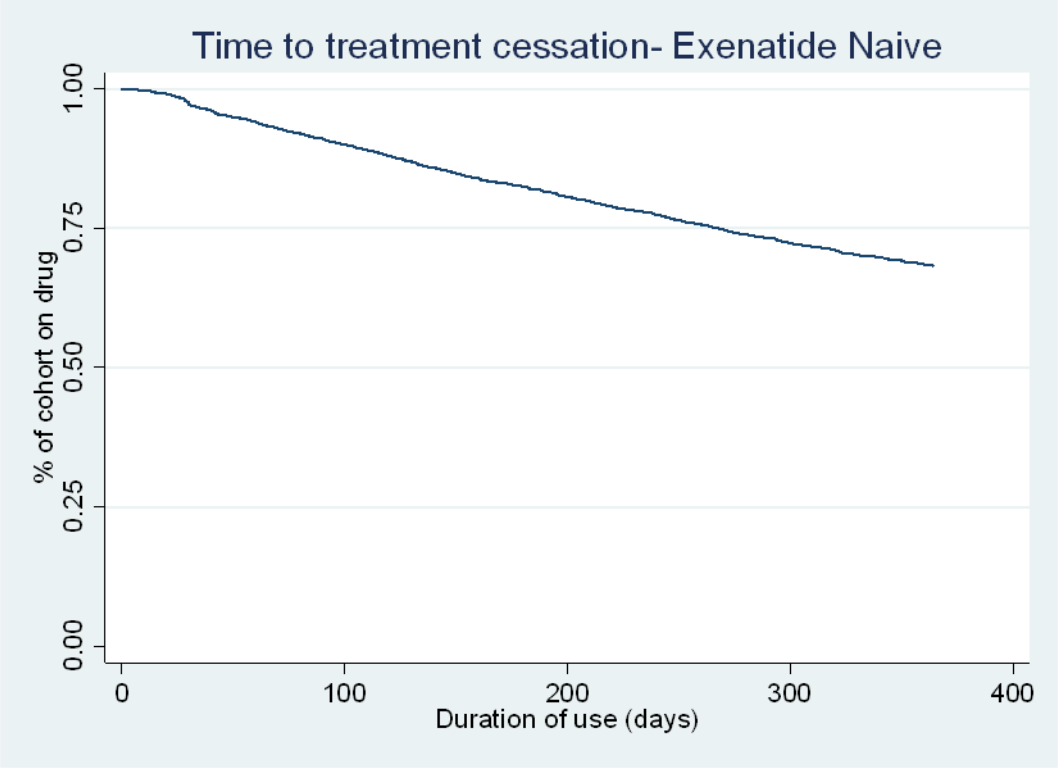
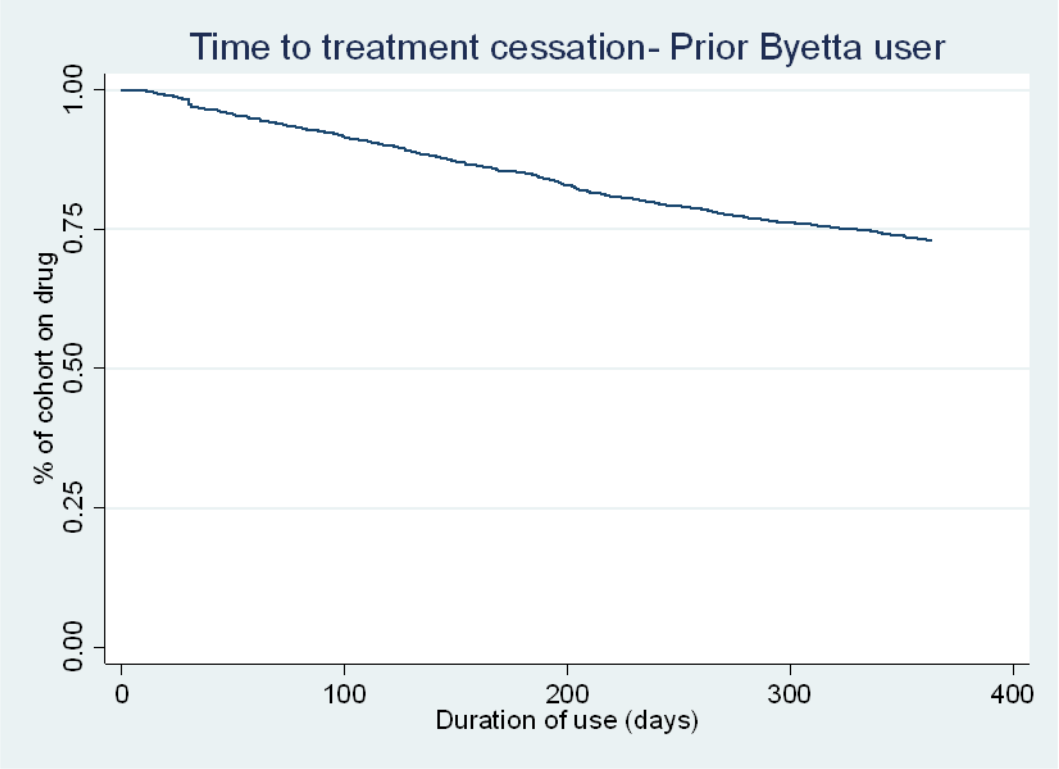


Figure 7c. Time to treatment cessation within the 12-month observation period for previous Byetta® users



10.2.3.5 Use in special populations

Information that would assist in identifying potentially vulnerable populations (according to special warnings/precautions for use within the SmPC) was collected from data on the 12-month questionnaire. This relates to the secondary objective, i.e. to describe the risk profile of events in the 12-month observation period 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). Table 23 summarises the number of patients prescribed Bydureon® with baseline characteristics meeting special populations criteria for the purposes of this report. These special population indicator definitions have been constructed from tick-box responses and free text information reported on the 12-month questionnaire. For the purpose of this analysis, missing data has been treated as a negative response.

The SmPC recommends that prolonged-release exenatide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. (1) In this M-PEM study, use of Bydureon® was reported in 16 patients with type 1 diabetes mellitus at index. These patients have been excluded from the evaluable cohort for this report but have been provided as counts in Table 23 and summarised in Appendix 5. In addition, caution is recommended in patients with a history of pancreatitis; in this study there were 38 patients (0.6% of cohort) with a past medical history of acute pancreatitis.

Furthermore, there was limited information on the use of Bydureon® in the elderly population (≥75 years) at the time the study protocol was written and it was recommended for renal function to be considered within this population. Information on the safety and efficacy of Bydureon® in paediatric (≤17 years) patients

has not yet been established. (1) As expected, use in the elderly (≥75 years) was more common (n=291, 4.6% of cohort) than use in young (<18 years) patients (n=2) (Table 23).

There is a lack of data regarding the safety of Bydureon® during pregnancy and lactation. Use in pregnancy or lactation during the study was uncommon (n=9, 0.3% of females) and eight patients stopped Bydureon® treatment as a result of the pregnancy (please see Section 10.4.7 for further details). Concomitant use with thiazolidinediones was also relatively low (6.8% of cohort).

Table 23. Prevalence of use of Bydureon® in selected special populations

	Exenatide naïve (N=4556)		Previous Byetta® user (N=1629)		Total cohort (N=6294)	
Special population	**n**	**%**	**n**	**%**	**n**	**%**
Special warning and precautions for use						
Type 1 diabetes mellitus	13	N/A[a]	1	N/A[a]	16	N/A[a]
History of acute pancreatitis	27	0.6	9	0.6	38	0.6
Important missing information						
Use in pregnancy and lactation[b]	5	0.2	4	0.5	9	0.3
Use in combination with thiazolidinedione[c]	325	7.1	101	6.2	428	6.8
Use in the very elderly (≥75 years)	225	4.9	58	3.6	291	4.6
Use in the paediatric population (≤17 years)[d]	1	0.0	0	0.0	2	0.0

[a] Percentage not applicable as these patients were excluded from the evaluable cohort.

[b] Missing information category in the RMP was "pregnant women". This count includes all women reported to be pregnant in the study. Please see section 10.4.7 for further details. Denominator for % is females only (exenatide naïve N=2013, previous Byetta® user N=754, total cohort N=2819).

[c] Missing information category in the RMP was "patients using exenatide in combination with other agents (TZDs and insulins)". Counts provided in this table refers to reported concomitant use of thiazolidinediones at index (please see Table 16).

[d] Missing information category in the RMP was "adolescents".

10.3 Outcome Data

10.3.1 Primary objective outcome- Acute Pancreatitis

The following section relates to primary objective, (i) to quantify the cumulative incidence of acute pancreatitis in the first 12 months after starting treatment with Bydureon®. Of note, a new event of acute pancreatitis has been defined as first report of the event during treatment irrespective of a prior history.

Cases of acute pancreatitis have been derived using tick-box responses and/or free text events meeting the definition of acute pancreatitis. Free text events of acute pancreatitis were obtained using the pre-defined standardised MedDRA query (SMQ) of 'Acute Pancreatitis' from data on the 12-month questionnaire (e.g. from other events, reasons for stopping, immediate cause of deaths), cause of death supplementary questionnaire and potential acute pancreatitis supplementary questionnaires. In addition to the pre-specified tick-box response, the following rules were applied in order to identify cases of acute pancreatitis for inclusion in the main analysis:

- Narrow scope 'acute pancreatitis' SMQ preferred terms were applied to free text events reported on the 12-month questionnaire
- Broad scope 'acute pancreatitis' SMQ preferred terms were applied for events reported on the 12-month questionnaire if supplementary information for the particular event was present. If only broad scope 'acute pancreatitis' SMQ preferred terms were present on the 12-month questionnaire, narrow scope 'acute pancreatitis' SMQ preferred terms were applied to the corresponding supplementary questionnaire of that specific broad preferred term event. This scenario did not occur in the study, but we have summarised this rule for completeness.

10.4 Main results

10.4.1 Acute pancreatitis

10.4.1.1 Cumulative incidence

Table 24 provides the count and cumulative incidence (with 95% CI) of incident reports of acute pancreatitis on treatment (plus the 10-week washout period) within the 12-month observation period. It is important to note that where events occurred without an event date provided (except if reported as a reason for stopping in Q11) or where the treatment exit date was not provided, that patient was removed from the numerator for the incidence calculation for that event.

In total, there were 14 reports of acute pancreatitis during treatment with Bydureon® (plus the 10-week washout period) within the 12-month observation period. For the total cohort, the cumulative incidence of acute pancreatitis was 0.2% (95% CI [0.1, 0.4]).

After stratifying by previous exenatide use, the cumulative incidence of acute pancreatitis was the same in both groups; 0.2% (95% CI [0.1, 0.4]) for exenatide naïve patients and 0.2% (95% CI [0.0, 0.5]) for previous Byetta® users.

Table 24. Number of patients reporting acute pancreatitis during treatment with Bydureon® within the 12-month observation period and cumulative incidence estimates (+95% CI)[a]

	Yes			No		Non-response	
Acute pancreatitis -during Bydureon®	**n**	**%**	**95% CI**	**n**	**%**	**n**	**%**
Exenatide naïve (N=4556)	10	0.2	0.1, 0.4	3537	77.6	1009	22.1
Previous Byetta® users (N=1629)	3	0.2	0.0, 0.5	1331	81.7	295	18.1
Total cohort (N=6294)	14	0.2	0.1, 0.4	4931	78.3	1349	21.4

Cumulative incidence = (Total number of new cases during 12-month observation period / Population initially at risk)*100. Note, where events are reported with no supporting event date or treatment exit date, these have been excluded from the numerator of the cumulative risk calculation. [a] 95% CI calculated using Binomial exact

Case narratives for these 14 events of acute pancreatitis have been provided in Appendix 15 and the characteristics of these patients are summarised in a case series, Table 31. In addition, there was one event of acute pancreatitis without an event date. This has not been included in the cumulative incidence estimates in Table 24, however, further information on this event in the form of a case narrative has been

provided in Appendix 15. There was also one case of acute pancreatitis occurring beyond the study 12-month observation period, which has been summarised in Appendix 15[17].

It is important to note that all cases of GP reported acute pancreatitis have been included in the cumulative incidence estimates; for some patients, where the GP had reported acute pancreatitis, supplementary information on that event revealed a mildly raised amylase (i.e., not meeting the criteria of three times upper limit of normal). However, these have been included based on GP reporting of the clinical diagnoses of pancreatitis[18]. Bydureon® was stopped in 12 of the 14 cases due to the event. A single case reported complications of pancreatitis, including necrosis, pseudo-cyst and surgical removal of the pancreas. A further case was reported to have died from multiple organ failure (cause of death Ia), acute pancreatitis (cause of death Ib) and liver cirrhosis (cause of death II). Of the 14 cases of acute pancreatitis, five cases were managed in primary care, eight were treated in hospital and for one patient further information on the event was not available. For this patient we could not confirm that the pancreatitis event occurred on treatment with Bydureon® as there was no supplementary information and so information from a clinic letter provided with the main questionnaire was used to infer that the event was on treatment. This case was included as the event fulfilled the criteria of the MedDRA SMQ 'acute pancreatitis' and was reported in a clinic letter dated post index with the GP specifying no prior history in Q9 on the 12-month questionnaire. Further information on all cases of acute pancreatitis can be found in Appendix 15.

A sensitivity analysis for cumulative incidence was performed which included acute pancreatitis events occurring during treatment with Bydureon® within the 12-month observation period but excluding the 10-week washout period; results are shown in Appendix 16 and demonstrate no significant differences with the results seen in Table 24.

10.4.1.2 Incidence rate

Table 25 provides estimates of the incidence rate of acute pancreatitis occurring on treatment with Bydureon® (plus the 10-week washout period) during the 12-month observation period. As can be seen in Table 25, incidence rates of acute pancreatitis are low.

[17] In addition, there was a further event of acute pancreatitis reported on a 12-month questionnaire returned after data-lock. This patient has not been included in the evaluable cohort for this report however, as specified in Section 10.1, the event has been summarised in Appendix 4.

[18] The total number of patients for whom the GP reported raised amylase have been provided in the general event section (10.4.4). These counts may include patients for whom the GP had additionally specified a diagnosis of acute pancreatitis (thus reported in this section here) or patients for whom pancreatitis was not specified as a diagnosis (therefore not included in this section).

Table 25. Incidence rate of acute pancreatitis during treatment with Bydureon® within the 12-month observation period (+95% CI)[a]

Acute pancreatitis - during Bydureon®	n	Total person-time (per 1000 person-years)	Incidence rate (per 1000 person-years)	95% CI (per 1000 person-years)
Exenatide naïve (N=4548)	10	1461.6	2.5	1.4, 4.6
Previous Byetta® users (N=1624)	3	529.6	2.1	0.7, 6.4
Total cohort (N=6280)	14	2026.1	2.5	1.5, 4.3

Incidence Rate (IR) = (Number of events / Total person-time) where person-time is derived from index date until the earliest of time until acute pancreatitis, date at which patient is censored or end of 12-month observation period; Total person-time (1000 years) = Total person-time /(365.25*1000);
[a] 95% CI calculated using Poisson exact

A sensitivity analysis for incidence rate was performed which included acute pancreatitis events occurring during treatment with Bydureon® within the 12-month observation period but excluding the 10-week washout period; results are shown in Appendix 16 and demonstrate no significant differences with the results provided in Table 25.

10.4.1.3 Prior history

For patients with an event of acute pancreatitis occurring during treatment with Bydureon® (as reported in Table 24), prior history of acute pancreatitis was explored and results are presented in Table 26 below. The denominator in Table 26 is the number of patients with acute pancreatitis on treatment with Bydureon® (plus the 10-week washout period) occurring within the 12-month observation period. For the 14 patients who experienced an event of acute pancreatitis, only two patients (14.3% of acute pancreatitis events) had a prior history of the event. Both of these patients were within the exenatide naïve group. For the remaining 12 patients with acute pancreatitis there was no evidence to suggest a history of acute pancreatitis prior to starting treatment with Bydureon®. All prior history information for these patients has been described in the case narratives in Appendix 15.

Table 26. Number of patients with acute pancreatitis during treatment with Bydureon® within the 12-month observation period with a prior history of acute pancreatitis or present at start of treatment

Acute pancreatitis prior to or present at start of Bydureon®	Yes		No		Non-response	
	n	%	n	%	n	%
Exenatide naïve (N[a]=10)	2	20.0	8	80.0	0	0.0
Previous Byetta® users (N[a]=3)	0	0.0	3	100.0	0	0.0
Total cohort (N[a]=14)	2	14.3	12	85.7	0	0.0

[a] N= number of patients with acute pancreatitis reported during Bydureon® (as reported in **Table 24**)

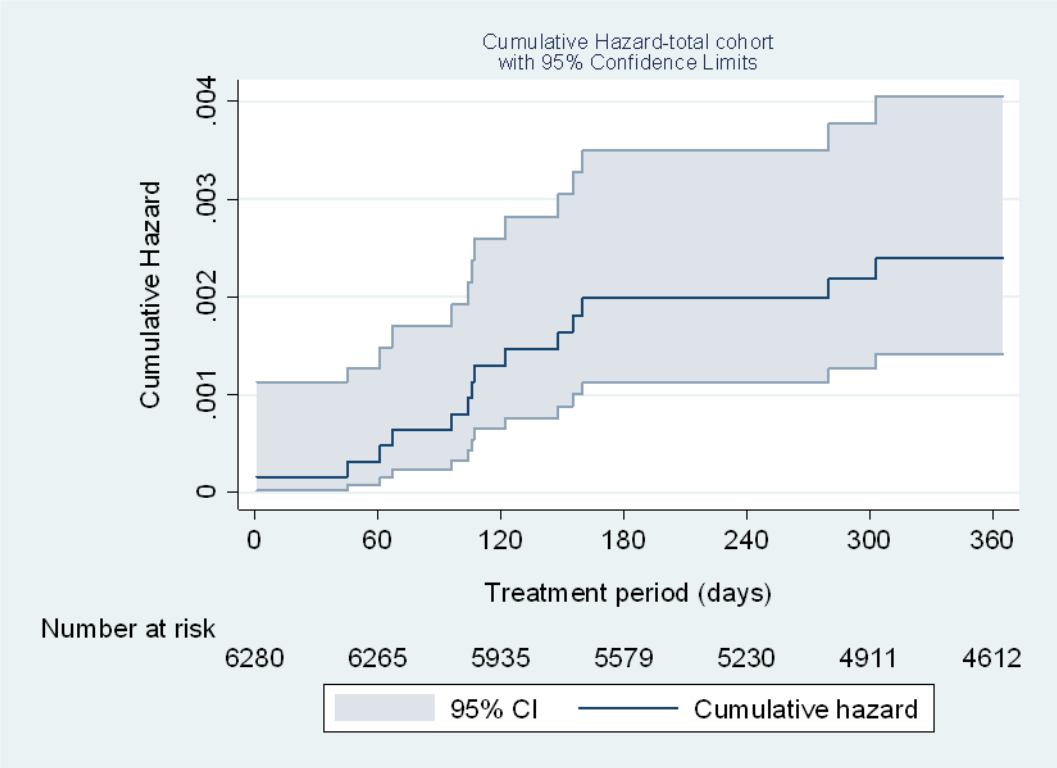
10.4.1.4 Hazard over time of acute pancreatitis

Time-to-first acute pancreatitis event analyses have been performed for the total cohort, exenatide naïve patients and previous Byetta® users to explore the risk of having the event over time. Results for events of acute pancreatitis occurring within the 12-month observation period (including the 10-week washout

period) are presented below and in Appendix 17. At least 10 reports were deemed necessary for modelling purposes.

Figure 8a provides the Nelson-Aalen cumulative hazard function and the life table for the 14 acute pancreatitis events in the total cohort. More than 50% of cases had occurred during the first 120 days of treatment. The smoothed hazard function is provided in 8b, which shows no clear pattern in the hazard function over time for the total cohort within this dataset.

Figure 8a. Nelson-Aalen cumulative hazard function and Life table for acute pancreatitis for the total cohort

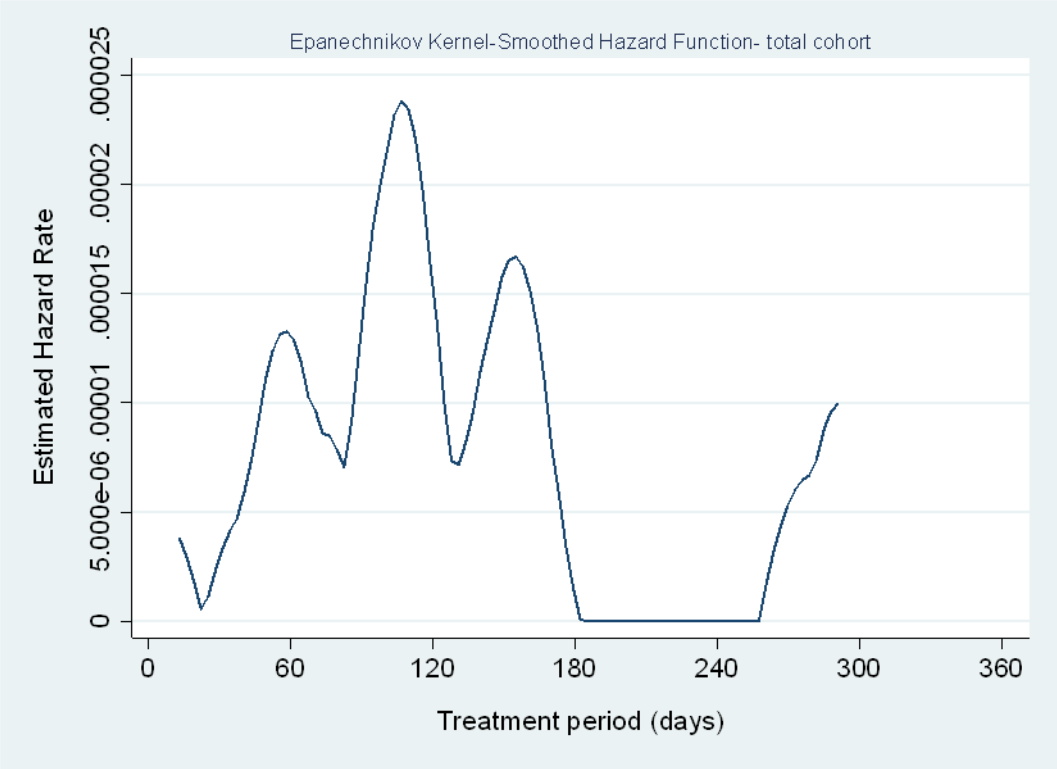


Interval		Total at risk at start	Events	Censored	Survival	Standard Error	95% CI	
0	30	6280[a]	1	9	0.9998	0.0002	0.9989	1.0000
30	60	6270	1	4	0.9997	0.0002	0.9987	0.9999
60	90	6265	2	75	0.9994	0.0003	0.9983	0.9998
90	120	6188	4	249	0.9987	0.0005	0.9974	0.9994
120	150	5935	2	174	0.9984	0.0005	0.9970	0.9991
150	180	5759	2	178	0.998	0.0006	0.9965	0.9989
180	210	5579	0	181	0.998	0.0006	0.9965	0.9989
210	240	5398	0	168	0.998	0.0006	0.9965	0.9989
240	270	5230	0	155	0.998	0.0006	0.9965	0.9989
270	300	5075	1	163	0.9978	0.0006	0.9962	0.9987

Interval		Total at risk at start	Events	Censored	Survival	Standard Error	95% CI	
300	330	4911	1	155	0.9976	0.0006	0.9959	0.9986
330	360	4755	0	143	0.9976	0.0006	0.9959	0.9986
360	390	4612	0	4612	0.9976	0.0006	0.9959	0.9986

[a] Exposure duration not available for 14 patients in the cohort, so these were excluded from time to event analyses.

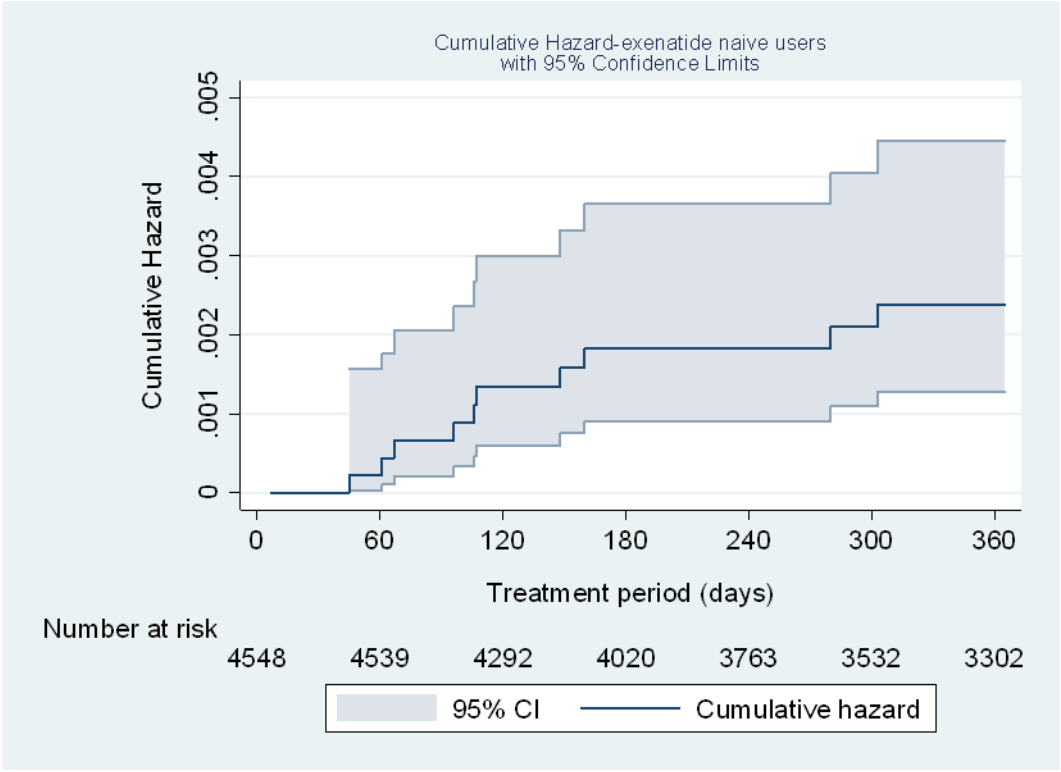
Figure 8b. Smoothed hazard function for acute pancreatitis for total cohort



Bandwidth=10. Only patients with a valid event or censor date have been included in the analysis.

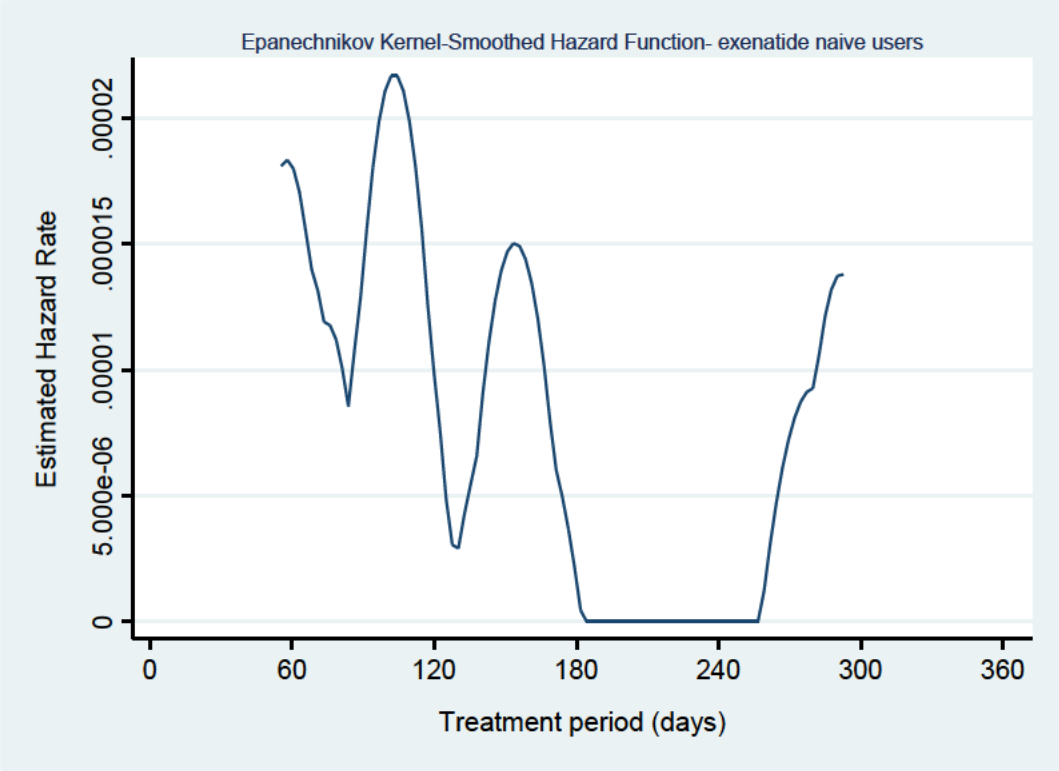
Figure 8c provides the Nelson-Aalen cumulative hazard function and the life table for the 10 acute pancreatitis events for exenatide naïve patients only. A total of 60% of cases had occurred during the first 120 days of treatment. The smoothed hazard function is provided in 8d, which suggests that there is no clear pattern in the hazard function over time for exenatide naïve patients within this dataset.

Figure 8c. Nelson-Aalen cumulative hazard function and Life table for acute pancreatitis for exenatide naïve patients



Interval		Total at risk at start	Events	Censored	Survival	Standard Error	95% CI	
0	30	4548	0	6	1	0	.	.
30	60	4542	1	2	0.9998	0.0002	0.9984	1.0000
60	90	4539	2	51	0.9993	0.0004	0.9979	0.9998
90	120	4486	3	191	0.9987	0.0005	0.9970	0.9994
120	150	4292	1	132	0.9984	0.0006	0.9967	0.9992
150	180	4159	1	138	0.9982	0.0006	0.9963	0.9991
180	210	4020	0	140	0.9982	0.0006	0.9963	0.9991
210	240	3880	0	117	0.9982	0.0006	0.9963	0.9991
240	270	3763	0	111	0.9982	0.0006	0.9963	0.9991
270	300	3652	1	119	0.9979	0.0007	0.9960	0.9989
300	330	3532	1	123	0.9976	0.0008	0.9955	0.9987
330	360	3408	0	106	0.9976	0.0008	0.9955	0.9987
360	390	3302	0	3302	0.9976	0.0008	0.9955	0.9987

Figure 8d. Smoothed hazard function for acute pancreatitis for exenatide naïve patients

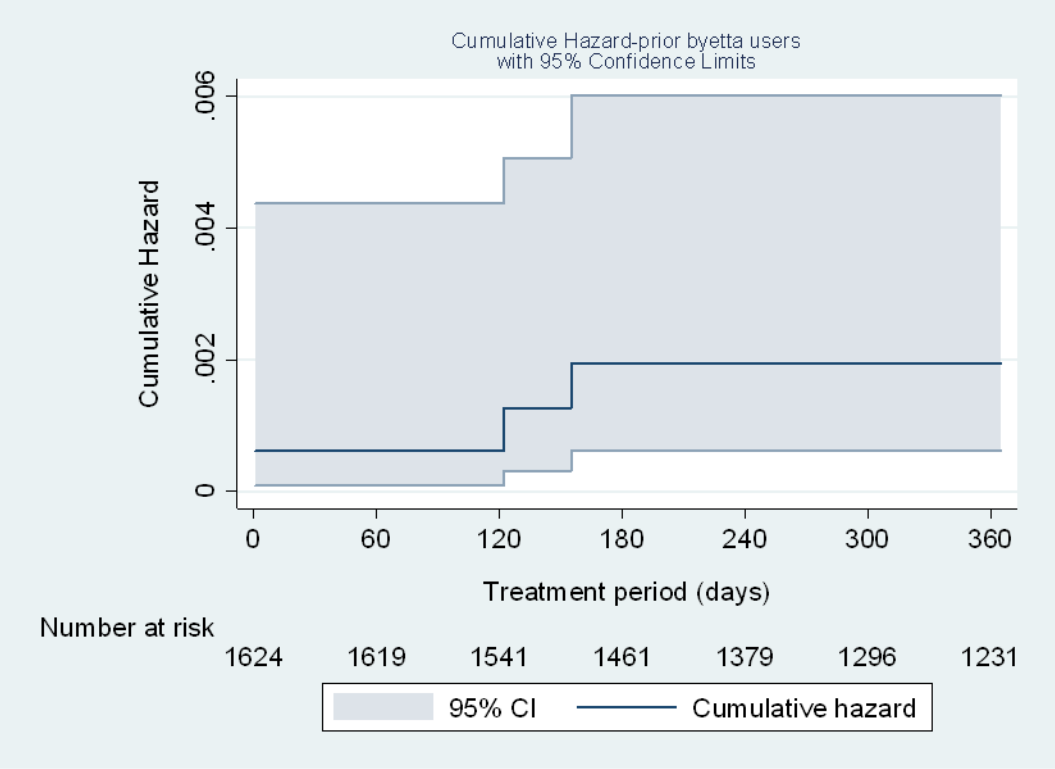


Bandwidth=10. Only patients with a valid event or censor date have been included in the analysis.

The Weibull parametric model plots for the total cohort and exenatide naïve patients are provided in Appendix 17 (Figures 1-2). Model parameters are also provided in Appendix 17 (Table 1), which confirm shape parameter coefficient less than one. The akaike information criteria (AIC) suggests that the exenatide naïve model fit the exenatide naïve patient data better than the total cohort model.

Figure 8e provides the Nelson-Aalen cumulative hazard function and the life table for the three acute pancreatitis events for previous Byetta® users only. All cases occurred during the first 180 days of treatment. Survival analysis was not performed for previous Byetta® users due to the small number of events.

Figure 8e. Nelson-Aalen cumulative hazard function and Life table for acute pancreatitis for previous Byetta® users



Interval		Total at risk at start	Events	Censored	Survival	Standard Error	95% CI	
0	30	1624	1	2	0.9994	0.0006	0.9956	0.9999
30	60	1621	0	2	0.9994	0.0006	0.9956	0.9999
60	90	1619	0	22	0.9994	0.0006	0.9956	0.9999
90	120	1597	0	56	0.9994	0.0006	0.9956	0.9999
120	150	1541	1	41	0.9987	0.0009	0.9949	0.9997
150	180	1499	1	37	0.9981	0.0011	0.9940	0.9994
180	210	1461	0	39	0.9981	0.0011	0.9940	0.9994
210	240	1422	0	43	0.9981	0.0011	0.9940	0.9994
240	270	1379	0	43	0.9981	0.0011	0.9940	0.9994
270	300	1336	0	40	0.9981	0.0011	0.9940	0.9994
300	330	1296	0	32	0.9981	0.0011	0.9940	0.9994
330	360	1264	0	33	0.9981	0.0011	0.9940	0.9994
360	390	1231	0	1231	0.9981	0.0011	0.9940	0.9994

The results for time-to-first acute pancreatitis events occurring within the 12-month observation period (excluding the 10-week washout period) have been provided in Appendix 18.

10.4.2 Other targeted outcomes

The following section relates to the following outcomes described in secondary and exploratory objectives:

- Pancreatic cancer

- Thyroid neoplasm
- Gallstones, biliary colic or cholecystitis
- Acute renal failure
- Allergic reactions (type 1 hypersensitivity)
- Cardiac events

Of note, a new event has been defined as first report of the event during treatment irrespective of a prior history. The above cases have been obtained using tick-box responses[19] and/or free text events meeting the respective definitions.

Free text events of acute renal failure were obtained using the pre-defined standardised MedDRA query (SMQ) of 'acute renal failure' from data on the 12-month questionnaire (e.g. from other events, reasons for stopping, immediate cause of deaths), cause of death supplementary questionnaire and potential acute renal failure supplementary questionnaires. Free text events of allergic reactions (type 1 hypersensitivity) were obtained using the pre-defined standardised MedDRA query (SMQ) of 'hypersensitivity' from data on the 12-month questionnaire (e.g. other events, reasons for stopping, immediate cause of deaths), cause of death supplementary questionnaire and potential hypersensitivity supplementary questionnaires. The following rules were applied for inclusion of these events in the main analysis:

- Narrow scope 'acute renal failure' or 'hypersensitivity' SMQ preferred terms were applied to free text events reported on the 12-month questionnaire.
- Broad scope 'acute renal failure' or 'hypersensitivity' SMQ preferred terms were applied for events reported on the 12-month questionnaire if supplementary information for the particular event was present. If only broad scope MedDRA preferred terms of 'acute renal failure' or 'hypersensitivity' were present on the 12-month questionnaire, narrow scope SMQ preferred terms of 'acute renal failure' or 'hypersensitivity' were applied to the corresponding supplementary questionnaire of that specific broad scope preferred term event. This scenario did not occur in the study, but we have summarised this rule for completeness.

Hypersensitivity events were further reviewed to exclude MedDRA preferred terms that related to type II-IV hypersensitivity; only preferred terms specific to type 1 reactions were included for this outcome[20].

For the targeted outcome of 'cardiac events', all free text events under the MedDRA system organ class 'Cardiac disorders' reported on the 12-month questionnaire and/or immediate cause of death on a cause of death supplementary questionnaire were included in the incidence estimates.

[19] For pancreatic cancer, thyroid neoplasm, and gallstones, biliary colic and cholecystitis only. Acute renal failure, allergic reactions (type 1 hypersensitivity) and cardiac events have been derived from free text only.

[20] Note, this excluded non-specific terms such as rash.

10.4.2.1 Pancreatic cancer and thyroid neoplasm

Cases of pancreatic cancer and thyroid neoplasm have been presented as counts only and summarised in the narrative below. It is important to note that this M-PEM study only characterises cases of pancreatic cancer and thyroid neoplasm; inference on the true incidence of these neoplasms cannot be made from the M-PEM cohort, as the study length has not been designed for this.

There were four cases (0.1%) of pancreatic cancer reported to occur on treatment with Bydureon® (plus the 10-week washout period) during the 12-month observation period. Two of these cases of pancreatic cancer were reported in exenatide naïve patients; one patient was a previous Byetta® user and for the remaining patient, previous Byetta® use was not known. For three of the four patients, information reported on the 12-month and supplementary questionnaire confirms that the patient had pancreatic cancer. For the remaining case, the GP reported that the patient had stopped Bydureon® due to 'possible pancreatic cancer risk', however, further information was not provided. The GP did not confirm pancreatic neoplasm as a diagnosis but instead reported this as a risk under reason for stopping Bydureon®. Individual case narratives for each of these patients have been provided in Appendix 19. These cases have also been summarised in a case series format in Table 31 of this report.

Furthermore, there was an additional case of pancreatic cancer but this was diagnosed more than 12 months after starting Bydureon® and beyond the 10-week washout period after stopping Bydureon®. This case has been described in Appendix 19[21].

There were no cases of thyroid neoplasm reported to occur on treatment with Bydureon® (plus the 10-week washout period) during the 12-month observation period. There were also no further reports of thyroid neoplasm beyond the 12-month observation period or the 10-week washout period after stopping Bydureon®[22].

10.4.2.2 Cumulative incidence of other targeted events

Table 27 below summarises the cumulative incidence (+ 95% CI) of the remaining other targeted events of 'gallstones, biliary colic or cholecystitis', 'acute renal failure', 'allergic reactions (type 1 hypersensitivity)' and 'cardiac events'. A patient may have experienced more than one type of event, thus counts are not mutually exclusive. Only events reported to occur on treatment with Bydureon® (plus the 10-week washout period) during the 12-month observation period have contributed to Table 27; events with a missing event date have been excluded.

There were 38 reports of gallstones, biliary colic or cholecystitis occurring during the 12-month observation period on treatment with Bydureon® (plus the 10-week washout period) (0.6%; 95% CI [0.4,

[21] There were also two reports of benign pancreatic neoplasms; for one patient the GP reported 'microcystic serous cystoadenoma of pancreas' and for the second patient the GP specified 'pancreatic cyst'. These have not been provided as case narratives in Appendix 19.

[22] There were however six patients for whom the GP had reported 'goitre'. Two of these were reported within the 12-month observation period and the remaining four were reported beyond the 12-month observation period. For five patients a 'multinodular goitre' was specified; for one of these patients the GP reported that a fine needle aspiration of the thyroid nodule originally revealed 'Thy3a papillary' and the patient underwent a hemithryoidectomy as a result. However, histology was of a multinodular goitre. For the remaining one patient the GP reported a 'simple euthyroid goitre'.

0.8]). The cumulative incidence was observed to be nearly twice as high for previous Byetta® users (0.9%; 95% CI [0.5, 1.4]) as compared to patients who were exenatide naïve (0.5%; 95% CI [0.3, 0.8]), however overlapping of the 95% CIs indicates no statistically significant difference between the two prior exenatide user groups.

A similar cumulative incidence was observed for hypersensitivity (type 1 reactions) for the total cohort (n=44; 0.7% (95% CI [0.5, 0.9])). Cumulative incidence for exenatide naïve patients was slightly lower than for previous Byetta® users (0.6% vs. 0.9%, respectively), however the 95% CIs overlapped indicating no statistically significant difference between the two prior exenatide user groups. Note, the preferred terms for hypersensitivity were selected according to the information available. For some cases it was not possible to definitively confirm whether the events were true type 1 hypersensitivity reactions; these events were however included as potential cases for completeness and a list of the reported narrow scope preferred terms within this event definition are provided in Appendix 20.

The cumulative incidence of acute renal failure was low; in the total cohort 29 patients were reported to have acute renal failure (0.5%; 95% CI [0.3, 0.7]). The cumulative incidence of acute renal failure for exenatide naïve patients and previous Byetta® users was similar (0.5% vs. 0.4%, respectively). A list of all the reported narrow scope preferred terms within the MedDRA SMQ of 'acute renal failure' has been provided in Appendix 20; of note, some preferred terms are non-specific (e.g. renal failure, renal impairment), however, these have been included in the counts according the rule base described in Section 10.4.2 above.

In total, there were 227 patients for whom an event was reported within the MedDRA system organ class 'Cardiac disorders' (3.6%; 95% CI [3.2, 4.1]). The cumulative incidence of cardiac events was slightly higher for previous Byetta® users (n=69; 4.2% (95% CI [3.3, 5.3])) as compared to exenatide naïve patients (n=154; 3.4% (95% CI [2.9, 3.9])), but with overlapping 95% CIs. A list of all the preferred terms reported within the MedDRA SOC of 'cardiac disorders' can be found in Appendix 20. The most commonly reported event was 'dizziness' followed by 'chest pain'. In terms of the most frequently reported clinical diagnoses, there were 26 events that fulfilled the criteria of acute coronary syndrome[23].

In addition, counts and cumulative incidence estimates of the above events reported on treatment with Bydureon® within the 12-month observation period but minus the 10-week washout have been provided in Appendix 21. Results demonstrate no significant differences with the results seen in Table 27.

Events where the event date was missing have also been reported as counts in Appendix 21.

In addition, a further sensitivity analysis was performed which reported events that occurred beyond the 12-month observation period and within the 10-week washout period (not stratified by plus/minus washout). These results are provided in Appendix 21.

[23] Preferred terms; 'acute coronary syndrome' n=4, 'acute myocardial infarction' n=10, 'myocardial infarction' n=10, 'angina unstable' n=2

Table 27. Number of patients reporting other targeted events during treatment with Bydureon® (plus the 10-week washout period) within the 12-month observation period and cumulative incidence estimates (+95% CI[a])

	Exenatide Naïve (N=4556)							Previous Byetta® users (N=1629)							Total Cohort (N=6294)						
Targeted Event-During Bydureon®	Yes			No		Non-response		Yes			No		Non-response		Yes			No		Non-response	
	n	%	95% CI	n	%	n	%	n	%	95% CI	N	%	n	%	n	%	95% CI	n	%	n	%
Gallstones, biliary colic or cholecyst-itis	24	0.5	0.3, 0.8	3525	77.4	1007	22.1	14	0.9	0.5, 1.4	1318	80.9	297	18.2	38	0.6	0.4, 0.8	4907	78.0	1349	21.4
Acute renal failure[b]	22	0.5	0.3, 0.7					6	0.4	0.1, 0.8					29	0.5	0.3, 0.7				
Allergic reactions (type 1 hyperse-nsitivity)[c]	29	0.6	0.4, 0.9					15	0.9	0.5, 1.5					44	0.7	0.5, 0.9				
Cardiac events[d]	154	3.4	2.9, 3.9					69	4.2	3.3, 5.3					227	3.6	3.2, 4.1				

[a] 95% CI calculated using Binomial exact

[b] Defined by MedDRA PTs within the Acute renal failure SMQ

[c] Defined by MedDRA PTs within the Hypersensitivity SMQ. Preferred terms relating to Type II-IV hypersensitivity have been excluded; only PTs relating to Type 1 reactions have been included for this outcome

[d] All cardiac events reported within the MedDRA System Organ Class (SOC) 'Cardiac disorders

10.4.2.3 Prior history of other targeted events

Prior history of other targeted events has been derived from pre-specified tick box responses only and therefore this analysis only applies to the event of 'gallstones, biliary colic or cholecystitis'. Note, the denominator in Table 28 is the number of patients with the event reported to occur on treatment (plus the 10-week washout period) during the 12-month observation period.

Of the 38 patients in total who had 'gallstones, biliary colic or cholecystitis', 15 patients (39.5%) had a prior history of one of these events. A prior history was more prevalent in the previous Byetta® user group as compared to exenatide naïve patients (42.9% vs. 37.5%, respectively).

Table 28. Number of patients with other targeted events during treatment with Bydureon® within the 12-month observation period with a prior history of the event being present at the start of treatment

Targeted Event- Prior to or present at start of Bydureon®	Exenatide Naïve (N[a]=24)						Previous Byetta® users (N[a]=14)						Total Cohort (N[a]=38)					
	Yes		No		Non-response		Yes		No		Non-response		Yes		No		Non-response	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Gallstones, biliary colic or cholecystitis[b]	9	37.5	13	54.2	2	8.3	6	42.9	7	50.0	1	7.1	15	39.5	20	52.6	3	7.9

[a] Number of patients with the event reported during Bydureon® (as reported in **Table 27**)

[b] Only the event of 'gallstones, biliary colic or cholecystitis' is applicable for this table. The events of 'acute renal failure', 'allergic reactions (type 1 hypersensitivity)', and 'cardiac events' are not applicable to this analysis as these events are not based on pre-specified tick box responses.

10.4.2.4 Incidence densities for other targeted events

Incidence densities were also calculated for the above targeted events of 'gallstones, biliary colic or cholecystitis', 'acute renal failure', 'allergic reactions (type 1 hypersensitivity)' and 'cardiac events' occurring on treatment (plus the 10-week washout period) during the 12-month observation period. These have been presented in Table 29.

Within the total cohort, the composite event of 'gallstones, biliary colic or cholecystitis' had an ID_A of 0.7 across the observation period. The ID_A for this event was twice as high for previous Byetta® users as compared to exenatide naïve patients (1.1 vs. 0.5, respectively).

The ID_A for 'acute renal failure' in the total cohort was 0.4 and was similar after stratifying by prior exenatide use. For 'allergic reactions (type 1 hypersensitivity)', the ID_A in the total cohort was 0.6; for exenatide naïve patients only it was 0.6 and for previous Byetta® users the ID_A was 0.8. The ID_A for 'cardiac events' was the highest at 3.3 for the total cohort. After stratifying by prior exenatide use, the ID_A was greater for previous Byetta® users (3.8) than exenatide naïve patients (3.1).

Table 29. Incidence densities of other targeted events[a] reported on treatment, by two-month period and for total 12-month period

Event	N	N	N	N	N	N	ID	ID	ID	ID	ID	ID	NA	IDA
Month	0-2	2-4	4-6	6-8	8-10	10-12	0-2	2-4	4-6	6-8	8-10	10-12		
Exenatide naïve														
Gallstones, biliary colic or cholecystitis	3	1	9	3	3	5	0.3	0.1	1.1	0.4	0.4	0.7	24	0.5
Acute renal failure	5	3	3	5	1	5	0.6	0.3	0.4	0.6	0.1	0.7	22	0.4
Allergic reactions (type 1 hypersensitivity)	5	6	3	5	7	3	0.6	0.7	0.4	0.6	1.0	0.4	29	0.6
Cardiac events	35	22	24	32	18	23	3.9	2.5	2.9	4.1	2.5	3.4	154	3.1
Previous Byetta® users														
Gallstones, biliary colic or cholecystitis	7	0	3	2	2	0	2.2	0.0	1.0	0.7	0.7	0.0	14	1.1
Acute renal failure	2	1	1	0	0	2	0.6	0.3	0.3	0.0	0.0	0.8	6	0.3
Allergic reactions (type 1 hypersensitivity)	5	4	4	1	1	0	1.5	1.3	1.3	0.4	0.4	0.0	15	0.8
Cardiac events	18	14	14	12	4	7	5.5	4.4	4.7	4.2	1.5	2.8	69	3.8
Total cohort														
Gallstones, biliary colic or cholecystitis	10	1	12	5	5	5	0.8	0.1	1.0	0.5	0.5	0.5	38	0.7
Acute renal failure	7	4	5	5	1	7	0.6	0.3	0.4	0.5	0.1	0.7	29	0.4
Allergic reactions (type 1 hypersensitivity)	10	10	7	6	8	3	0.8	0.8	0.6	0.6	0.8	0.3	44	0.6
Cardiac events	53	36	41	45	22	30	4.2	2.9	3.6	4.2	2.2	3.2	227	3.3

N=Number of Events, ID=Incidence Density; N_A = Number of first reports of an event during all 12-months observation; ID_A = ID for all 12-months observation

In addition to the above, analysis of M-PEM data for purposes of signal detection includes calculating the difference in incidence densities for targeted events between different time periods. For each event, the arithmetic difference between two time periods (e.g. ID_{0-2} and ID_{2-4}) has been calculated with a 95% CI to examine the null hypothesis that the rate of the event is not increasing or decreasing between the two time periods. Table 30 presents ID differences for other targeted events; these results have been summarised below.

For the event of 'gallstones, biliary colic or cholecystitis' within the total cohort, ID differences comparing ID_{2-4}, ID_{6-8}, ID_{8-10}, ID_{10-12} with the reference time period of ID_{0-2} were all positive. However, only the ID_{2-4} result (ID difference=0.7; 95% CI [0.2, 1.2]) was significant with the exclusion of the value zero from the 95% CI. This result suggests that rate of 'gallstones, biliary colic or cholecystitis' in the first two months of treatment with Bydureon® was significantly greater than the rate in months two to four. After stratifying by prior exenatide use, significant results were only observed for previous Byetta® users for ID_{2-4} (ID difference=2.2; 95% CI [0.6, 3.8]) and ID_{10-12} (ID difference=2.2; 95% CI [0.6, 3.8]). This suggests that for previous Byetta® users, the rate of 'gallstones, biliary colic or cholecystitis' in the first two months was significantly greater than the rate in months two to four and 10 to 12. Given the wide confidence interval and the small sample size of previous Byetta® users, it is possible this finding is due to chance. All the remaining 95% CIs in both previous Byetta® users and exenatide naïve patients included the null value of zero and thus results were inconclusive. Results may suggest a potential signal for early onset of events of 'gallstones, biliary colic or cholecystitis', however, there is no clear and consistent pattern of an increasing or decreasing rate indicating any clinical significance. In addition, it is possible that the high rate in the first two months can be attributed to a pre-existing condition. For 50% of these events in the first two months of treatment, a prior history of these events was reported (n=5).

Within the total cohort, for the event of 'acute renal failure', a statistically significant positive ID difference was observed comparing ID_{8-10} with the reference time period of ID_{0-2} (ID difference=0.5; 95% CI [0.0, 0.9]). This suggests that the rate of 'acute renal failure' was greater in the first two months as compared to months eight to ten, however these findings were not observed for the remaining two monthly time periods for the total cohort as the 95% CIs included the null value of zero. It is possible this finding is due to chance, given that the lower end of the confidence interval is close to the null value. In addition, no other statistically significant ID differences were observed for 'acute renal failure' events after stratifying by prior exenatide use. These results suggest that there were no clear signals generated for 'acute renal failure' occurring shortly after starting treatment with Bydureon® or for events with a delayed onset.

For the event of 'allergic reactions (type 1 hypersensitivity)', no statistically significant results were observed within the total cohort or after stratification for the previous exenatide use group. However a significant result was observed for previous Byetta® users for ID_{10-12} (ID difference=1.5; 95% CI [0.2, 2.9]). All the remaining 95% CIs for ID differences were not statistically significant. This suggests that the rate of 'allergic reactions (type 1 hypersensitivity)' was not increasing or decreasing between time periods. Given the wide

confidence interval and the small sample size of previous Byetta® users, it is possible that this finding is due to chance.

Within the total cohort, for 'cardiac events', positive ID differences were observed for all two monthly time periods (ID_{2-12}) as compared to the reference time period (ID_{0-2}). However, a statistically significant result was only observed for ID_{8-10} (ID difference=2.1; 95% CI [0.6, 3.5]), suggesting that the rate of 'cardiac events' was higher in the first two months as compared to months eight to ten. After stratifying by prior exenatide use, significant results were only observed for previous Byetta® users; the rate of 'cardiac events' in the reference time period was approximately four times greater than the rate in months eight to ten (ID difference=4.1; 95% CI [1.1, 7.0]) but event counts were low. All the remaining 95% CIs in both previous Byetta® users and exenatide naïve patients included the null value of zero, thus results were inconclusive. Given the wide confidence interval and the small sample size of previous Byetta® users, it is possible this finding is due to chance.

Table 30. Incidence density (ID) differences for other targeted events reported on treatment

Event	Time period	Patient-months exposure	No of events	ID	ID difference[a]	95% CI
Exenatide naïve						
Gallstones, biliary colic or cholecystitis	Month 0-2	9087.7	3	0.3	n/a	n/a
	Month 2-4	8906.9	1	0.1	0.2	-0.2, 0.7
	Month 4-6	8314.7	9	1.1	-0.8	-1.6, 0.0
	Month 6-8	7768.9	3	0.4	-0.1	-0.6, 0.1
	Month 8-10	7303.4	3	0.4	-0.1	-0.7, 0.5
	Month 10-12	6708.1	5	0.7	-0.4	-1.2, 0.3
Acute renal failure	Month 0-2	9087.7	5	0.6	n/a	n/a
	Month 2-4	8906.9	3	0.3	0.2	-0.4, 0.8
	Month 4-6	8314.7	3	0.4	0.2	-0.4, 0.8
	Month 6-8	7768.9	5	0.6	-0.1	-0.8, 0.6
	Month 8-10	7303.4	1	0.1	0.4	-0.1, 1.0
	Month 10-12	6708.1	5	0.7	-0.2	-1.0, 0.6
Allergic reactions (type 1 hypersensitivity)	Month 0-2	9087.7	5	0.6	n/a	n/a
	Month 2-4	8906.9	6	0.7	-0.1	-0.8, 0.6
	Month 4-6	8314.7	3	0.4	0.2	-0.4, 0.8
	Month 6-8	7768.9	5	0.6	-0.1	-0.8, 0.6
	Month 8-10	7303.4	7	1.0	-0.4	-1.3, 0.5
	Month 10-12	6708.1	3	0.4	0.1	-0.6, 0.8
Cardiac events	Month 0-2	9087.7	35	3.9	n/a	n/a
	Month 2-4	8906.9	22	2.5	1.4	-0.3, 3.0
	Month 4-6	8314.7	24	2.9	1.0	-0.8, 2.7
	Month 6-8	7768.9	32	4.1	-0.3	-2.2, 1.6
	Month 8-10	7303.4	18	2.5	1.4	-0.3, 3.1
	Month 10-12	6708.1	23	3.4	0.4	-1.5, 2.3
Previous Byetta® users						
Gallstones, biliary colic or cholecystitis	Month 0-2	3244.6	7	2.2	n/a	n/a
	Month 2-4	3178.0	0	0.0	2.2	0.6, 3.8

Event	Time period	Patient-months exposure	No of events	ID	ID difference[a]	95% CI
	Month 4-6	2999.0	3	1.0	1.2	-0.8, 3.1
	Month 6-8	2840.1	2	0.7	1.5	-0.4, 3.3
	Month 8-10	2673.6	2	0.7	1.4	-0.5, 3.3
	Month 10-12	2480.6	0	0.0	2.2	0.6, 3.8
	Month 0-2	3244.6	2	0.6	n/a	n/a
	Month 2-4	3178.0	1	0.3	0.3	-0.8, 1.4
Acute renal failure	Month 4-6	2999.0	1	0.3	0.3	-0.8, 1.4
	Month 6-8	2840.1	0	0.0	0.6	-0.2, 1.5
	Month 8-10	2673.6	0	0.0	0.6	-0.2, 1.5
	Month 10-12	2480.6	2	0.8	-0.2	-1.6, 1.2
	Month 0-2	3244.6	5	1.5	n/a	n/a
	Month 2-4	3178.0	4	1.3	0.3	-1.5, 2.1
Allergic reactions (type 1 hypersensitivity)	Month 4-6	2999.0	4	1.3	0.2	-1.7, 2.1
	Month 6-8	2840.1	1	0.4	1.2	-0.3, 2.7
	Month 8-10	2673.6	1	0.4	1.2	-0.4, 2.7
	Month 10-12	2480.6	0	0.0	1.5	0.2, 2.9
	Month 0-2	3244.6	18	5.5	n/a	n/a
	Month 2-4	3178.0	14	4.4	1.1	-2.3, 4.6
Cardiac events	Month 4-6	2999.0	14	4.7	0.9	-2.7, 4.4
	Month 6-8	2840.1	12	4.2	1.3	-2.2, 4.8
	Month 8-10	2673.6	4	1.5	4.1	1.1, 7.0
	Month 10-12	2480.6	7	2.8	2.7	-0.6, 6.0
Total cohort						
	Month 0-2	12547.2	10	0.8	n/a	n/a
	Month 2-4	12295.6	1	0.1	0.7	0.2, 1.2
Gallstones, biliary colic or cholecystitis	Month 4-6	11517.1	12	1.0	-0.2	-1.0, 0.5
	Month 6-8	10798.7	5	0.5	0.3	-0.3, 1.0
	Month 8-10	10148.8	5	0.5	0.3	-0.4, 1.0
	Month 10-12	9350.1	5	0.5	0.3	-0.4, 0.9
Acute renal failure	Month 0-2	12547.2	7	0.6	n/a	n/a

Event	Time period	Patient-months exposure	No of events	ID	ID difference[a]	95% CI
Allergic reactions (type 1 hypersensitivity)	Month 2-4	12295.6	4	0.3	0.2	-0.3, 0.8
	Month 4-6	11517.1	5	0.4	0.1	-0.4, 0.7
	Month 6-8	10798.7	5	0.5	0.1	-0.5, 0.7
	Month 8-10	10148.8	1	0.1	0.5	0.0, 0.9
	Month 10-12	9350.1	7	0.7	-0.2	-0.9, 0.5
	Month 0-2	12547.2	10	0.8	n/a	n/a
	Month 2-4	12295.6	10	0.8	0.0	-0.7, 0.7
	Month 4-6	11517.1	7	0.6	0.2	-0.5, 0.9
	Month 6-8	10798.7	6	0.6	0.2	-0.4, 0.9
	Month 8-10	10148.8	8	0.8	0.0	-0.7, 0.7
	Month 10-12	9350.1	3	0.3	0.5	0.0, 1.1
Cardiac events	Month 0-2	12547.2	53	4.2	n/a	n/a
	Month 2-4	12295.6	36	2.9	1.3	-0.2, 2.8
	Month 4-6	11517.1	41	3.6	0.7	-0.1, 2.2
	Month 6-8	10798.7	45	4.2	0.1	-1.6, 1.7
	Month 8-10	10148.8	22	2.2	2.1	0.6, 3.5
	Month 10-12	9350.1	30	3.2	1.0	-0.6, 2.6

[a] Reference period = month 0-2

10.4.3 Qualitative case series analysis for selected events

The following section relates to the exploratory objective, i.e. to describe the characteristics of selected important identified and potential risks in the first 12-months after starting treatment, which are:

- Acute pancreatitis
- Pancreatic cancer[24]
- Thyroid neoplasm

Information for qualitative case series analyses (Table 31) has been derived from the 12-month questionnaire and supplementary questionnaires, where available. Quantitative analyses on these events has already been provided in Section 10.4.1 and 10.4.2.1 of this report.

In total, 14 events of acute pancreatitis were considered to occur during treatment with Bydureon® (plus the 10-week washout period) within the 12-month study observation period (Table 31). Ten of these events were reported in exenatide naïve patients, three in previous Byetta® users and for one patient prior use of Byetta® was not known. The overall median (IQR) time to event was 106.5 (67.0, 155.0) days; median exposure duration-time at risk was slightly longer for previous Byetta® users as compared to exenatide naïve patients (122.0 days vs. 106.5 days, respectively). For 12 patients, Bydureon® was stopped as a result of the acute pancreatitis and for one patient a fatal outcome was reported. Quantitative analyses for these events can be found in Section 10.4.1 of this report and case narratives for each event of acute pancreatitis can be found in Appendix 15.

There were only four patients reported to have a diagnosis of pancreatic cancer during treatment with Bydureon® (plus the 10-week washout period) within the 12-month observation period (Table 31). Two of these cases were reported in exenatide naïve patients, one in a previous Byetta® user and for the remaining one patient prior use of Byetta® was not known. The overall median (IQR) time to event was 146.5 (72.5, 199.0) days. Three of the four cases of pancreatic cancer resulted in a fatal outcome. Further information on these cases can be found in Section 10.4.2.1 of this report and individual case narratives are provided in Appendix 19.

As can be seen in Table 31, there were no cases of thyroid neoplasm reported during the 12-month observation period.

[24] It is important to note that this M-PEM study only characterises cases of pancreatic cancer and thyroid neoplasm that are reported during the 12-month observation period. The study cannot provide any inference on the incidence of these neoplasms in the M-PEM cohort, as the study length and size has not been designed for this.

Table 31. Qualitative case series summary for selected events of acute pancreatitis, pancreatic cancer and thyroid neoplasm

Event	Exenatide naïve			Previous Byetta® users			Total cohort		
	Acute pancreatitis	Pancreatic cancer	Thyroid neoplasm	Acute pancreatitis	Pancreatic cancer	Thyroid neoplasm	Acute pancreatitis	Pancreatic cancer	Thyroid neoplasm
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Events during observation irrespective of treatment status (T)	10	2	0	3	1	0	14	4	0
Events during treatment only (N/T, %)	10 (100.0)	2 (100.0)	0 (0.0)	3 (100.0)	1 (100.0)	0 (0.0)	14 (100.0)	4 (100.0)	0 (0.0)
Follow up response (n/N, %)	9 (90.0)	1 (50.0)	0 (0.0)	3 (100.0)	0 (0.0)	0 (0.0)	13 (92.9)	2 (50.0)	0 (0.0)
Sex (n/N, %)									
Male	10 (100.0)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (78.6)	3 (75.0)	0 (0.0)
Female	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)	1 (100.0)	0 (0.0)	3 (21.4)	1 (25.0)	0 (0.0)
Age (years)									
Median (IQR)	54.5 (52, 62)	61, 72	0 (0.0)	60 (41, 75)	73	0 (0.0)	54.5 (52, 62)	68.5 (65, 72)	0 (0.0)
Dose at event (n/N, %)									
2mg once weekly	9 (90.0)	1 (50.0)	0 (0.0)	3 (100.0)	1 (100.0)	0 (0.0)	12 (85.7)	2 (50.0)	0 (0.0)
Other	1 (10.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2[a] (14.3)	2[b] (50.0)	0 (0.0)
Exposure duration-time at risk (days)[c]									
Median (IQR)	106.5 (67, 160)	95, 200	0 (0.0)	122 (1, 155)	198	0 (0.0)	106.5 (67, 155)	146.5 (72.5, 199)	0 (0.0)
Event as reason for stopping[d] (n/N, %)	8 (80.0)	0 (0.0)	0 (0.0)	3 (100.0)	1 (100.0)	0 (0.0)	12 (85.7)	1 (25.0)	0 (0.0)

Event	Exenatide naïve			Previous Byetta® users			Total cohort		
	Acute pancreatitis	Pancreatic cancer	Thyroid neoplasm	Acute pancreatitis	Pancreatic cancer	Thyroid neoplasm	Acute pancreatitis	Pancreatic cancer	Thyroid neoplasm
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Event had fatal outcome (n/N, %)	1 (10.0)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	3 (75.0)	0 (0.0)
Prior history (or present at start of treatment) (n/N, %)	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (14.3)	0 (0.0)	0 (0.0)
Co-morbidities (n/N, %)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)[e]	0 (0.0)	0 (0.0)
Risk factors (n/N, %)	8 (80.0)	2 (100.0)	0 (0.0)	3 (100.0)	0 (0.0)	0 (0.0)	12 (85.7)[f]	2[g] (50.0)	0 (0.0)
Concomitant meds prescribed at event(n/N, %)	10 (100.0)	2 (100.0)	0 (0.0)	3 (100.0)	1 (100.0)	0 (0.0)	14 (100.0)[h]	4 (100.0)[i]	0 (0.0)

[a] Not specified (n=2)
[b] 'As directed' (n=1), not specified (n=1)
[c] Derived from index date, exit date and event date (days)
[d] Derived from information on treatment cessation
[e] Co-morbidities reported by the GP at index. Hypertriglyceridaemia (n=1)
[f] Risk factors as reported by the GP; Excessive alcohol consumption (n=11) and smoking (n=5), gallstones, biliary colic or cholecystitis (n=11)
[g] Risk factors as reported by the GP; Smoking history (n=2)
[h] Thyroxine (n=1), omeprazole (n=4), paracetamol (n=5), metformin (n=9), sulphonylurea (n=1), bisoprolol (n=2), finasteride (n=1), perindopril (n=2), simvastatin (n=2), tamsulosin (n=1), warfarin (n=1), nicotine (n=1), quinidine sulphate (n=1), aspirin (n=3), diltiazem (n=1), atorvastatin (n=5), fostair (n=1), salbutamol (n=1), fluoxetine (n=2), gliclazide (n=5), tostran (n=1), ramipiril (n=3), tramadol (n=1), topiramate (n=1), analgesics (n=1), levemir (n=1), novorapid (n=1), lisinopril (n=1), amytriptyline (n=1), lantus (n=1), desunin (n=1), olanzapine (n=1), movicol (n=1), codeine (n=1), co-amoxilav (n=1)
[i] Insulatard (n=1), meformin (n=4), gliclazide (n=2), diazepam (n=1), glyceryl trinitate (n=1), paracetamol (n=1), lansoprazole (n=1), adcal-d3 (n=1), amlodipine (n=2), aspirin (n=2), atenolol (n=1), bendroflumethiazide (n=1), doxazosin (n=2), fluvastatin (n=1), thyroxine sodium (n=1), naproxen (n=1), sulphonylurea (n=1), allopurinol (n=1), co-proxamol (n=1), pravastatin (n=1), humulin m3 (n=1), digoxin (n=1), indapamide (n=1), enalapril (n=1), bisoprolol (n=1), atorvastatin (n=1), furosemide (n=1), warfarin (n=1), hydromol (n=1)

10.4.4 General Event Surveillance

In addition to the selected events of interest which have been described above, GPs were also asked to specify any other events recorded in the patient's medical charts on treatment with Bydureon® or within the first three months after stopping treatment.

The top 10 events reported to occur on treatment (plus the 10-week washout period) within the 12-month observation period specified as free text on the 12-month questionnaires are presented in **Table 32** according to MedDRA Higher level terms[25]. Note, the general event analysis includes events which may have been presented in other sections of the report (e.g. reasons for stopping, target events) but excludes events reported in the death section. The complete list of all events have been provided in Appendix 22a with the MedDRA preferred terms presented within each higher level term. Note, events have been reported as specified by the GP on the 12-month questionnaire. Some of these events are simply records of healthcare encounters with the GP (e.g. death of a relative) and so the list needs to be interpreted with caution. In addition, more than one event could be reported for an individual patient, so counts are not mutually exclusive.

In total, 8572 counts of 577 different general events (at higher level term level) have been reported on treatment (plus the 10-week washout period) during the 12-month observation period (Appendix 22a). The most frequently reported higher level term in the total cohort was 'therapeutic and non-therapeutic responses' (n=493, 7.8% of cohort) (Table 32). In keeping with the known safety profile of Bydureon®, 'nausea and vomiting symptoms' were also frequently reported (n=343, 5.4% of cohort); the incidence was higher for exenatide naïve patients than previous Byetta® users (6.0% vs. 4.1%, respectively). 'Injection site reactions' were also very common (n=187, 3.0% of cohort) and more frequent for exenatide naïve patients (3.2%) as compared to previous Byetta® users (2.4%).

Of note, 'amylase increased' or 'amylase abnormal' were reported in a total of eight patients (0.1%) on treatment during the 12-month observation period (Appendix 22a). General events also included diabetic complications such as 'hypoglycaemia' (n=36; 0.6%), 'diabetic ketoacidosis' (n=4; 0.1%)) and 'ketoacidosis' (n=1). Events synonymous with hepatic steatosis were also commonly reported ('hepatic steatosis' n=35, 'non-alcoholic fatty liver' n=6, non-alcoholic steatohepatitis' n=5).

Table 32. Ten most frequently reported events (1st reports) per major system organ class and higher level terms reported during treatment (plus the 10-week washout period) within the 12-month observation period

System Organ Class	Higher Level Term	n	Cumulative incidence (%)
Exenatide Naïve (N= 4556)			
General disorders and administration site conditions	Therapeutic and nontherapeutic responses	373	8.2

[25] Where MedDRA terms are not applicable, events have been reported according to the reported event term (RET).

System Organ Class	Higher Level Term	n	Cumulative incidence (%)
Surgical and medical procedures	Therapeutic procedures NEC	292	6.4
Gastrointestinal disorders	Nausea and vomiting symptoms	273	6.0
General disorders and administration site conditions	General signs and symptoms NEC	233	5.1
Investigations	Carbohydrate tolerance analyses (incl diabetes)	194	4.3
Musculoskeletal and connective tissue disorders	Musculoskeletal and connective tissue pain and discomfort	172	3.8
Investigations	Physical examination procedures and organ system status	159	3.5
Gastrointestinal disorders	Diarrhoea (excl infective)	150	3.3
General disorders and administration site conditions	Injection site reactions	145	3.2
Social circumstances	Social issues NEC	123	2.7
Previous Byetta® user (N=1629)			
General disorders and administration site conditions	Therapeutic and nontherapeutic responses	110	6.8
Surgical and medical procedures	Therapeutic procedures NEC	85	5.2
General disorders and administration site conditions	General signs and symptoms NEC	79	4.8
Gastrointestinal disorders	Nausea and vomiting symptoms	67	4.1
Musculoskeletal and connective tissue disorders	Musculoskeletal and connective tissue pain and discomfort	58	3.6
Investigations	Physical examination procedures and organ system status	47	2.9
Investigations	Carbohydrate tolerance analyses (incl diabetes)	47	2.9
Gastrointestinal disorders	Diarrhoea (excl infective)	40	2.5
General disorders and administration site conditions	Injection site reactions	39	2.4
Infections and infestations	Lower respiratory tract and lung infections	38	2.3
Total cohort (N=6294)			
General disorders and administration site conditions	Therapeutic and nontherapeutic responses	493	7.8
Surgical and medical procedures	Therapeutic procedures NEC	387	6.1
Gastrointestinal disorders	Nausea and vomiting symptoms	343	5.4
General disorders and administration site conditions	General signs and symptoms NEC	315	5.0
Investigations	Carbohydrate tolerance analyses (incl diabetes)	244	3.9
Musculoskeletal and connective tissue disorders	Musculoskeletal and connective tissue pain and discomfort	234	3.7
Investigations	Physical examination procedures and organ system status	210	3.3
Gastrointestinal disorders	Diarrhoea (excl infective)	193	3.1
General disorders and administration site conditions	Injection site reactions	187	3.0
Social circumstances	Social issues NEC	157	2.5

Appendix 22b also provides cumulative incidence estimates for all general events reported to occur on treatment within the 12-month observation period but excluding the 10-week washout period. In addition,

Appendix 22c lists all reported general events occurring within the 12-month observation period between the 10-week washout period and 12-weeks observation post stopping (i.e., a two-week window).

Any additional general events reported to occur on treatment beyond the 12-month observation period have also been provided in Appendix 22d. This analysis includes the 10-week washout period and no further stratification including/excluding the washout period has been performed.

Finally, Appendix 22e includes all reported general events beyond the 12-month observation period between the 10-week washout period and 12 weeks observation after stopping (i.e., a two-week window).

10.4.5 Assessment of Selected Events

All 12-month questionnaires were evaluated for selected events of interests (RAIDAR events) as listed in the protocol (Appendix 1). As described throughout this report, any free text events reported by the GP were coded to the MedDRA dictionary and all events occurring on treatment within the 12-month observation period (plus the 10-week washout period) were analysed for RAIDAR events[26]. These events were identified for further evaluation using a pre-defined list of MedDRA preferred terms[27] which were synonymous with and/or met the definition criteria of each RAIDAR event. The section below provides an assessment of selected events of interest (RAIDAR events) listed in the protocol (Appendix 1) occurring on treatment (plus the 10-week washout period) within the 12-month observation period. The assessment utilised all the relevant information on the 12-month questionnaire and supplementary questionnaires, where available. For events where counts were low, these results were presented as narratives.

Acute renal failure

There were 29 events of 'acute renal failure' as defined by the narrow scope MedDRA SMQ and reported in Section 10.4.2 of this report. These cases have been summarised in Table 33 below. Median time to onset was 164 days for the total cohort. After stratifying by previous exenatide use, median time to onset was twice as long for exenatide naïve patients as compared to previous Byetta® users (187.5 days vs. 92 days, respectively). For 15 patients, the event was reported as a reason for stopping Bydureon®, however a positive de-challenge was only reported for three patients. There were no reports of a fatal outcome.

[26] In addition, a few events included in the EMA designated medical events (DME) list but not included in the DRSU RAIDAR list but considered relevant were evaluated (e.g. drug-induced liver injury).

[27] List compiled by the DSRU for each RAIDAR event.

Table 33. Case series relatedness assessments of acute renal failure

Acute renal failure		Exenatide Naïve n (%)	Previous Byetta® users n (%)	Total cohort n (%)
Events during treatment	*(N)*	22	6	29
Sex				
Male	*(n/N; %)*	13 (59.1)	3 (50.0)	16 (55.2)
Female	*(n/N; %)*	9 (40.9)	3 (50.0)	13 (44.8)
Age (years) Median (IQR)		69.5 (62, 73)	57 (56, 59)	67 (57, 72)
Dose at event (n/N, %)				
2mg once weekly	*(n/N; %)*	21 (95.4)	6 (100.0)	28 (96.5)
Unspecified[a]	*(n/N; %)*	1 (4.6)	0	1 (3.5)
Exposure duration- time at risk (days)[b]				
Median (IQR)		187.5 (62, 282)	92 (48, 303)	164 (62, 282)
Event as reason for stopping[c]	*(n/N; %)*	11 (50.0)	3 (50.0)	15 (51.7)
Positive de-challenge[d]	*(n/N; %)*	2 (9.1)	1 (16.7)	3[e] (10.3)
Positive re-challenge[d]	*(n/N; %)*	0	0	0
Event had fatal outcome	*(n/N; %)*	0	0	0
Prior history of same event (or present at start of treatment)	*(n/N; %)*	1 (4.6)	1 (16.7)	2 (6.9)
Co-morbidities[f]	(n/N, %)	11 (50.0)	2 (33.3)	14 (48.3)
Risk factors[g]	*(n/N; %)*	5 (22.7)	0 (0.0)	6 (20.7)
Concomitant meds prescribed at event[h]	*(n/N; %)*	10 (45.5)	1 (16.7)	12 (41.4)

*information available from 12-month, and supplementary questionnaires; IQR: Interquartile range; [a] No dose at index or event specified; [b] derived from index date, exit date and event date (days); [c] derived from information on treatment cessation; [d] derived from information on outcome relating to treatment cessation; [e] case narratives for positive -re-challenge to be provided in an appendix; [f] morbidities at index date and during treatment (Chronic kidney disease (n=3), glomerular filtration rate abnormal (n=2)), glomerular filtration rate decreased (n=1), renal impairment (n=1), IgA nephropathy (n=1) and nephritis (n=1), renal stones (n=1)); [g] as reported on the supplementary questionnaire by the GP in response to a question on risk factors (Infected leg ulcers (n=1), sepsis (n=2), dehydration (n=1), diarrrhoea (n=1), vomiting (n=1), e.coli bacteria (n=1)); [h] (metformin n=7, amlodipine n=6, aspirin n=5, atorvastatin n=5, gliclazide n=5, doxazosin n=4, simvastatin n=4, bendroflumethiazide n=3, bisoprolol n=3, candesartan n=3, furosemide n=3, omeprazole n=3, amitriptyline n=2, clopidogrel n=2, co-codamol n=2, docusate sodium n=2, gabapentin n=2, insulin lispro n=2, lisinopril n=2, paracetamol n=2, ramipril n=2 and 1 report each of: allopurinol, atenolol, cavilon durable barrier cream, codeine, codeine phosphate, dihydrocodeine, diprobase, dothiepin, enalapril, ferrous sulphate, fluoxetine, glimepiride, glucose, glyceryl trinitrate, humalog, humulin m3, hydrocortisone/ clotrimazole, indapamide, insulin, insulin degludec, insulin glargine, irbesartan, ivabradine, lansoprazole, liraglutide, monomil xl, nefopam, oxybutynin, perindopril, pravastatin, proshield foam & spray skin cleanser, proshield plus skin protectant, quinine sulphate, ranitidine, repaglinide, senna, sildenafil, sitagliptin, sukkarto, thyroxine, white soft paraffin/ liquid paraffin, zomorph)

Anaphylactic reaction (n=1)

One event of anaphylactic reaction was reported in male patient in his forties, who was prescribed Bydureon® at a dose of 2mg once weekly. Time to onset was 11 days after starting and the Bydureon® was stopped due to the event. The event resolved on stopping. The patient had no prior history of the event or risk factors. Concomitant medications reported at the time of the event were amitriptyline, amlodipine, aspirin, atenolol, metformin, movicol, paracetamol, perindopril, ranitidine, simvastatin, tamsulosin, duloxetine, gabapentin and glyceryl trinitrate.

Angioedema (n=2)

There were two events of angioedema. One event was reported in a female patient in her sixties, who was prescribed Bydureon® at a dose of 2mg once weekly. Time to onset was 134 days after starting and Bydureon® was stopped due to the event. It was unknown whether the event resolved on stopping. It was also not known if the patient had a prior history of the event or if they were taking any concomitant medications at the time of the event.

The second case was an event of hereditary angioedema reported in a female patient in her forties, who was prescribed Bydureon® at a dose of 2mg once weekly. Time to onset was 86 days after starting and the drug was not stopped due to the event. The GP reported 'increased frequency of relapses of type 1 hereditary angioedema'. It was unknown if the event resolved. The patient had a prior history of the event. Concomitant medications at the time of the event were unknown.

Possible drug-induced liver injury (n=1)

In total, there were 32 patients for whom the GP reported a free text event or laboratory measurements synonymous with abnormal liver function. All reports of abnormal liver function tests considered to occur on treatment (plus the 10-week washout period) during the 12-month observation period were assessed for potential cases of drug-induced liver injury (DILI). The following thresholds were used: (a) Alanine aminotransferase (ALT) value ≥5× upper limit of normal (ULN), (b) Alkaline phosphatase (ALP) value ≥2× ULN OR (c) ALT value ≥3× ULN and Total Bilirubin (TB) ≥2× ULN. (35) In this study, where complete measurements were reported for the above liver function tests within 12-months after index, the above criteria for potential DILI was met for only one patient and this case has been described below.

This male patient in his early sixties was started on Bydureon® at a dose of 2mg once weekly in February 2014. The GP reported 'deranged liver function tests related to nitrofurantoin' approximately two months after starting Bydureon® (April 2014). The GP also reported that the patient stopped Bydureon® approximately nine months after starting (November 2014) as it was 'not working'. A supplementary questionnaire was sent which provided multiple attachments in the form of letters. These have been summarised below.

Liver function tests at the time of the original reported event (April 2014) were not provided on the supplementary questionnaire, however, it was noted that approximately four months after (7th August 2014), the patient was admitted to hospital for two days with abnormal liver function tests (LFTs). The following measurements were provided at the time of the admission[28]; TB 40 µmol/l, ALP 196 U/L, ALT 248 U/L, (aspartate aminotransferase) AST 150 U/L, (gamma-glutamyl transpeptidase) GGT 2414 U/L. The primary diagnosis reported on the discharge summary for the hospital admission in August was of 'deranged LFTs secondary to codeine, antibiotics and fatty liver' and the codeine was stopped. Abdominal ultrasound revealed fatty infiltration of the liver, a thin walled gallbladder with multiple stones but no

[28] Normal reference ranges; TB <21.0 µmol/l, ALP 30.0-130.0 U/L, ALT <41.0U/L, AST <40.0 U/L, GGT <60.0 UL

evidence of cholecystitis. Concomitant medications reported were as amlodipine, atenolol, gliclazide, cetirizine, nefopam, enalapril, metformin, bendroflumethiazide and simvastatin.

The patient was subsequently seen in clinic six days after hospital discharge (18th August 2014) with right sided abdominal ache, jaundice and further deterioration of LFTs (TB 80 µmol/L, ALP 352 U/L, ALT 411 U/L, AST 151 U/L, and GGT 2826 U/L). A further clinic appointment six days later (21st August 2014) reported symptoms of crampy abdominal pain, loss of appetite, dark urine, slightly yellow stool and shivers. It was also noted that the patient had recently suffered from a urinary tract infection and had been treated with cephalexin; this was however after the peak in LFTs and the onset of jaundice. The plan was to request an urgent magnetic resonance cholangiopancreatography (MRCP), further blood tests and follow-up in clinic. The specialist queried whether common bile duct stones were causing the findings.

Blood tests dated from approximately one month later (24th September 2014) were as follows; TB 23 µmol/l, ALP 84 U/L, ALT 37 U/L. A further clinic letter from approximately one month after (8th October 2014) noted that the acute liver injury had resolved and the ALT was back to normal. The specialist noted that originally, the impression was of non-alcoholic fatty alcoholic liver disease and possible development of cirrhosis but it was unclear what caused the deterioration. It was noted that the patient did not start any new drugs over the several weeks prior to the beginning of the event when the first 'hikes' in transaminases were noted. The MRCP showed gallstones but no bile duct stones and the hepatitis viral screen was negative.

It is important to note that despite reporting that the patient did not stop Bydureon® until November 2014 on the 12-month questionnaire, on the supplementary questionnaire (sent for abnormal LFTs reported in April 2014) the GP specified 'no' to if the patient was taking Bydureon® at the time of the event and Bydureon® was also not listed in the hospital discharge summary from August 2014.

Supplementary information revealed a relevant past medical history of non-alcoholic fatty liver disease (2009), hepatic fibrosis, gilbert's syndrome and gallstones.

For the remaining 31 patients with abnormal liver function reported, two patients were reported to have an ALT ≥3× ULN (120 U/L and 127 U/L), however, for one patient the TB was normal and for the other patient the value had not been reported. Both patients were reported as having 'fatty liver'. For the other 29 patients with abnormal liver function, either the reported values did not meet the criteria as defined above or no specific measurements were provided.

Erythema multiforme (n=1)

One event of erythema multiforme was reported in a male patient in his forties, who was prescribed Bydureon® at an unspecified dose. Time to onset was 145 days after starting and Bydureon® was stopped due to the event. It was unknown if the event resolved on stopping. The patient had no prior history of the

event and relevant co-morbidities reported were diabetes mellitus. Concomitant medications taken at the time of the event were aspirin, metformin, ramipril and simvastatin.

Electrocardiogram QT prolonged (n=1)

One event of prolonged QT was reported in a female patient in her late fifties, who was prescribed Bydureon® at an unknown dose. Time to onset was 128 days after starting and Bydureon® was not stopped due to the event. It was unknown if the event resolved. The patient had no prior history of the event and relevant co-morbidities were bronchitis. Concomitant medications at the time of the event were aripiprazole, aspirin, cholecalciferol, cyclizine, diazepam, docusate sodium, furosemide, gabapentin, glyceryl trinitrate, haloperidol, humulin M3, loratadine, metformin, mirtazapine, oxycodone hydrochloride, oxygen, ranitidine, senna, sertraline, simvastatin, sotalol, nicorandil, doxycycline and nefopam.

Interstitial lung disease (n=2)

There were two reports of interstitial lung disease. One event of interstitial lung disease was reported in a female patient in her fifties, who was prescribed Bydureon® at a dose of 2mg once weekly. Time to onset was 114 days after starting and Bydureon® was not stopped due to the event. It was unknown if the event resolved. It was also not known if the patient had a prior history of the event and risk factors were very poor diabetes control. Concomitant medications at the time of the event were unknown.

For the second patient the GP reported 'pulmonary fibrosis'. This was reported in a male patient in his sixties, who was prescribed Bydureon® at a dose of 2mg once weekly. Time to onset was 338 days after starting and Bydureon® was not stopped due to the event. It was unknown if the event resolved. It was also not known whether the patient had a prior history of the event. Concomitant medications taken at the time of the event were unknown.

Decreased white blood cell count (n=1)

One event of 'white blood cell count decreased' was reported in a male patient in his sixties, who was prescribed Bydureon® at a dose of 2mg once weekly. Time to onset was 179 days after starting and Bydureon® was not stopped due to the event. It was unknown if the event resolved. It was also not known if the patient had a prior history of the event. Anaemia was reported as a relevant co-morbidity, however, concomitant medications taken at the time of the event were unknown.

Thrombocytopenia (n=5)

Five events of thrombocytopenia were reported in three male and two female patients, aged between 40 and 80 years. All were prescribed Bydureon® at a dose of 2mg once weekly. Time to onset was between approximately 60 and 300 days and Bydureon® was stopped due to the event in two of the five cases. The event resolved after stopping for one patient and this was unknown for the other patient. One patient did not have a prior history of the event and relevant co-morbidities were empyema. For the other four patients prior history of the event was unknown. Relevant co-morbidities for the other patients included gallstones,

biliary sepsis, toxic megacolon, non-alcoholic steatohepatitis and metabolic syndrome. Concomitant medications at the time of the event for one patient were clenil modulate, dapagliflozin, gliclazide, metformin, ramipril and Ventolin. For the other four patients, concomitant medications at the time of the event were unknown. Note, only events which the GP reported as thrombocytopenia or provided a laboratory value which met the definition of thrombocytopenia (<150x10^9/L) are included in these counts. For three patients, the GP specified thrombocytopenia (without providing any lab values); for the remaining two patients only a platelet count was provided in attachments (142 x10^9/l and 122x10^9/L).

10.4.6 Deaths

The total number of deaths reported during the 12-month observation period have been presented in Table 34. In total, 43 patients (0.7% of cohort) were reported to have died during the 12-month observation period. Of these reported deaths, 25 (0.4% of cohort, 58.1% of all deaths during the 12-month observation period) occurred on treatment with Bydureon® (plus the 10-week washout period); for nine patients (0.1% of cohort, 20.9% of all deaths during the 12-month observation period), the treatment status was not known at the time of death and for the remaining nine patients (0.1% of cohort, 20.9% of all deaths during the 12-month observation period), the death was reported to occur off treatment.

The majority of patients who died were reported to be exenatide naïve (n=32, 74.4% of patients who died). However, the incidence of death overall (irrespective of treatment status) was similar for exenatide naïve patients and previous Byetta® users (0.7% and 0.6%, respectively). Eight of the nine deaths reported in previous Byetta® users (0.5% of previous Byetta® users, 88.9% of all deaths in previous Byetta® users) occurred on treatment with Bydureon® (plus the 10-week washout period); for exenatide naïve patients half of the reported deaths (n=16, 0.4% of exenatide naïve patients, 50.0% of all deaths in exenatide naïve patients) occurred during treatment with Bydureon® (plus the 10-week washout period).

Table 34. Number of deaths reported during the 12-month observation period

	Exenatide naïve (N=4556)		Previous Byetta® user (N=1629)		Total cohort (N=6294)	
Treatment status	**n**	**%**	**n**	**%**	**n**	**%**
On treatment[a]	16	0.4	8	0.5	25	0.4
Off treatment	9	0.2	0	0.0	9	0.1
Treatment status unknown	7	0.2	1	0.1	9	0.1
Total	32	0.7	9	0.6	43	0.7

[a] Including the 10-week washout period

The number of deaths reported within the 12-month observation period (minus the 10-week washout period) have been summarised in Appendix 23. In addition, deaths reported to occur outside the 12-month observation period on treatment (plus the 10-week washout period) are also presented in Appendix 23.

For deaths occurring on treatment with Bydureon® (n=25) during the 12-month observation period, the immediate causes of death (where specified) have been presented in Table 35 according to MedDRA Preferred Terms. Information on the cause of death has been obtained from free text events reported as the 'immediate cause of death' or under 'section I(a)' as per the death certificate, on either the 12-month questionnaire or a supplementary cause of death questionnaire.

For the total cohort, immediate cause of death was specified for 19 deaths (76.0% of deaths) reported to occur on treatment (plus the 10-week washout period) during the 12-month observation period. The most frequently reported cause of death, where specified, was 'cardiac failure', 'pneumonia' or 'pneumonia aspiration', all with two counts. The remaining causes of deaths were all reported in single counts. Of note, 'pancreatitis' was provided as a cause of death for one patient; this was reported in an exenatide naïve patient and further information on this case can be found in Section 10.4.1. 'Pancreatic carcinoma metastatic' was also reported in a patient for whom previous exposure to Byetta® was not specified. Further information on this case has been provided in Section 10.4.2. In addition, the case of 'hepatic failure' has been further characterised in Section 10.4.5.

Table 35. Immediate cause of death reported on treatment[a] during the 12-month observation period

Immediate cause of death	n	%
Exenatide naïve (N=4556)		
Cardiac failure congestive	1	0.0
Congestive cardiomyopathy	1	0.0
Hepatic failure	1	0.0
Lung cancer metastatic	1	0.0
Metabolic acidosis	1	0.0
Metastases to lung	1	0.0
Metastatic neoplasm	1	0.0
Myocardial infarction	1	0.0
Oesophageal varices haemorrhage	1	0.0
Pancreatitis	1	0.0
Pneumonia	1	0.0
Pneumonia aspiration	1	0.0
Death cause not specified	4	0.1
Total	16	0.4
Previous Byetta® users (N=1629)		
Cardiac failure	2	0.1
Cerebral haemorrhage	1	0.1
Hepatic cirrhosis	1	0.1
Pneumonia	1	0.1
Pneumonia aspiration	1	0.1
Death cause not specified	2	0.1
Total	8	0.5

Immediate cause of death	n	%
Total cohort (N=6294)		
Cardiac failure	2	0.0
Pneumonia	2	0.0
Pneumonia aspiration	2	0.0
Cardiac failure congestive	1	0.0
Cerebral haemorrhage	1	0.0
Congestive cardiomyopathy	1	0.0
Hepatic cirrhosis	1	0.0
Hepatic failure	1	0.0
Lung cancer metastatic	1	0.0
Metabolic acidosis	1	0.0
Metastases to lung	1	0.0
Metastatic neoplasm	1	0.0
Myocardial infarction	1	0.0
Oesophageal varices haemorrhage	1	0.0
Pancreatic carcinoma metastatic	1	0.0
Pancreatitis	1	0.0
Death cause not specified	6	0.1
Total	25	0.4

[a] Including the 10-week washout period

All immediate causes of death reported on treatment (minus the 10-week washout period) within the 12-month observation period, off treatment and where treatment status was not known have been provided in Appendix 23. In addition, Appendix 23 also includes the immediate cause death reported on treatment beyond the 12-month observation period within the 10-week washout period (not stratified by +/- washout).

Duration from index to death on treatment (plus the 10-week washout period) during the 12-month observation period has been presented in Table 36; the immediate cause of death has been grouped according to MedDRA System Organ Class (SOC) and Higher Level Term (HLT). Causes of death were most frequently specified for patients who had died more than six months after index (n=14, 56.0% of deaths on treatment). Within the first six months, the highest frequency of deaths were reported in month three (n=4, 16.0% of deaths on treatment). A graphical presentation of immediate cause of death by System Organ Class is provided in Figure 9.

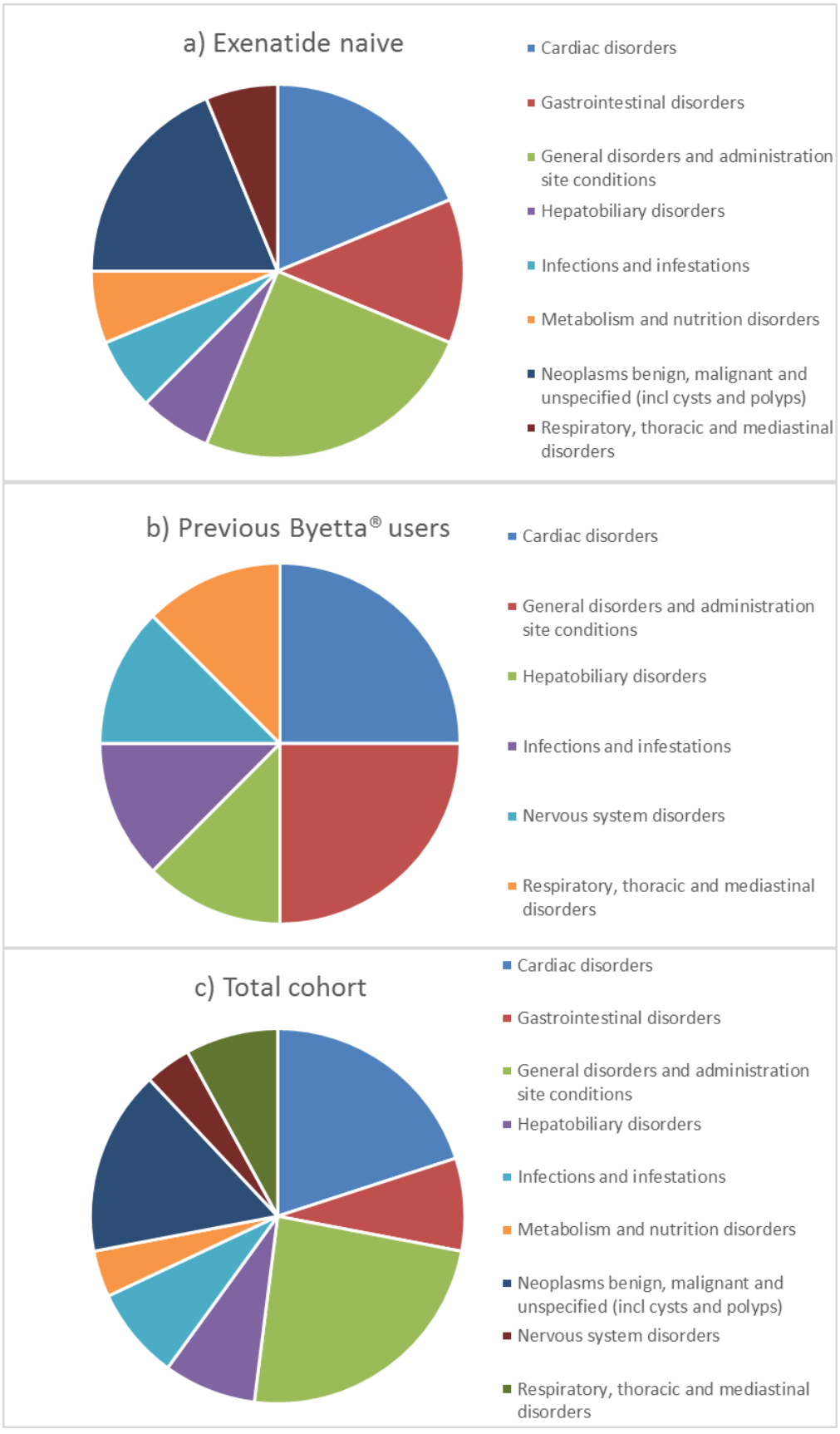
Table 36. Immediate causes of death reported on treatment during the 12-month observation period grouped by System Organ Class and Higher Level Term

Cause of death		Months (days) of treatment							
System Organ Class (SOC)	**Higher level term (HLT)**	1 (0-30)	2 (31-60)	3 (61-90)	4 (91-120)	5 (121-150)	6 (151-180)	>6 (181)	All
Exenatide Naïve									
Cardiac disorders	Cardiomyopathies	0	1	0	0	0	0	0	1
	Heart failures NEC	0	0	0	0	0	0	1	1
	Ischaemic coronary artery disorders	0	0	1	0	0	0	0	1
Gastrointestinal disorders	Acute and chronic pancreatitis	0	0	0	1	0	0	0	1
	Gastric and oesophageal haemorrhages	0	0	0	0	0	0	1	1
General disorders and administration site conditions	Death and sudden death	0	0	1	0	0	0	3	4
Hepatobiliary disorders	Hepatic failure and associated disorders	0	0	0	0	0	1	0	1
Infections and infestations	Lower respiratory tract and lung infections	0	0	0	0	0	0	1	1
Metabolism and nutrition disorders	Metabolic acidoses (excl diabetic acidoses)	0	0	0	0	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastases to specified sites	0	0	0	0	0	0	1	1
	Neoplasms malignant site unspecified NEC	0	0	1	0	0	0	0	1
	Respiratory tract and pleural neoplasms malignant cell type unspecified NEC	0	0	0	0	0	0	1	1
Respiratory, thoracic and mediastinal disorders	Lower respiratory tract inflammatory and immunologic conditions	1	0	0	0	0	0	0	1
Previous Byetta® users									
Cardiac disorders	Heart failures NEC	0	0	0	0	1	0	1	2
General disorders and administration site conditions	Death and sudden death	1	0	0	0	0	0	1	2
Hepatobiliary disorders	Hepatic fibrosis and cirrhosis	0	0	0	0	0	0	1	1
Infections and infestations	Lower respiratory tract and lung infections	0	0	0	0	0	0	1	1

Cause of death		Months (days) of treatment							
System Organ Class (SOC)	**Higher level term (HLT)**	1 (0-30)	2 (31-60)	3 (61-90)	4 (91-120)	5 (121-150)	6 (151-180)	>6 (181)	All
Nervous system disorders	Central nervous system haemorrhages and cerebrovascular accidents	0	0	0	0	0	0	1	1
Respiratory, thoracic and mediastinal disorders	Lower respiratory tract inflammatory and immunologic conditions	0	0	0	0	0	1	0	1
Total cohort									
Cardiac disorders	Cardiomyopathies	0	1	0	0	0	0	0	1
	Heart failures NEC	0	0	0	0	1	0	2	3
	Ischaemic coronary artery disorders	0	0	1	0	0	0	0	1
Gastrointestinal disorders	Acute and chronic pancreatitis	0	0	0	1	0	0	0	1
	Gastric and oesophageal haemorrhages	0	0	0	0	0	0	1	1
General disorders and administration site conditions	Death and sudden death	1	0	1	0	0	0	4	6
Hepatobiliary disorders	Hepatic failure and associated disorders	0	0	0	0	0	1	0	1
	Hepatic fibrosis and cirrhosis	0	0	0	0	0	0	1	1
Infections and infestations	Lower respiratory tract and lung infections	0	0	0	0	0	0	2	2
Metabolism and nutrition disorders	Metabolic acidoses (excl diabetic acidoses)	0	0	0	0	0	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastases to specified sites	0	0	0	0	0	0	1	1
	Neoplasms malignant site unspecified NEC	0	0	1	0	0	0	0	1
	Pancreatic neoplasms malignant (excl islet cell and carcinoid)	0	0	1	0	0	0	0	1
	Respiratory tract and pleural neoplasms malignant cell type unspecified NEC	0	0	0	0	0	0	1	1
Nervous system disorders	Central nervous system haemorrhages and cerebrovascular accidents	0	0	0	0	0	0	1	1
Respiratory, thoracic and mediastinal disorders	Lower respiratory tract inflammatory and immunologic conditions	1	0	0	0	0	1	0	2

Cause of death		Months (days) of treatment							
System Organ Class (SOC)	**Higher level term (HLT)**	1 (0-30)	2 (31-60)	3 (61-90)	4 (91-120)	5 (121-150)	6 (151-180)	>6 (181)	All
Total (N)		2	1	4	1	1	2	14	25

Figure 9. Pie chart showing immediate causes of death reported on treatment during the 12-month observation period by System Organ Class (SOC) for a) exenatide naïve patients b) previous Byetta® users c) total cohort



Immediate causes of death, grouped according to MedDRA System Organ Class and Higher Level Term, for deaths occurring during the 12-month observation period excluding the 10-week washout period and beyond the 12-month observation period (including the 10-week washout period) have been presented in Appendix 23.

In addition to the immediate cause of death, GPs were also requested to report underlying cause/condition(s) leading or contributing to death. Multiple cause/conditions could be reported per patient, so counts are not mutually exclusive. Table 37 provides reported underlying cause/condition(s) in those patients where the cause of death information was completed and includes events reported under 'section I(b), I(c), and II' as per the death certificate for deaths occurring on treatment (including the 10-week washout period) during the 12-month observation period (n=25). Results reveal 18 counts of 16 different underlying/cause conditions reported for the 25 patients who had died on treatment within the first 12 months after index. The most commonly reported underlying cause/condition was 'hepatocellular carcinoma' (n=3); all other underlying cause/conditions were reported once.

Table 37. Reported underlying cause/conditions of death on treatment[a] during the 12-month observation period

Underlying cause/condition	n	%
Exenatide naïve (N=4556)		
Hepatocellular carcinoma	2	0.0
Hypertensive heart disease	1	0.0
Klebsiella sepsis	1	0.0
Malignant neoplasm of unknown primary site	1	0.0
Metastases to liver	1	0.0
Upper gastrointestinal haemorrhage	1	0.0
Total	7	0.2
Previous Byetta® user (N=1629)		
Dilatation ventricular	1	0.1
Hepatitis B	1	0.1
Hepatocellular carcinoma	1	0.1
Hypopituitarism	1	0.1
Interstitial lung disease	1	0.1
Left ventricular dysfunction	1	0.1
Neurosarcoidosis	1	0.1
Obesity	1	0.1
Pulmonary sarcoidosis	1	0.1
Type 2 diabetes mellitus	1	0.1
Ventricular hypertrophy	1	0.1
Total	11	0.7
Total cohort (N=6294)		
Hepatocellular carcinoma	3	0.0
Dilatation ventricular	1	0.0
Hepatitis B	1	0.0

Underlying cause/condition	n	%
Hypertensive heart disease	1	0.0
Hypopituitarism	1	0.0
Interstitial lung disease	1	0.0
Klebsiella sepsis	1	0.0
Left ventricular dysfunction	1	0.0
Malignant neoplasm of unknown primary site	1	0.0
Metastases to liver	1	0.0
Neurosarcoidosis	1	0.0
Obesity	1	0.0
Pulmonary sarcoidosis	1	0.0
Type 2 diabetes mellitus	1	0.0
Upper gastrointestinal haemorrhage	1	0.0
Ventricular hypertrophy	1	0.0
Total	18	0.3

[a] Including the 10-week washout period

All underlying cause/conditions of death reported on treatment (minus the 10-week washout period) within the 12-month observation period, off treatment and where treatment status was not known have been provided in Appendix 23.

10.4.7 Pregnancies

In total there were nine patients with a pregnancy reported after index in the study. Eight of these patients had a pregnancy confirmed to occur within the 12-month observation period; for one patient the pregnancy was confirmed to occur outside the 12-month observation period. Table 38 below summarises the eight pregnancies which occurred within the 12-month observation period.

For five of the eight pregnancies reported within the 12-month observation period, Bydureon® was thought to have been taken during the first trimester based on the information available; three of these pregnancies resulted in a live birth with no complications reported, however, for one patient the child was born with congenital abnormalities (cardiovascular malformations). In addition to maternal diabetes with a history of suboptimal glycaemic control, other potential risk factors for congenital anomalies in this case included reported current smoking and morbid obesity. Also, while it was reported that the patient did not have 'excessive alcohol consumption' during Bydureon® treatment, no further information on alcohol consumption during pregnancy was provided. Further information on this case can be found in a report which was submitted to AstraZeneca (Appendix 24). For the remaining one case where it was known that the patient had taken Bydureon® during the first trimester, the GP reported 'patient fell pregnant' within the reason for prescribing section along with other reasons for prescribing (initiated in secondary care by an endocrinologist). It is possible that the patient may have had further exposure to Bydureon® in the second and/or third trimester but this information is not available, as the patient had left the practice at the end of the first trimester. The outcome for this pregnancy was not therefore known.

In addition to the above, there were three pregnancies where the exact Bydureon® exposure status was uncertain based on the information available. For two of these pregnancies the outcome was not known; one patient had a positive pregnancy test reported, which was later negative on repeat testing. The GP reported that there were no signs of miscarriage and that they 'doubted the patient was pregnant'; the patient had stopped Bydureon® potentially in the first trimester when she thought she was pregnant. For the other patient the GP reported that Bydureon® was stopped because of the pregnancy but there was no follow-up information returned to determine the outcome of the pregnancy. The remaining one pregnancy for which the exact exposure status was uncertain resulted in a spontaneous abortion. However, the GP did report that Bydureon® was stopped because the patient was pregnant. This patient subsequently went on to have a further pregnancy more than 12 months after index with a live-born delivery and no complications; from the information available it appears that Bydureon® was stopped before the time of the second pregnancy. This second pregnancy has not been summarised in Table 38 as it occurred outside the 12-month observation period.

For the additional patient with a pregnancy reported beyond the 12-month observation period, Bydureon® was thought to have been taken in the first trimester and the child was born with multiple congenital abnormalities. In addition to maternal diabetes, other potential risk factors for congenital anomalies in this case included reported current smoking and morbid obesity. Also, while it was reported that the patient did not have 'excessive alcohol consumption' during Bydureon® treatment, no further information on alcohol consumption during pregnancy was provided. The patient was also reported to be taking venlafaxine at index, however, this was not reported on the supplementary questionnaire for medications taken during pregnancy and from the information available it is unclear when venlafaxine was stopped. This case has not been summarised in Table 38 as it occurred outside the 12-month observation period, however, it has been described further as a case narrative in a report previously submitted to AstraZeneca (Appendix 24).

Table 38. Number and outcomes of confirmed pregnancies during the 12-month observation period in women of child-bearing age (12-60 years)

Exposure to Bydureon	Total	Live birth	Ectopic	Spontaneous abortion	Therapeutic termination	Still-born	Neonatal death	Congenital abnormalities	Not known
Drug stopped before last menstrual period	0	0	0	0	0	0	0	0	0
Drug taken in first trimester	5	3	0	0	0	0	0	1	1
Drug taken in second trimester	0	0	0	0	0	0	0	0	0
Exposure uncertain	3	0	0	1	0	0	0	0	2
Total (N)	8	3	0	1	0	0	0	1	3

10.5 Other Analyses

10.5.1 General health parameters

On the 12-month questionnaire GPs were requested to provide information on anthropometric measures and general health risk factors closest to the start date of Bydureon® and closest to 12 months after starting.

The following rule base was applied to the data for general health parameters:

- Baseline measurements were included in the analyses if the date of the measurement was within three months prior to index (or missing). Any measurements which were provided post-index were excluded from the baseline analyses.
- 12-month measurements were only included in the 12-month analyses if the measurement was reported to occur on drug (or within the 10-week washout period) and was reported to occur within 13 months after index. Any measurements reported to occur beyond the 10-week washout period or >13 months after index were excluded from the analyses. Therefore, changes in measurements were only applicable for patients who were still on Bydureon® at the time of the post index measurement.

10.5.1.1 Body Mass Index (BMI)

Body mass index (BMI) measurements (kg/m^2) at index (according to the rule base in Section 10.5.1) were provided for 2605 patients (41.4% of cohort; Table 39). Of these, the majority of patients had a BMI of ≥30 kg/m^2 (n=2390, 38.0% of cohort, 91.7% where BMI specified). Closest to the 12-month observation period (according to the rule base defined in Section 10.5.1), BMI measurements were provided for 2472 patients (39.3% of cohort). Similarly the majority of patients, where BMI was specified, had a BMI of ≥30 kg/m^2 (n=2184, 34.7% of cohort, 83.8% where BMI specified). Only one patient had a BMI below normal (<18.5 kg/m^2). The mean (SD) BMI at index was 38.1 (7.6) kg/m^2 and at 12 months was 37.1 (7.4) kg/m^2. Similar results were observed after stratifying by prior exenatide use; the mean BMI at baseline and at 12-months was similar for exenatide naïve patients and previous Byetta® users.

In the total cohort, for those patients where a potential change in BMI could be calculated[29], the mean (SD) of the differences in BMI from baseline to closest to 12 months was -1.0 (4.7) kg/m^2 and the median (IQR) of the differences in BMI was -0.8 (-2.0, 0.2) kg/m^2. After stratifying by prior exenatide use, the mean and median of the differences in BMI from baseline to closest to 12 months was greater for exenatide naïve patients than for previous Byetta® users. The respective mean (SD) and median (IQR) of the differences were -1.1 (4.7) kg/m^2 and -0.9 (-2.2, 0.0) kg/m^2 for exenatide naïve patients and -0.5 (4.6) kg/m^2 and -0.5 (-1.7, 0.6) kg/m^2 for previous Byetta® users.

[29] Calculable potential change in BMI: exenatide naïve (n=996), previous Byetta® users (n=316), total cohort (n=1321)

Table 39. BMI measurements immediately prior to or at start of Bydureon® treatment and at the end of the observation period (12 months)

	Exenatide naïve (N=4556)				Previous Byetta® users (N=1629)				Total cohort (N=6294)			
	Prior to/on start of treatment		Closest to 12-months observation		Prior to/on start of treatment		Closest to 12-months observation		Prior to/on start of treatment		Closest to 12-months observation	
BMI (kg/m²)	**N**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
<18.5 (below normal)	0	0.0	0	0.0	1	0.1	0	0.0	1	0.0	0	0.0
18.5-24.9 (normal)	9	0.2	20	0.4	4	0.2	10	0.6	13	0.2	31	0.5
25.0-29.9 (overweight)	139	3.1	196	4.3	59	3.6	57	3.5	201	3.2	257	4.1
30.0-39.9 (obese)	1152	25.3	1106	24.3	385	23.6	352	21.6	1549	24.6	1471	23.4
40.0+ (morbidly obese)	631	13.8	518	11.4	202	12.4	187	11.5	841	13.4	713	11.3
Non-response	2625	57.6	2716	59.6	978	60.0	1023	62.8	3689	58.6	3822	60.7
Total (N)	4556	100.0	4556	100.0	1629	100.0	1629	100.0	6294	100.0	6294	100.0
Mean (SD)	38.2 (7.6)		37.0 (7.1)		37.8 (7.9)		37.7 (8.3)		38.1 (7.6)		37.1 (7.4)	
Median (IQR)	37.0 (33.4-41.6)		35.8 (32.3- 40.6)		36.6 (33.0 - 41.4)		36.3 (32.6 - 41.6)		36.9 (33.3 - 41.4)		35.9 (32.4 - 40.8)	
Range (Min, Max)	21.1 - 99.0		19.3 - 93.0		10.3 - 99.0		20.4 - 96.5		10.3 - 99.0		19.3 - 96.5	

Change in the median values of BMI during the 12-month observation period have been presented as box plots (bars represent IQR) in Figures 10aa to 10cc, stratified by sex and repeated for the total cohort, exenatide naïve patients and previous Byetta® users. Results are presented for each group for all patients, for those with a decrease in BMI and those with an increase in BMI.

For the total cohort, where change in BMI was calculable, BMI was reported to have decreased for 897 patients (14.3% of cohort) and increased for 347 patients (5.5% of cohort).

Figure 10aa. Median (IQR) change in BMI from baseline to closest to 12 months for the total cohort

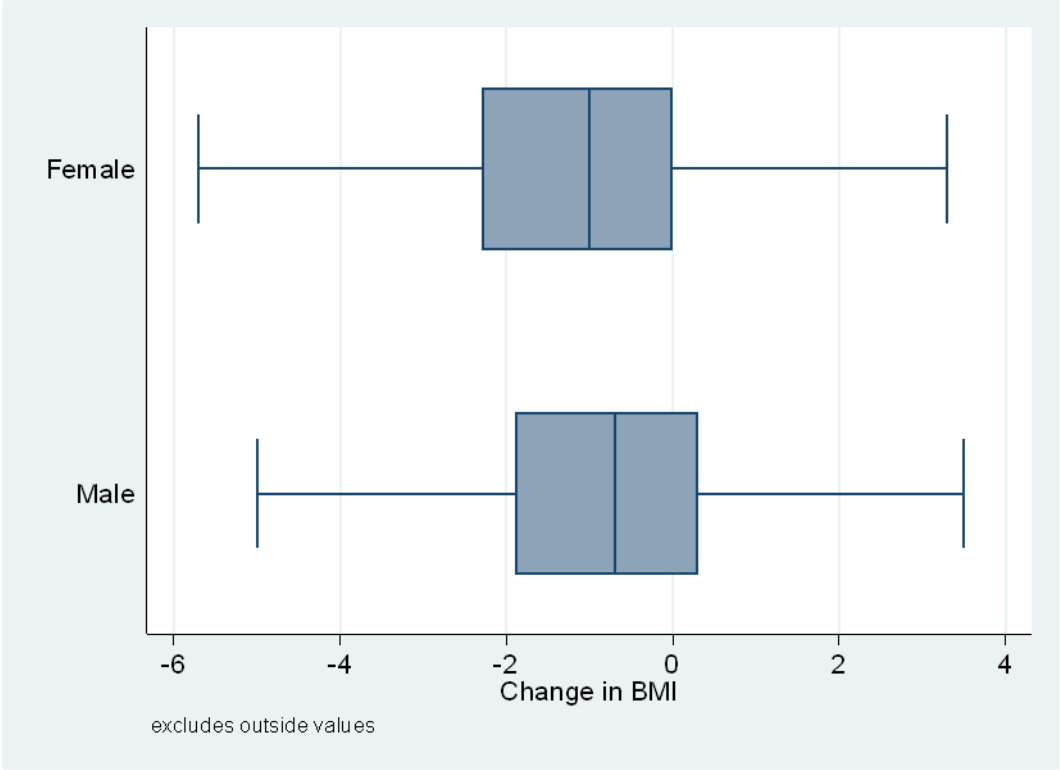


Figure 10ab. Median (IQR) change in BMI from baseline to closest to 12 months for the total cohort who had a decrease in BMI only (n=897)

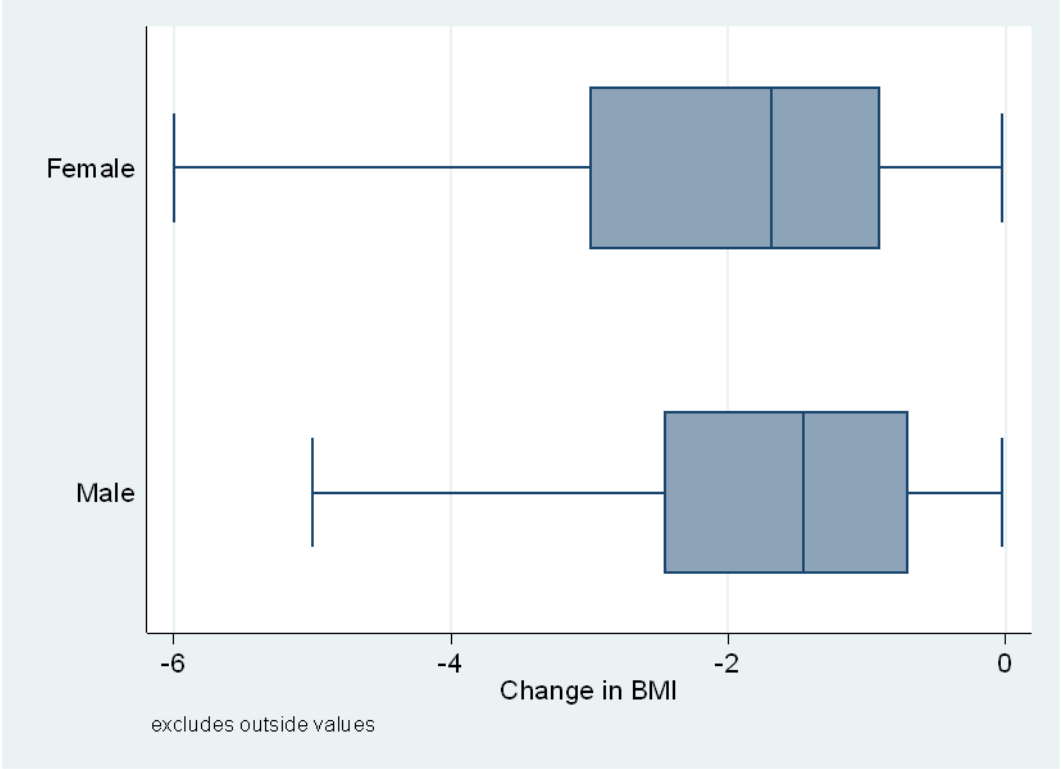
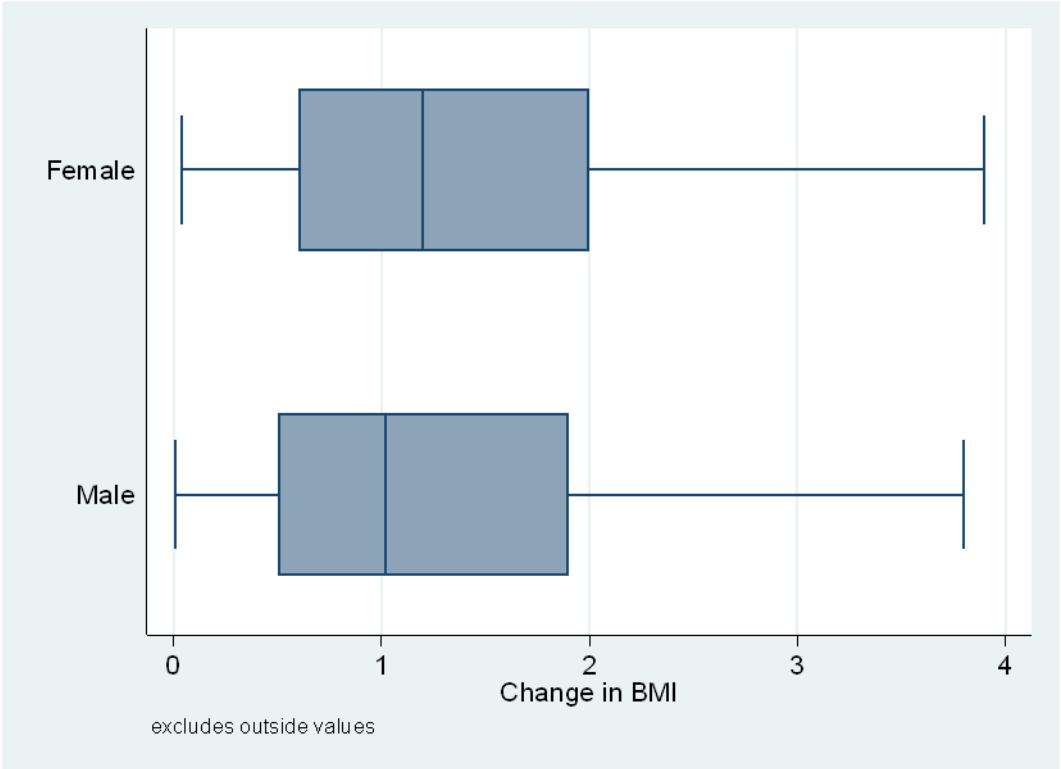


Figure 10ac. Median (IQR) change in BMI from baseline to closest to 12 months for the total cohort who had an increase in BMI only (n=347)



For exenatide naïve patients only, where change in BMI was calculable, BMI was reported to have decreased for 695 patients (15.3% of exenatide naïve patients) and increased for 238 patients (5.2% of exenatide naïve patients).

Figure 10ba. Median (IQR) change in BMI from baseline to closest to 12 months for all exenatide naïve patients

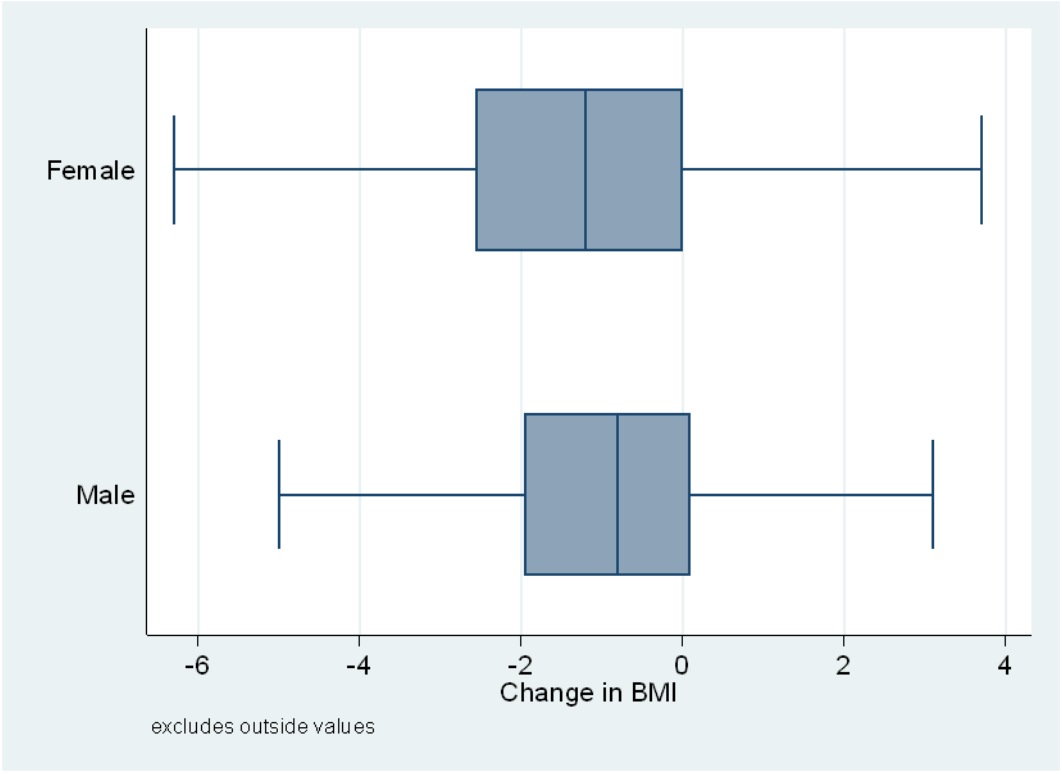


Figure 10bb. Median (IQR) change in BMI from baseline to closest to 12 months for exenatide naïve patients who had a decrease in BMI only (n=695)

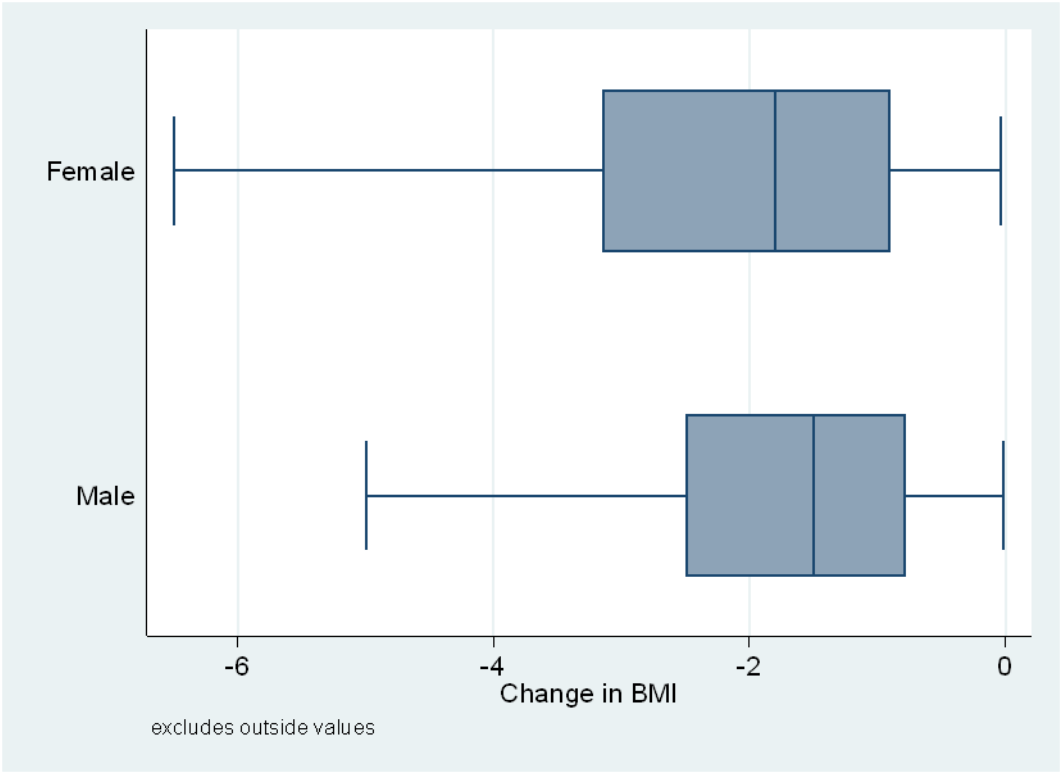
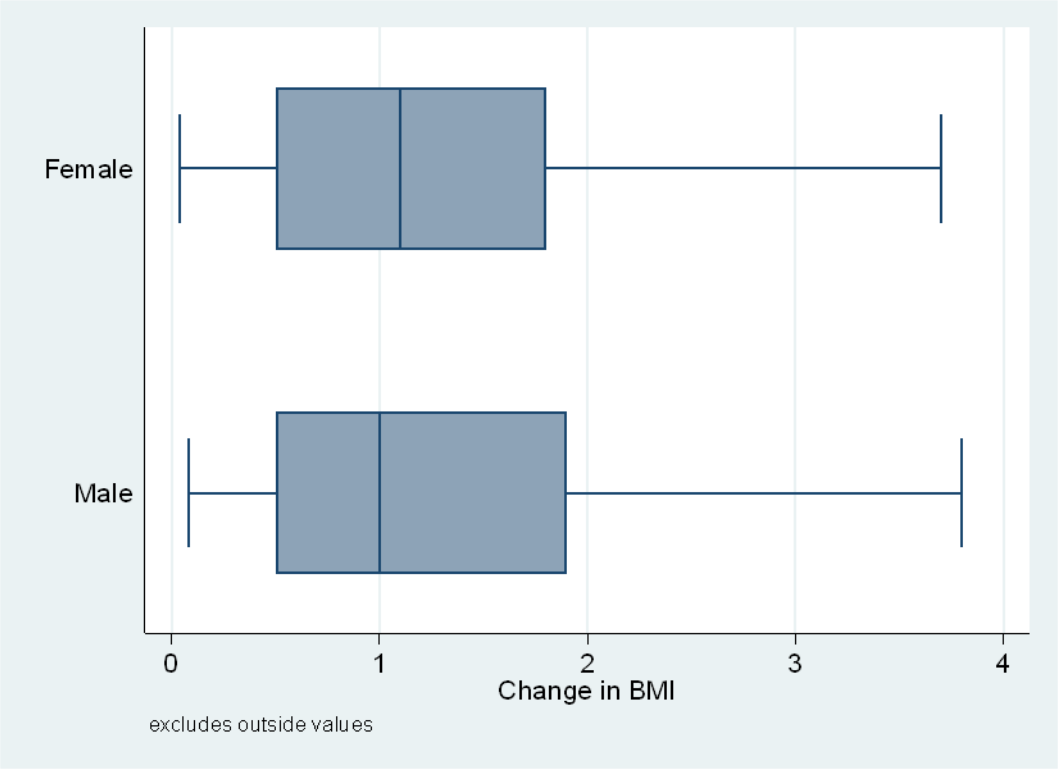


Figure 10bc. Median (IQR) change in BMI from baseline to closest to 12 months for exenatide naïve patients who had an increase in BMI only (n=238)



For previous Byetta® users, where change in BMI was calculable, BMI was reported to have decreased for 197 patients (12.1% of previous Byetta® users) and increased for 105 patients (6.4% of previous Byetta® users).

Figure 10ca. Median (IQR) change in BMI from baseline to closest to 12 months for all previous Byetta® users

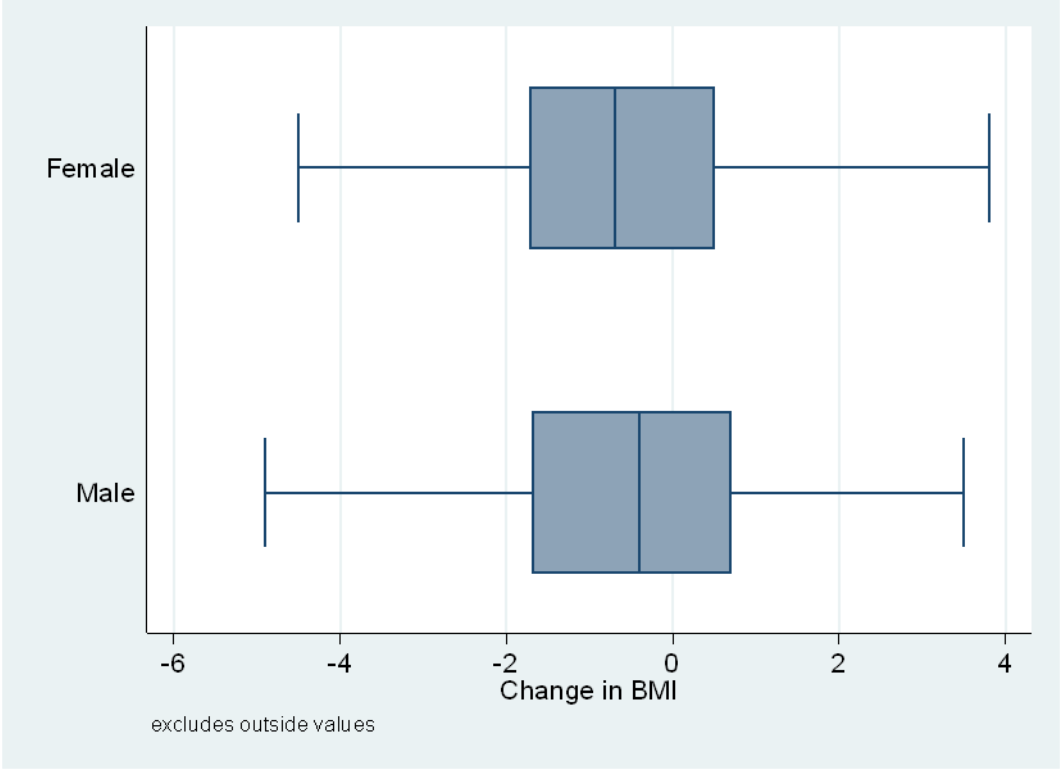


Figure 10cb. Median (IQR) change in BMI from baseline to closest to 12 months for previous Byetta® users who had a decrease in BMI only (n=197)

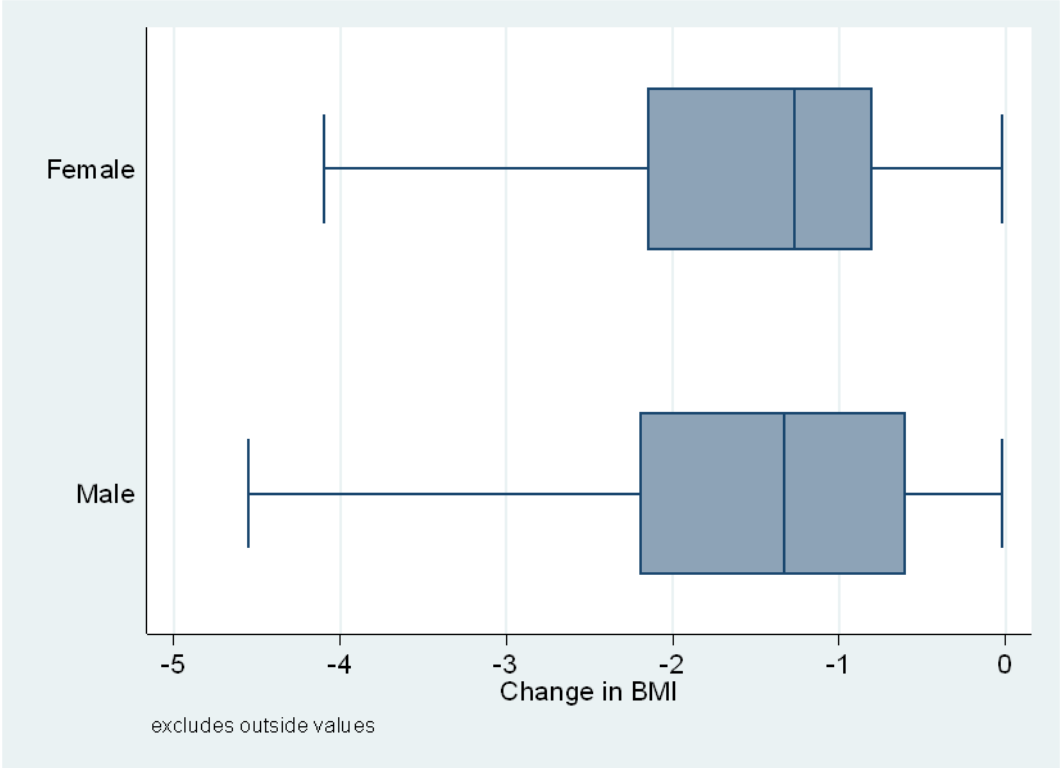
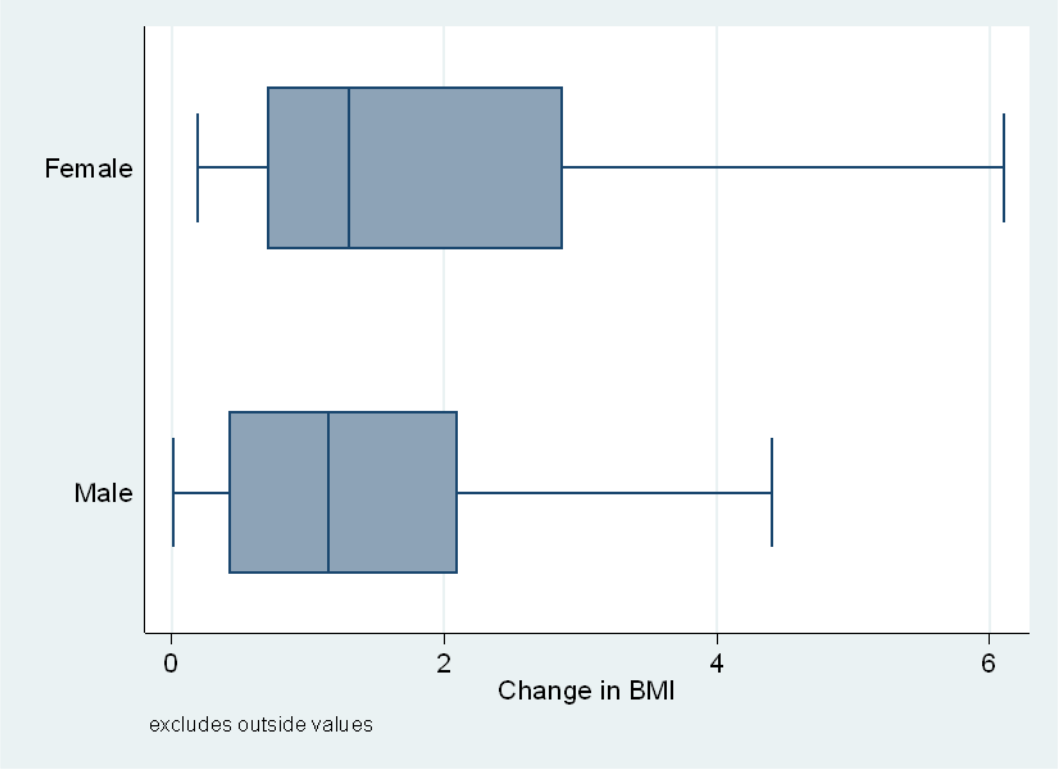


Figure 10cc. Median (IQR) change in BMI from baseline to closest to 12 months for previous Byetta® users who had an increase in BMI only (n=105)



Additional analyses on potentially clinically significant changes in BMI have been presented in Section 10.5.1.5.

10.5.1.2 Weight

Weight (kg) measurements at index (according to the rule base defined in Section 10.5.1) were provided for 2716 patients (43.2% of cohort; Table 40). Of these, the majority of patients had a weight of ≥90 kg (n=2193, 34.8% of cohort, 80.7% where weight specified). Closest to the 12-month observation period (according to the rule base in Section 10.5.1), weight measurements were provided for 2559 patients (40.7% of cohort). Similarly the majority of patients, where weight was specified, had a weight of ≥90 kg (n=1986, 31.6% of cohort, 77.6% where weight specified). The mean (SD) weight at index was 108.4 (21.9) kg and at 12 months it was 106.3 (22.5) kg. Similar results were observed after stratifying by exenatide use; the mean weight at baseline and at 12 months was similar for exenatide naïve patients and previous Byetta® users.

In the total cohort, for those patients where a potential change in weight could be calculated[30], the mean (SD) of the differences in weight from baseline to closest to 12 months was -3.0 (7.6) kg and the median (IQR) of the differences in weight was -2.5 (-6.0, 0.4) kg. After stratifying by previous exenatide use, the mean and median of the differences in weight from baseline to closest to 12 months was greater for

[30] Calculable potential change in weight: exenatide naïve (n=1063), previous Byetta® users (n=352), total cohort (n=1427)

exenatide naïve patients than for previous Byetta® users. The respective mean (SD) and median (IQR) of the differences were -3.5 (7.1) kg and -3.0 (-6.0, 0.0) kg for exenatide naïve patients and -1.4 (8.7) kg and -1.5 (-4.4, 2.0) kg for previous Byetta® users.

Table 40. Weight measurements immediately prior to or at start of Bydureon® treatment and at the end of the observation period (12 months)

	Exenatide naïve (N=4556)				Previous Byetta® users (N=1629)				Total cohort (N=6294)			
	Prior to/on start of treatment		Closest to 12-months observation		Prior to/on start of treatment		Closest to 12-months observation		Prior to/on start of treatment		Closest to 12-months observation	
Weight (kg)	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
<50	3	0.1	2	0.0	0	0.0	1	0.1	3	0.0	3	0.0
≥50 & <70	33	0.7	38	0.8	11	0.7	18	1.1	47	0.7	58	0.9
≥70 & <90	342	7.5	395	8.7	127	7.8	113	6.9	473	7.5	512	8.1
≥90 & <110	748	16.4	735	16.1	266	16.3	228	14.0	1021	16.2	976	15.5
≥110	871	19.1	721	15.8	290	17.8	279	17.1	1172	18.6	1010	16.0
Non-response	2559	56.2	2665	58.5	935	57.4	990	60.8	3578	56.8	3735	59.3
Total (N)	4556	100.0	4556	100.0	1629	100.0	1629	100.0	6294	100.0	6294	100.0
Mean (SD)	108.8 (22.2)		106.0 (22.6)		107.4 (20.8)		107.4 (22.6)		108.4 (21.9)		106.3 (22.5)	
Median (IQR)	106.0 (93.3, 121.9)		103.0 (90.7, 118.0)		107.0 (93.5, 119.8)		106.0 (92.0, 120.0)		106.2 (93.2, 121.0)		104.0 (91.0, 119.0)	
Range (Min, Max)	36.4, 215.6		42.0, 216.0		51.0, 194.0		37.7, 209.5		36.4, 215.6		37.7, 216.0	

Change in the median values of weight during the 12-month observation period have been presented as box plots (bars represent IQR) in Figures 11aa to 11cc, stratified by sex and repeated for the total cohort, exenatide naïve patients and previous Byetta® users. Results are presented for each group for all patients, for those with a decrease in weight and those with an increase in weight.

For the total cohort, where change in weight was calculable, weight was reported to have decreased for 984 patients (15.6% of cohort) and increased for 378 patients (6.0% of cohort).

Figure 11aa. Median (IQR) change in weight from baseline to closest to 12 months for the total cohort

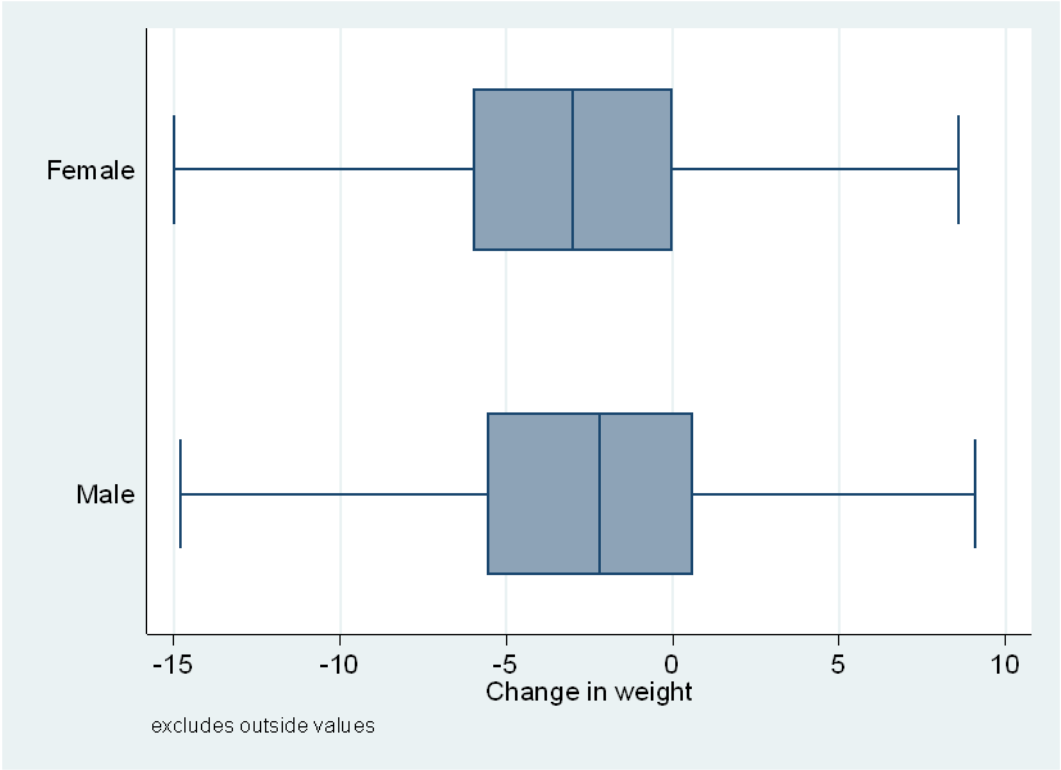


Figure 11ab. Median (IQR) change in weight from baseline to closest to 12 months for the total cohort who had a decrease in weight only (n=984)

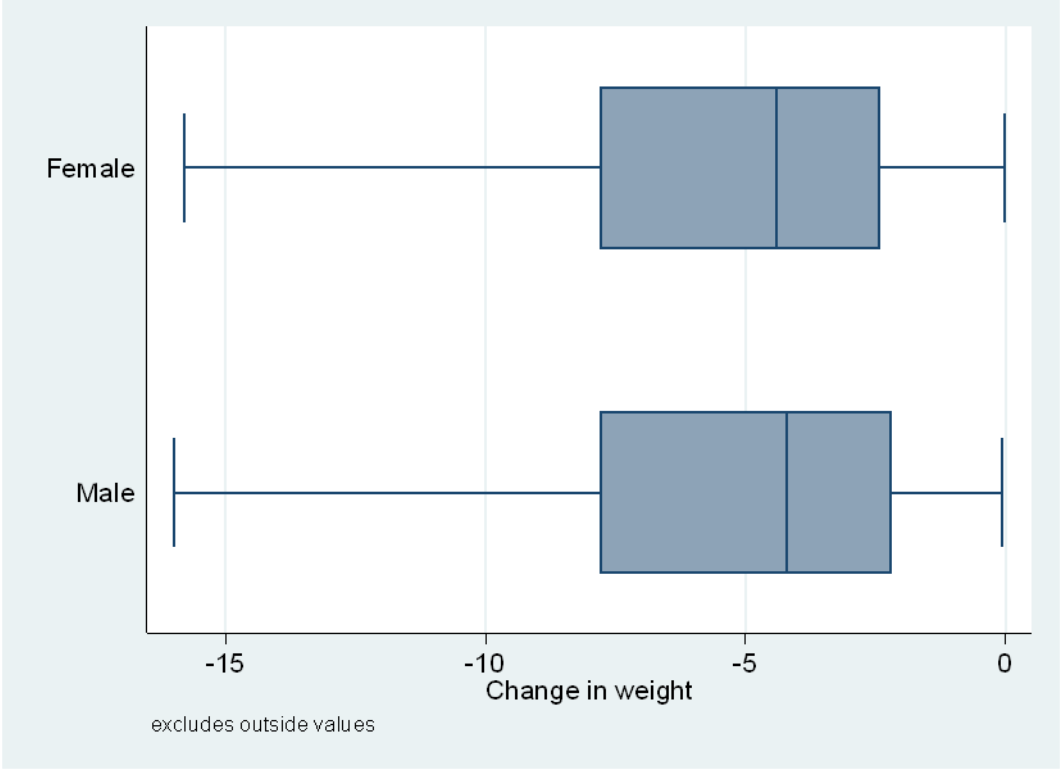
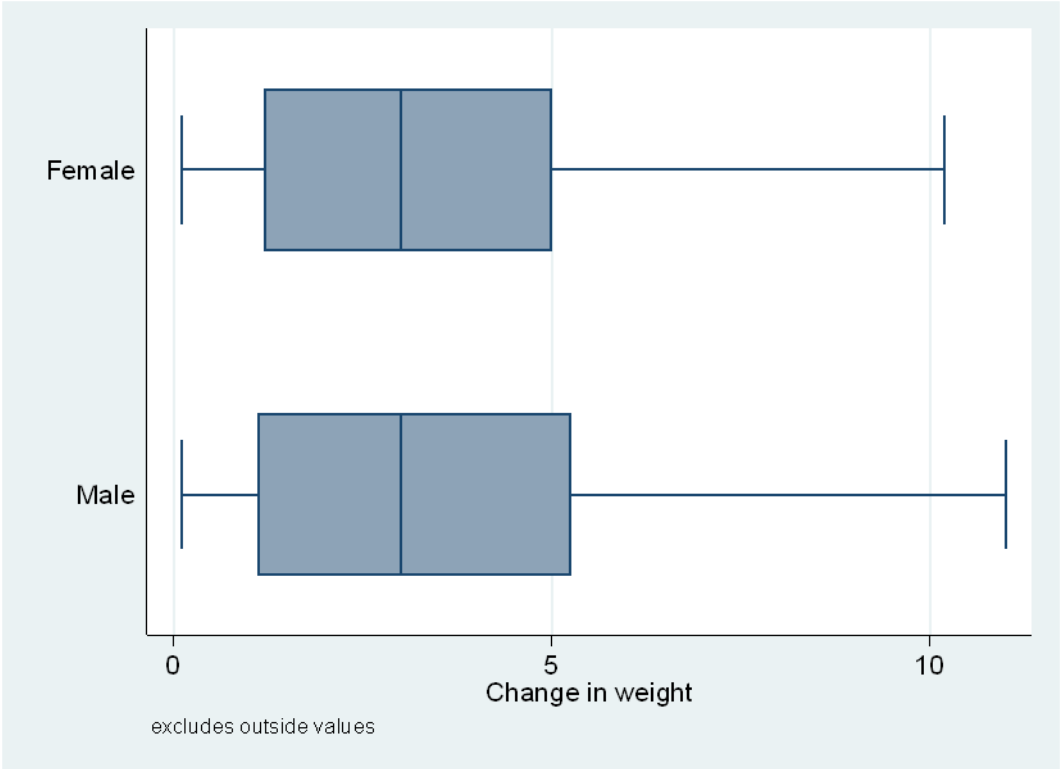


Figure 11ac. Median (IQR) change in weight from baseline to closest to 12 months for the total cohort who had an increase in weight only (n=378)



For exenatide naïve patients only, where change in weight was calculable, weight was reported to have decreased for 766 patients (16.8% of exenatide naïve patients) and increased for 242 patients (5.3% of exenatide naïve patients).

Figure 11ba. Median (IQR) change in weight from baseline to closest to 12 months for all exenatide naïve patients

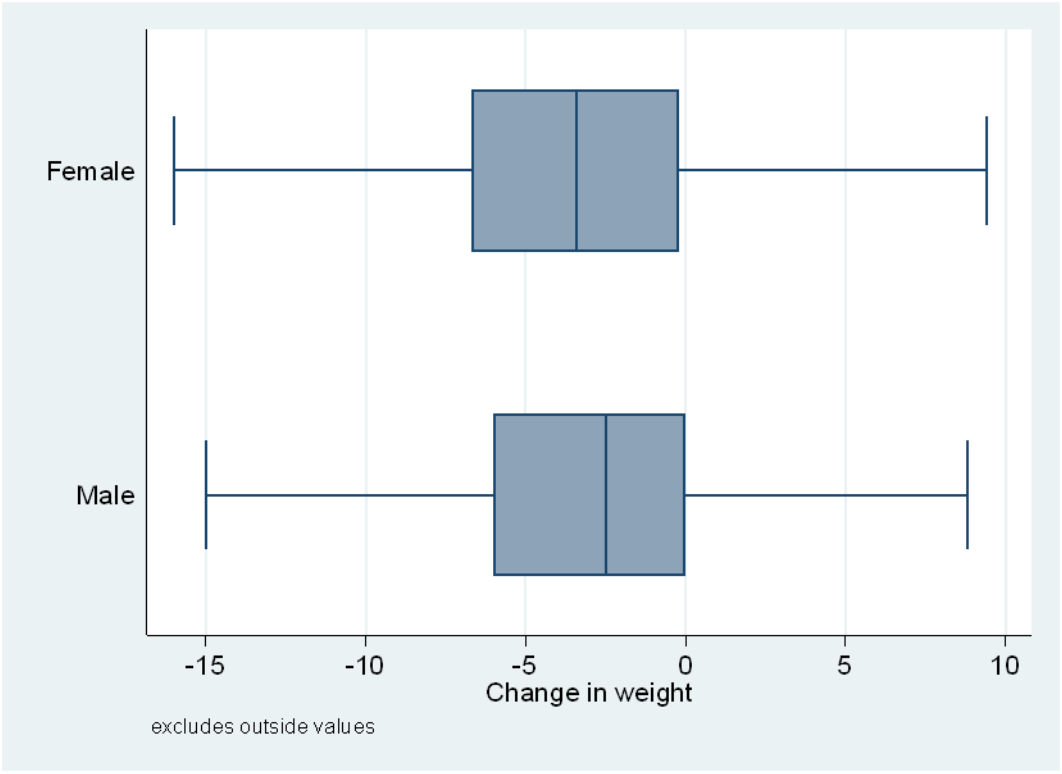


Figure 11bb. Median (IQR) change in weight from baseline to closest to 12 months for exenatide naïve patients who had a decrease in weight only (n=766)

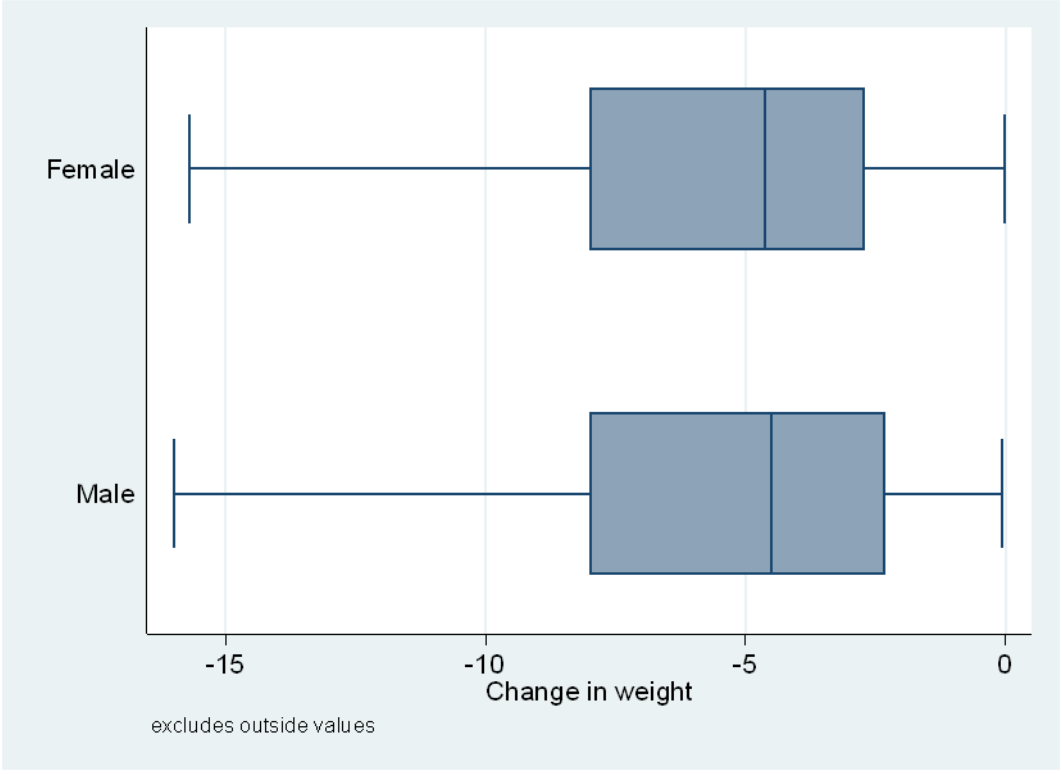
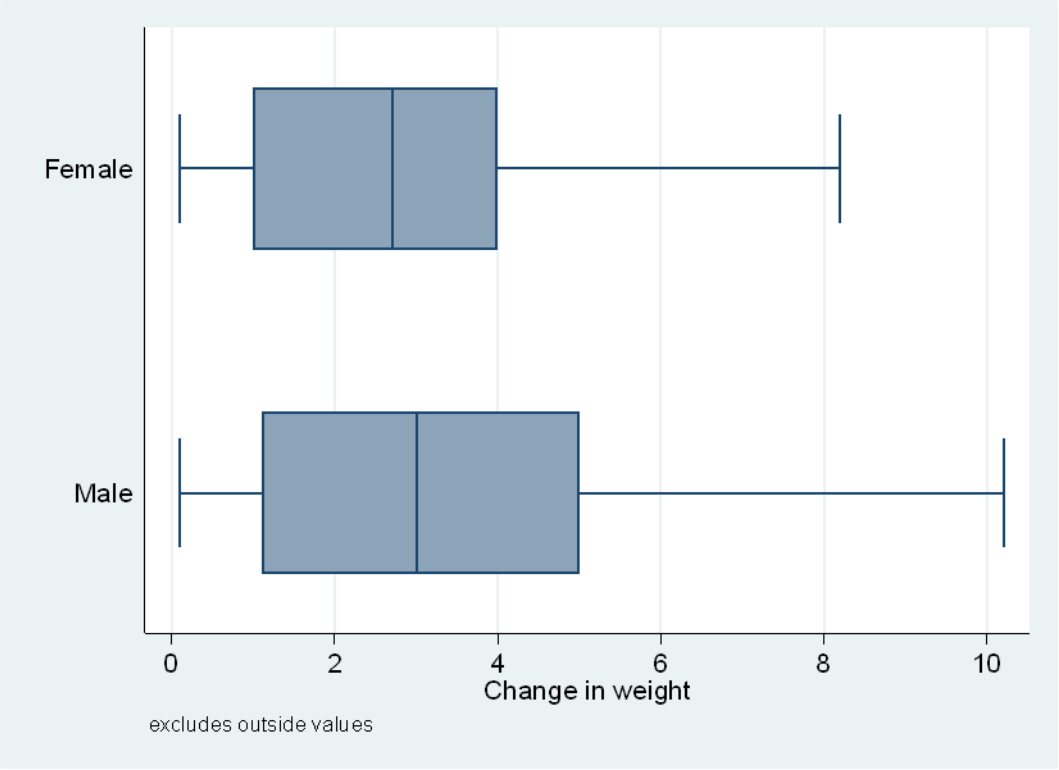


Figure 11bc. Median (IQR) change in weight from baseline to closest to 12 months for exenatide naïve patients who had an increase in weight only (n=242)



For previous Byetta® users, where change in weight was calculable, weight was reported to have decreased for 211 patients (13.0% of previous Byetta® users) and increased for 131 patients (8.0% of previous Byetta® users).

Figure 11ca. Median (IQR) change in weight from baseline to closest to 12 months for all previous Byetta® users

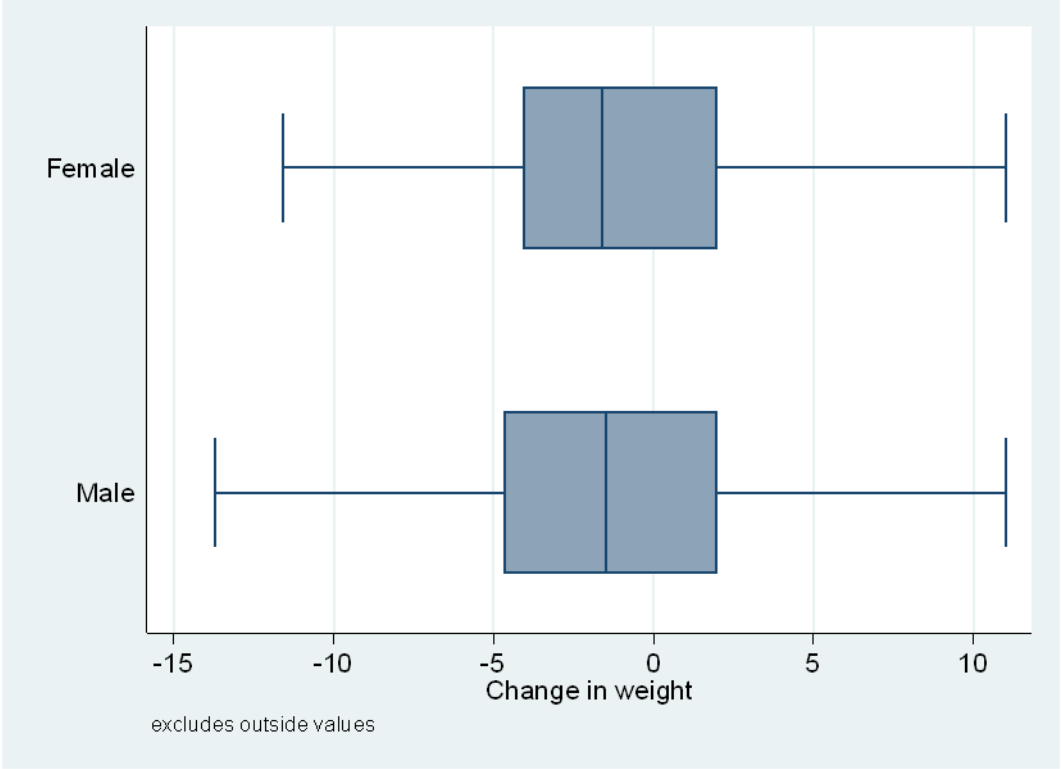


Figure 11cb. Median (IQR) change in weight from baseline to closest to 12 months for previous Byetta® users who had a decrease in weight only (n=211)

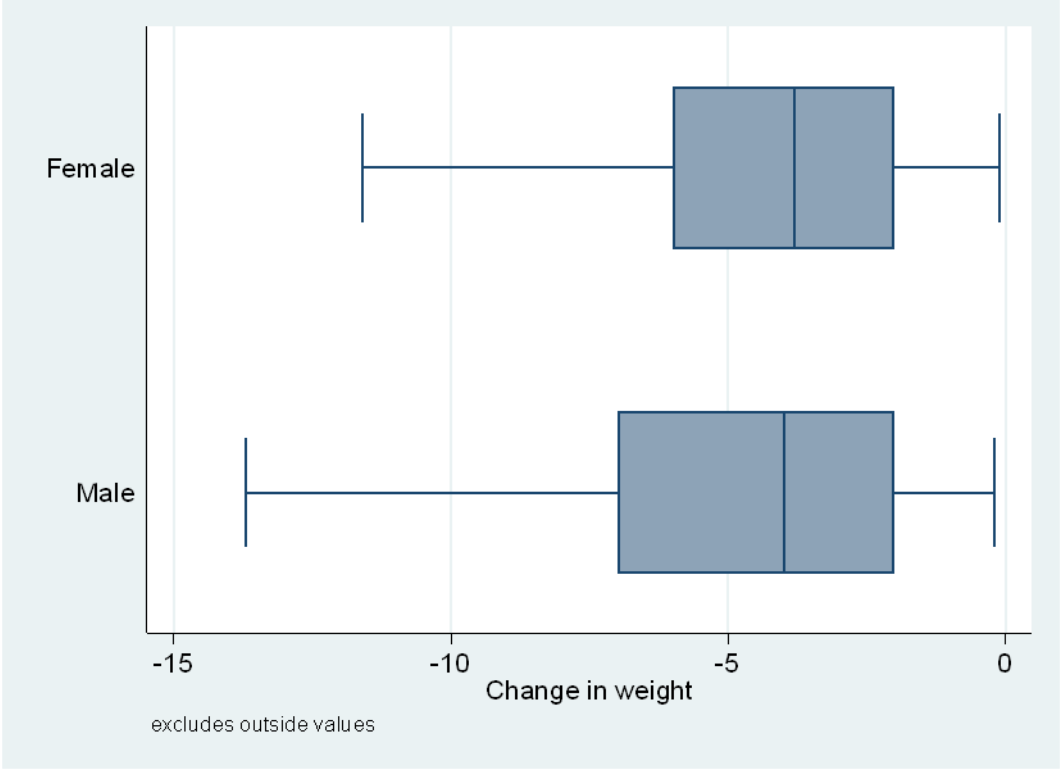
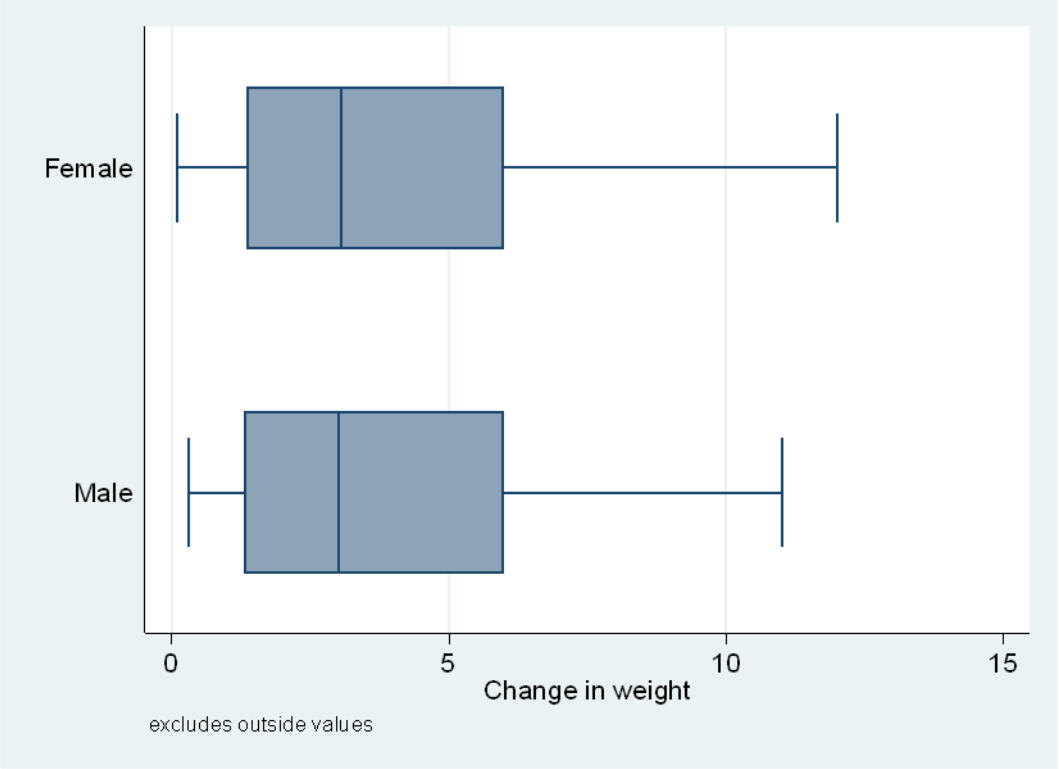


Figure 11cc. Median (IQR) change in weight from baseline to closest to 12 months for previous Byetta® users who had an increase in weight only (n=131)



Additional analyses on potentially clinically significant changes in weight have been presented in Section 10.5.1.5.

10.5.1.3 Blood pressure

On the 12-month questionnaire GPs were asked to report blood pressure (BP) measurements. Blood pressure measurements allow the assessment of the risk of cardiovascular disease in patients with diabetes, and hypertension is often present as part of a metabolic syndrome of insulin resistance in patients with type 2 diabetes. Table 41 shows that complete information on blood pressure (systolic (SBP) and diastolic (DBP) readings) at baseline (according to the rule base defined in Section 10.5.1) were provided for 2856 patients (45.4% of cohort). Closest to 12 months (according to the rule base defined in Section 10.5.1), 2736 patients (43.5% of cohort) had both a systolic and diastolic blood pressure provided. The median SBP/DBP at baseline was 133/79 mmHg and the median SBP/DBP closest to 12 months was 130/78 mmHg.

In the total cohort, 1022 patients (16.2% of cohort) at baseline had a raised SBP (≥140 mmHg), of which 238 patients (23.2% of patients with a raised SBP at index, 3.8% of cohort) also had a raised DBP (≥90 mmHg) reported. Closest to 12 months, 779 patients (12.4% of cohort) had a raised SBP (≥140 mmHg); 152 of these patients (19.5% of patients with a raised SBP closest to 12 months, 2.4% of cohort) also had a raised DBP (≥90 mmHg). In addition, there were 697 patients at index in the total cohort with a SBP (≥140 mmHg) but a DBP<90 mmHg (68.2% of patients with a raised SBP at index, 11.1% of cohort). Closest to 12 months, in the total cohort, 565 patients had a SBP of (≥140 mmHg) but a DBP <90 mmHg

(55.3% of patients with a raised SBP closest to 12 months, 9.0% of cohort). In contrast, there were 102 patients with an isolated raised DBP (>90 mmHg) at baseline (1.6% of cohort) and 70 patients with these findings closest to 12 months (1.1% of cohort). Similar results were observed after stratifying by prior exenatide use. The mean SBP/DBP at baseline and at 12 months was similar for exenatide naïve and previous Byetta® users.

In the total cohort, for those patients where a potential change in SBP could be calculated[31], the mean (SD) of the differences in SBP from baseline to closest to 12 months was -2.6 (15.9) mmHg and the median (IQR) of the differences in SBP was -2.0 (-12.0, 7.0) mmHg. After stratifying by previous exenatide use, the mean and median of the differences in SBP from baseline to closest to 12 months was greater for exenatide naïve patients than for previous Byetta® users. The respective mean (SD) and median (IQR) of the differences were -3.1 (15.6) mmHg and -2.0 (-12.0, 6.0) mmHg for exenatide naïve patients and -1.1 (16.7) mmHg and -1.0 (-10.0, 8.5) mmHg for previous Byetta® users.

[31] Calculable potential change in SBP: exenatide naïve (n=1203), previous Byetta® users (n=440), total cohort (n=1662)

Table 41. Blood pressure categories immediately prior to or at start of Bydureon® treatment and closest to the end of the observation period (12 months)

			Exenatide Naïve (N=4556)				Previous Byetta® users (N=1629)				Total Cohort (N=6294)			
			Prior to/on start of treatment		Closest to 12-months observation		Prior to/on start of treatment		Closest to 12-months observation		Prior to/on start of treatment		Closest to 12-months observation	
BP Measure	Systolic BP (mmHg)	Diastolic BP (mmHg)	n	%	N	%	n	%	n	%	n	%	n	%
	<120.0	<80.0	209	4.6	266	5.8	73	4.5	100	6.1	287	4.6	369	5.9
		80.0-84.9	44	1.0	42	0.9	13	0.8	13	0.8	57	0.9	56	0.9
		85.0-89.9	4	0.1	11	0.2	2	0.1	9	0.6	6	0.1	20	0.3
		90.0-99.9	5	0.1	2	0.0	2	0.1	1	0.1	7	0.1	3	0.0
		100.0-109.9	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		≥110.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Missing	21	0.5	18	0.4	11	0.7	12	0.7	32	0.5	30	0.5
		Total (N)	283	6.2	339	7.4	101	6.2	135	8.3	389	6.2	478	7.6
	130.0-139.9	<80.0	270	5.9	331	7.3	118	7.2	105	6.4	393	6.2	445	7.1
		80.0-84.9	124	2.7	139	3.1	36	2.2	42	2.6	162	2.6	181	2.9
		85.0-89.9	37	0.8	21	0.5	15	0.9	6	0.4	52	0.8	27	0.4
		90.0-99.9	28	0.6	11	0.2	5	0.3	3	0.2	34	0.5	15	0.2
		100.0-109.9	1	0.0	0	0.0	0	0.0	0	0.0	1	0.0	0	0.0
		≥110.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
		Missing	50	1.1	52	1.1	16	1.0	14	0.9	67	1.1	67	1.1
		Total (N)	510	11.2	554	12.2	190	11.7	170	10.4	709	11.3	735	11.7
		<80.0	340	7.5	369	8.1	135	8.3	139	8.5	478	7.6	519	8.2
		80.0-84.9	234	5.1	195	4.3	67	4.1	60	3.7	302	4.8	259	4.1
		85.0-89.9	59	1.3	51	1.1	22	1.4	22	1.4	82	1.3	73	1.2
		90.0-99.9	36	0.8	33	0.7	16	1.0	8	0.5	52	0.8	41	0.7
		100.0-109.9	7	0.2	10	0.2	1	0.1	0	0.0	8	0.1	10	0.2
		≥110.0	0	0.0	1	0.0	0	0.0	0	0.0	0	0.0	1	0.0
		Missing	53	1.2	55	1.2	19	1.2	25	1.5	73	1.2	81	1.3
		Total (N)	729	16.0	714	15.7	260	16.0	254	15.6	995	15.8	984	15.6

BP Measure	Systolic BP (mmHg)	Diastolic BP (mmHg)	Exenatide Naïve (N=4556)				Previous Byetta® users (N=1629)				Total Cohort (N=6294)			
			Prior to/on start of treatment		Closest to 12-months observation		Prior to/on start of treatment		Closest to 12-months observation		Prior to/on start of treatment		Closest to 12-months observation	
			n	%	N	%	n	%	n	%	n	%	n	%
	140.0-159.9	<80.0	199	4.4	159	3.5	68	4.2	63	3.9	270	4.3	222	3.5
		80.0-84.9	175	3.8	142	3.1	55	3.4	58	3.6	232	3.7	202	3.2
		85.0-89.9	83	1.8	69	1.5	28	1.7	23	1.4	112	1.8	92	1.5
		90.0-99.9	112	2.5	67	1.5	32	2.0	15	0.9	145	2.3	83	1.3
		100.0-109.9	16	0.4	9	0.2	6	0.4	6	0.4	23	0.4	15	0.2
		≥110.0	1	0.0	1	0.0	1	0.1	1	0.1	2	0.0	2	0.0
		Missing	52	1.1	44	1.0	13	0.8	6	0.4	68	1.1	53	0.8
		Total (N)	638	14.0	491	10.8	203	12.5	172	10.6	852	13.5	669	10.6
	160.0-179.9	<80.0	18	0.4	12	0.3	8	0.5	4	0.2	26	0.4	16	0.3
		80.0-84.9	22	0.5	11	0.2	9	0.6	10	0.6	31	0.5	21	0.3
		85.0-89.9	6	0.1	4	0.1	6	0.4	4	0.2	13	0.2	8	0.1
		90.0-99.9	32	0.7	20	0.4	9	0.6	8	0.5	41	0.7	28	0.4
		100.0-109.9	3	0.1	8	0.2	2	0.1	5	0.3	3	0.0	13	0.2
		≥110.0	3	0.1	1	0.0	0	0.0	0	0.0	5	0.1	1	0.0
		Missing	15	0.3	3	0.1	1	0.1	2	0.1	17	0.3	6	0.1
		Total (N)	99	2.2	59	1.3	35	2.1	33	2.0	136	2.2	93	1.5
	≥180.0	<80.0	3	0.1	1	0.0	2	0.1	0	0.0	5	0.1	1	0.0
		80.0-84.9	4	0.1	0	0.0	1	0.1	1	0.1	5	0.1	1	0.0
		85.0-89.9	2	0.0	1	0.0	1	0.1	1	0.1	3	0.0	2	0.0
		90.0-99.9	3	0.1	6	0.1	1	0.1	2	0.1	4	0.1	8	0.1
		100.0-109.9	8	0.2	1	0.0	2	0.1	0	0.0	10	0.2	1	0.0
		≥110.0	4	0.1	1	0.0	1	0.1	0	0.0	5	0.1	1	0.0
		Missing	1	0.0	3	0.1	1	0.1	0	0.0	2	0.0	3	0.0
		Total (N)	25	0.5	13	0.3	9	0.6	4	0.2	34	0.5	17	0.3

BP Measure	Systolic BP (mmHg)	Diastolic BP (mmHg)	Exenatide Naïve (N=4556)				Previous Byetta® users (N=1629)				Total Cohort (N=6294)			
			Prior to/on start of treatment		Closest to 12-months observation		Prior to/on start of treatment		Closest to 12-months observation		Prior to/on start of treatment		Closest to 12-months observation	
			n	%	N	%	n	%	n	%	n	%	n	%
Mean (SD) SBP/DBP			134.0 (14.6) / 78.4 (9.2)		131.3 (13.9) / 77.0 (9.0)		133.5 (15.0) / 77.6 (9.8)		131.6 (14.9) / 76.7 (9.2)		133.8 (14.7) / 78.2 (9.4)		131.4 (14.1) / 76.9 (9.0)	
Median (IQR) SBP/DBP			133 (125, 140) / 80 (72, 83)		130 (122, 140) / 78 (70, 81)		132 (124, 140) / 78 (70, 83)		131 (122, 140) / 78 (70, 80)		133 (124, 140) / 79 (71, 83)		130 (122, 140) / 78 (70, 81)	
Non-response SBP/DBP			2240 (49.2)		2374 (52.1)		823 (50.5)		854 (52.4)		3138 (49.9)		3299 (52.4)	

Change in the median values of SBP during the 12-month observation period have been presented as box plots (bars represent IQR) in Figures 12aa to 12cc, stratified by sex and repeated for the total cohort, exenatide naïve patients and previous Byetta® users. Results are presented for each group for all patients, for those with a decrease in SBP and those with an increase in SBP.

For the total cohort, where change in SBP was calculable, SBP was reported to have decreased for 896 patients (14.2% of cohort) and increased for 635 patients (10.1% of cohort).

Figure 12aa. Median (IQR) change in SBP from baseline to closest to 12 months for the total cohort

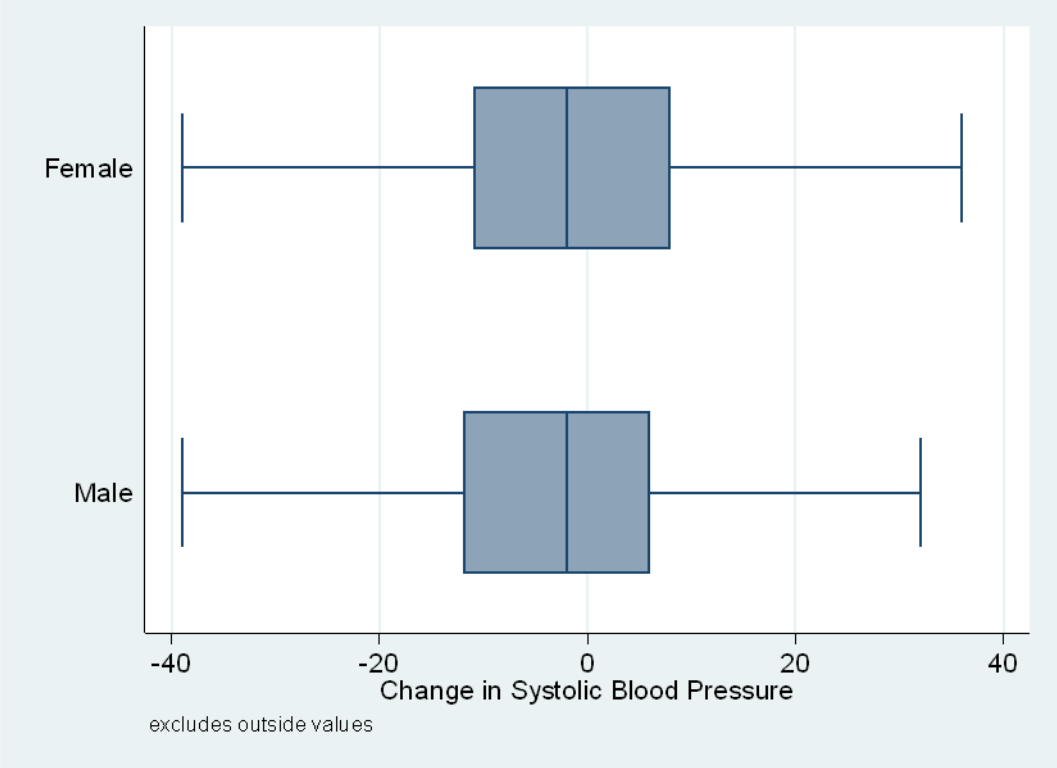


Figure 12ab. Median (IQR) change in SBP from baseline to closest to 12 months for the total cohort who had a decrease in SBP only (n=896)

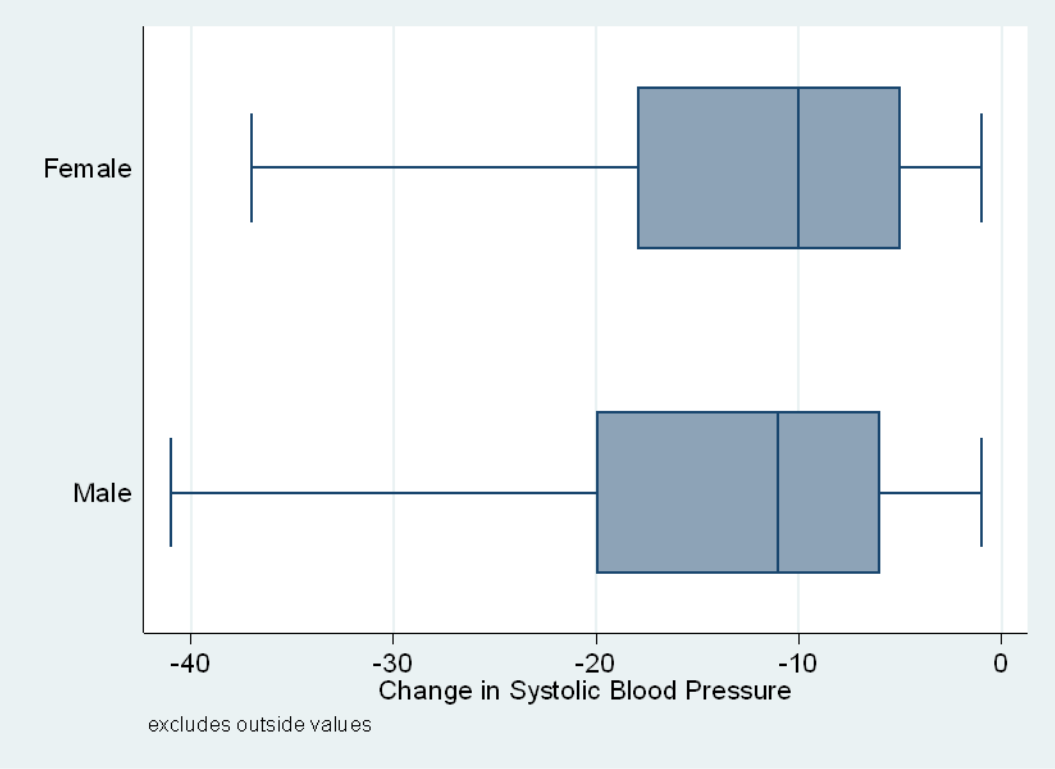
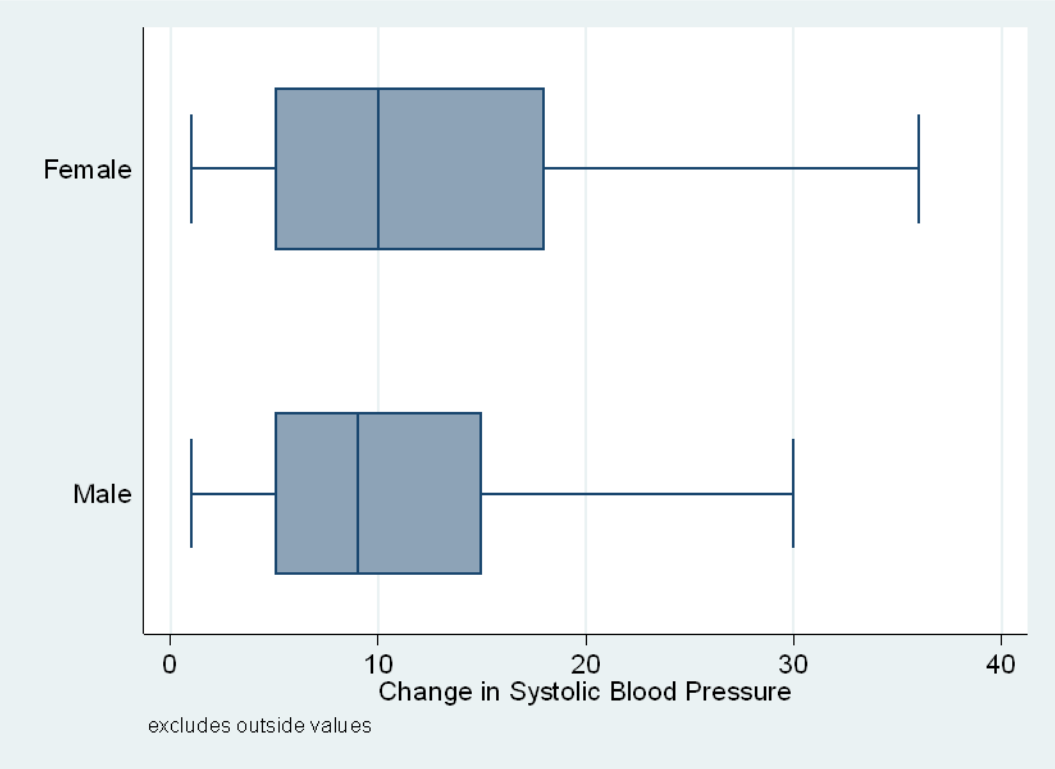


Figure 12ac. Median (IQR) change in SBP from baseline to closest to 12 months for the total cohort who had an increase in SBP only (n=635)



For exenatide naïve patients only, where change in SBP was calculable, SBP was reported to have decreased for 659 patients (14.5% of exenatide naïve patients) and increased for 446 patients (9.8% of exenatide naïve patients).

Figure 12ba. Median (IQR) change in SBP from baseline to closest to 12 months for all exenatide naïve patients

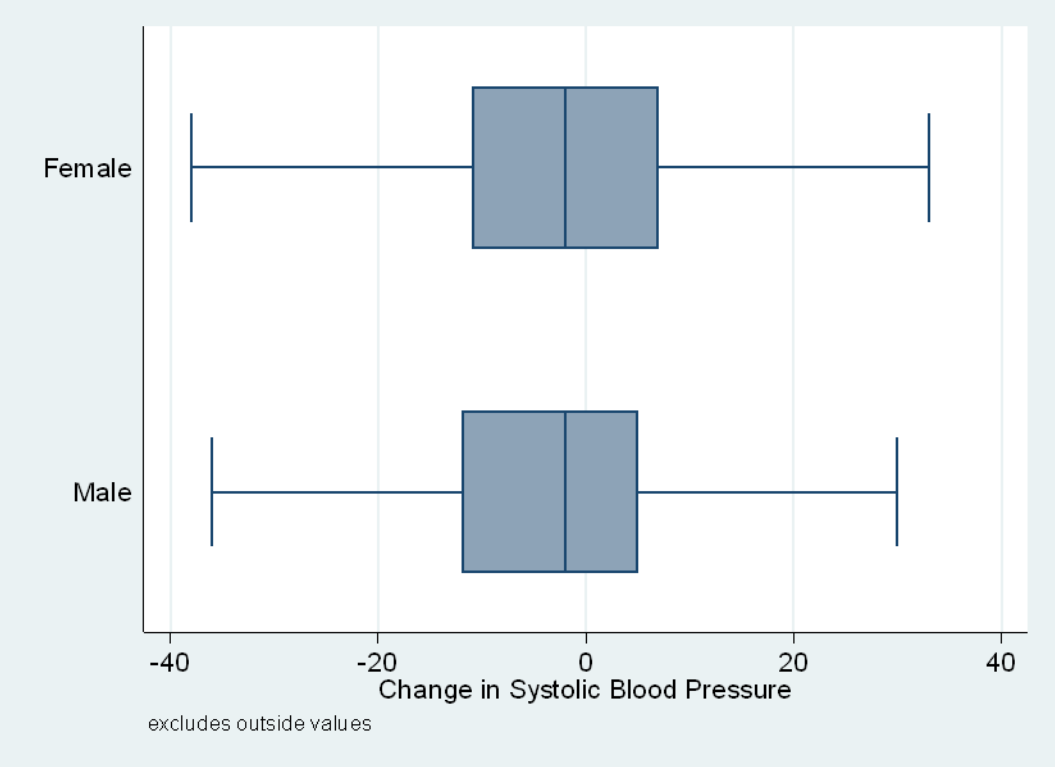


Figure 12bb. Median (IQR) change in SBP from baseline to closest to 12 months for exenatide naïve patients who had a decrease in SBP only (n=659)

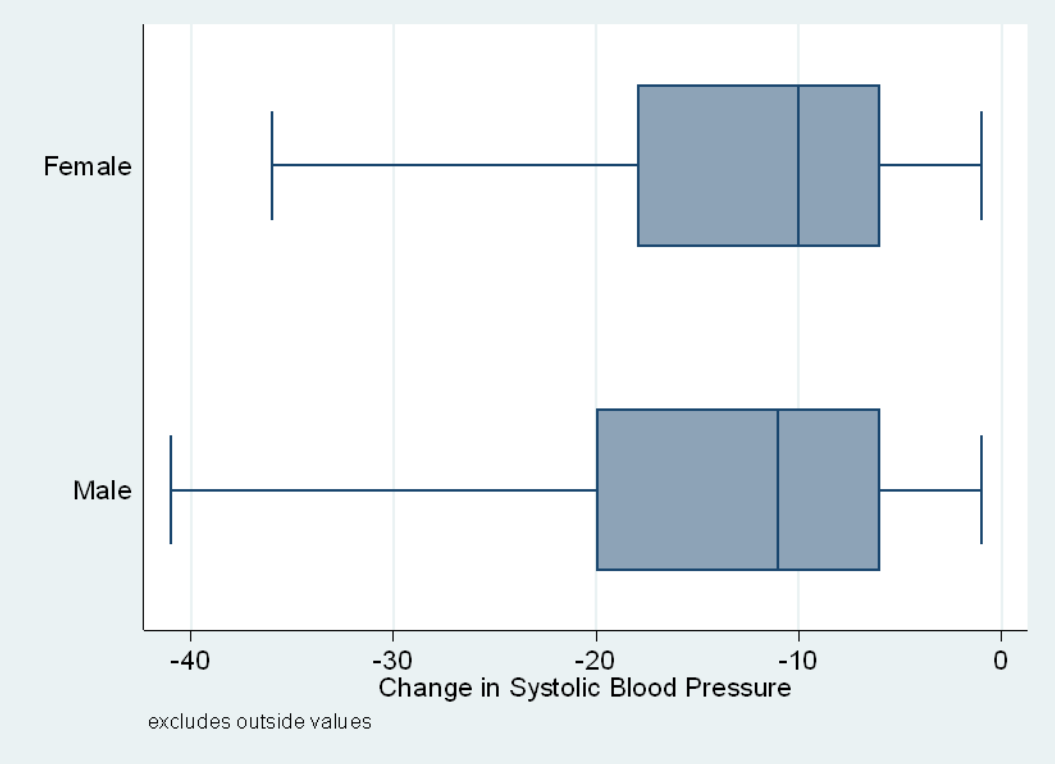
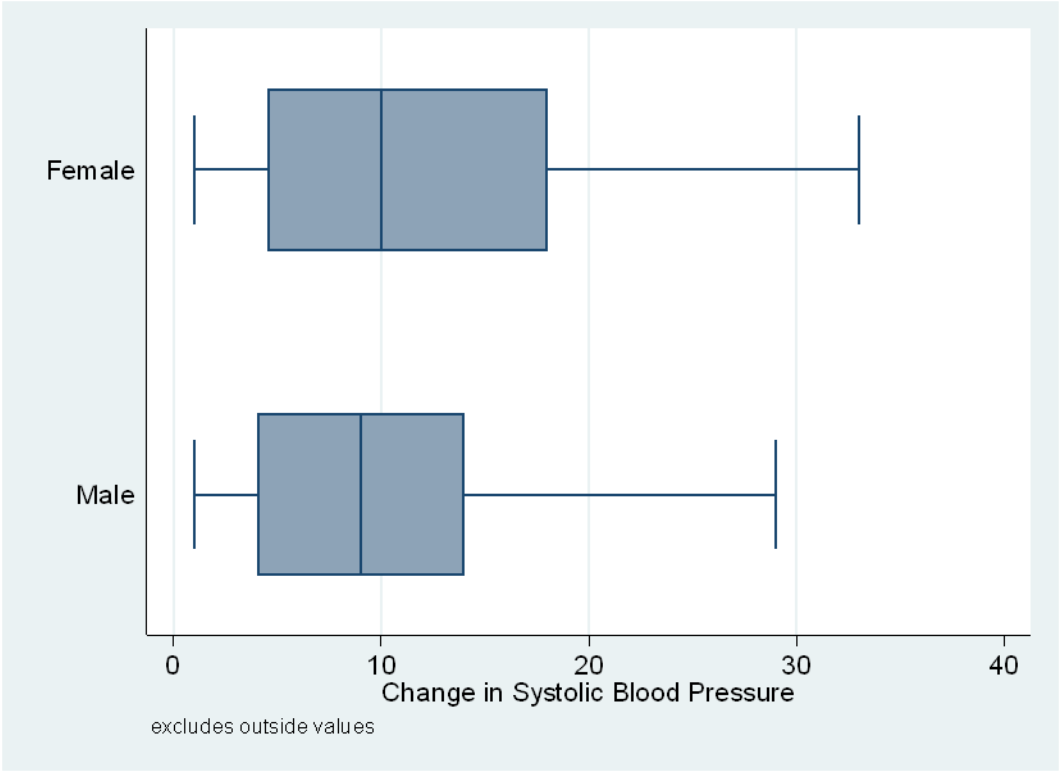


Figure 12bc. Median (IQR) change in SBP from baseline to closest to 12 months for exenatide naïve patients who had an increase in SBP only (n=446)



For previous Byetta® users, where change in SBP was calculable, SBP was reported to have decreased for 227 patients (13.9% of previous Byetta® users) and increased for 182 patients (11.2% of previous Byetta® users).

Figure 12ca. Median (IQR) change in SBP from baseline to closest to 12 months for all previous Byetta® users

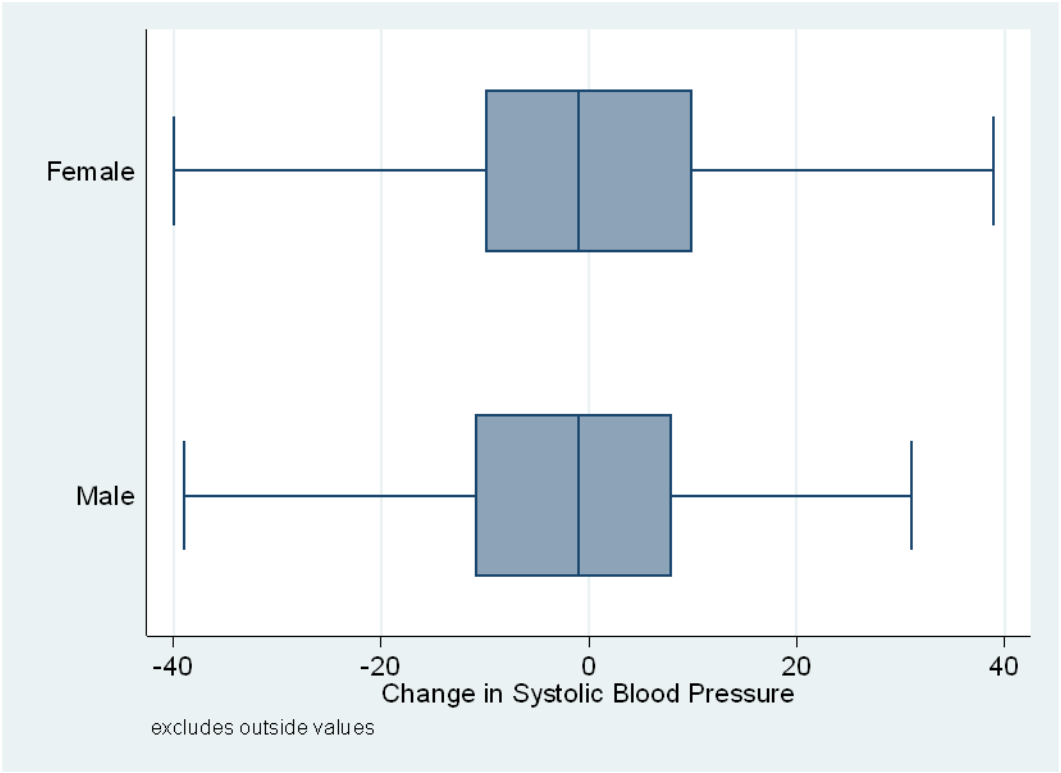


Figure 12cb. Median (IQR) change in SBP from baseline to closest to 12 months for previous Byetta® users who had a decrease in SBP only (n=227)

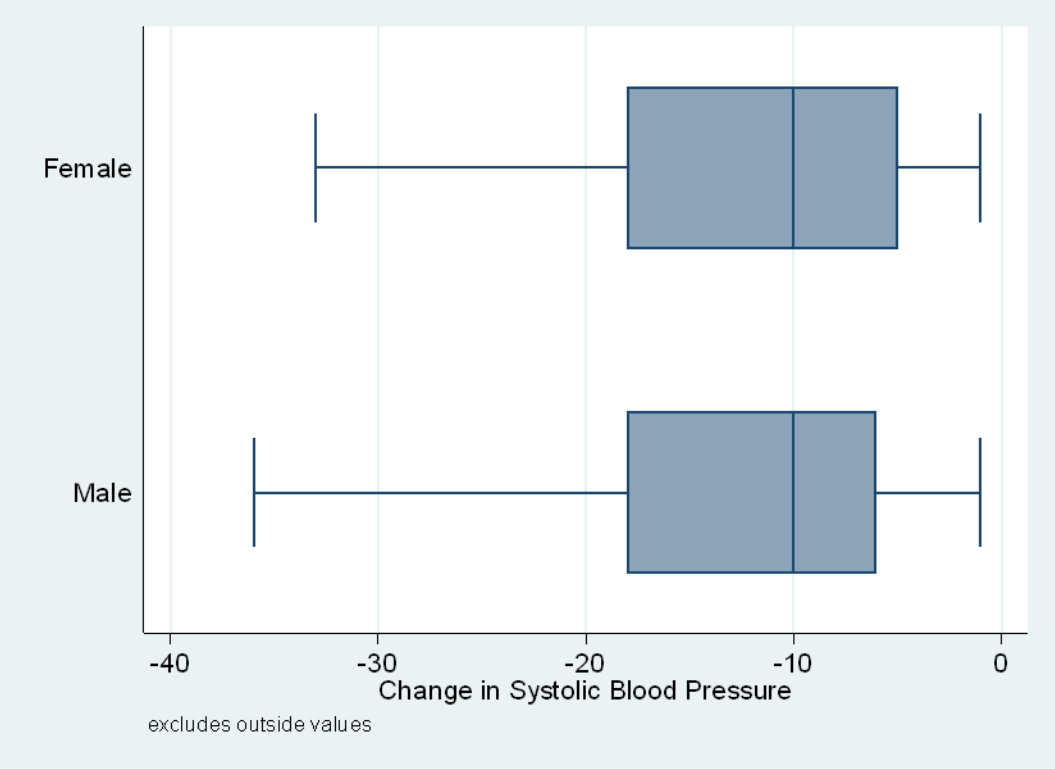
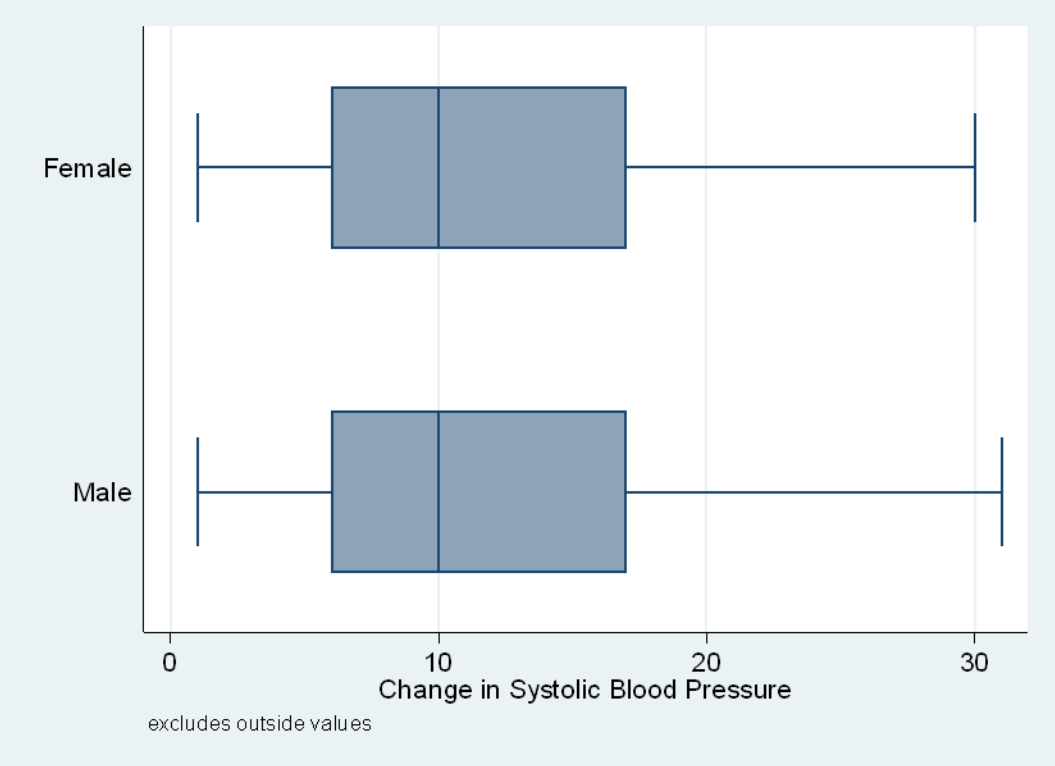


Figure 12cc. Median (IQR) change in SBP from baseline to closest to 12 months for previous Byetta® users who had an increase in SBP only (n=182)



Additional analyses on potentially clinically significant changes in SBP have been presented in Section 10.5.1.5.

10.5.1.4 Haemoglobin A1c

Haemoglobin A1c (HbA1c) measurements (mmol/mol) within three months prior to starting were provided for 2123 patients (33.7% of cohort). Approximately one-fifth of patients (n=1299, 20.6% of cohort, 61.1% where HbA1c within three months prior to starting specified) had an HbA1c of ≥75 mmol/mol (≥9.0%) indicating very poor control of their diabetes.

At index, HbA1c measurements (according to the rule base provided in Section 10.5.1) were provided for 2207 patients (35.1% of cohort; Table 42). Approximately one-third of patients had an HbA1c≥59 mmol/mol (≥7.5%) (n=1986, 31.6% of cohort; 90.0% where baseline HbA1c specified); of these 1311 patients (66.0% of patients with an HbA1c ≥7.5%, 20.8% of cohort; 59.4% where baseline HbA1c specified) had an HbA1c of ≥75 mmol/mol (≥9.0%) indicating very poor control of their diabetes. Closest to the 12-month observation period, HbA1c measurements (according to the rule base provided in Section 10.5.1) were provided for 2268 patients (36.0% of cohort). There were 1464 patients with an HbA1c≥59 mmol/mol (≥7.5%) (23.3% of cohort, 64.6% where 12-month HbA1c specified); of these 754 patients (51.5% of patients with an HbA1c ≥7.5%, 12.0% of cohort; 51.5% where 12-month HbA1c specified) had an HbA1c of ≥75 mmol/mol (≥9.0%) indicating very poor control of their diabetes.

The mean (SD) HbA1c at index was 80.7 (19.1) mmol/mol and at 12-months the mean was 68.9 (19.6) mmol/mol. After stratifying by prior exenatide use, the mean (SD) HbA1c at baseline was slightly higher for exenatide naïve patients as compared to previous Byetta® users (81.9 (18.8) mmol/mol vs. 77.0 (19.5) mmol/mol, respectively); the same was true at 12 months (69.0 (19.8) mmol/mol vs. 68.2 (18.7) mmol/mol, respectively).

In the total cohort, for those patients where a potential change in HbA1c could be calculated[32], the mean (SD) of the differences in HbA1c from baseline to closest to 12 months was -13.2 (19.6) mmol/mol and the median (IQR) of the differences in HbA1c was -12.0 (-25.0, -1.0) mmol/mol. After stratifying by prior exenatide use, the mean and median of the differences in HbA1c from baseline to closest to 12 months were greater for exenatide naïve patients than for previous Byetta® users. The respective mean (SD) and median (IQR) of the differences were -14.4 (20.0) mmol/mol and -14.0 (-26.0, -3.0) mmol/mol for exenatide naïve patients and -9.7 (17.0) mmol/mol and -9.0 (-22.0, 2.0) mmol/mol for previous Byetta® users.

[32] Calculable potential change in HbA1c: exenatide naïve (n=1310), previous Byetta® users (n=399), total cohort (n=1729)

Table 42. HbA1c measurements within 3 months prior to starting Bydureon®, at start of Bydureon® treatment and closest to 12 months after starting

	Exenatide naïve (N=4556)						Previous Byetta users (N=1629)						Total cohort (N=6294)					
	Within 3-months prior to starting		At start of treatment (baseline)		Closest to 12-months observation		Within 3-months prior to starting		At start of treatment (baseline)		Closest to 12-months observation		Within 3-months prior to starting		At start of treatment (baseline)		Closest to 12-months observation	
HbA1c mmol/mol (%)	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
<48 (<6.5%)	20	0.4	27	0.6	169	3.7	16	1.0	26	1.6	55	3.4	36	0.6	53	0.8	225	3.6
48-<59 (6.5-<7.5%)	81	1.8	103	2.3	441	9.7	60	3.7	63	3.9	131	8.0	141	2.2	168	2.7	579	9.2
59-<65 (7.5-<7.9%)	139	3.1	148	3.2	221	4.9	55	3.4	52	3.2	90	5.5	194	3.1	200	3.2	317	5.0
65-<75 (8.0-<8.9%)	359	7.9	362	7.9	294	6.5	89	5.5	109	6.7	93	5.7	453	7.2	475	7.5	393	6.2
≥75 (≥9.0%)	1022	22.4	1009	22.1	569	12.5	264	16.2	285	17.5	169	10.4	1299	20.6	1311	20.8	754	12.0
Non-response	2935	64.4	2907	63.8	2862	62.8	1145	70.3	1094	67.2	1091	67.0	4171	66.3	4087	64.9	4026	64.0
Total (N)	4556	100.0	4556	100.0	4556	100.0	1629	100.0	1629	100.0	1629	100.0	6294	100.0	6294	100.0	6294	100.0
Mean (SD)	83.0 (18.7)		81.9 (18.8)		69.0 (19.8)		79.1 (20.0)		77.0 (19.5)		68.2 (18.7)		82.1 (19.1)		80.7 (19.1)		68.9 (19.6)	
Median (IQR)	80 (69, 94)		80 (68, 93)		65 (54, 80)		78 (63, 92)		76 (63, 88)		64 (55, 78)		80 (68, 94)		79 (67, 92)		65 (55, 79)	
Range (Min, Max)	36, 180		18, 180		19, 173		38, 146		22.5, 161		26, 157		36, 180		18, 180		19, 173	

Change in the median values of HbA1c during the 12-month observation period have been presented as box plots (bars represent IQR) in Figures 13aa to 13cc, stratified by sex and repeated for the total cohort, exenatide naïve patients and previous Byetta® users. Results are presented for each group for all patients, for those with a decrease in HbA1c and those with an increase in HbA1c.

For the total cohort, where change in HbA1c was calculable, HbA1c was reported to have decreased for 1324 patients (21.0% of cohort) and increased for 369 patients (5.9% of cohort).

Figure 13aa. Median (IQR) change in HbA1c from baseline to closest to 12 months for the total cohort

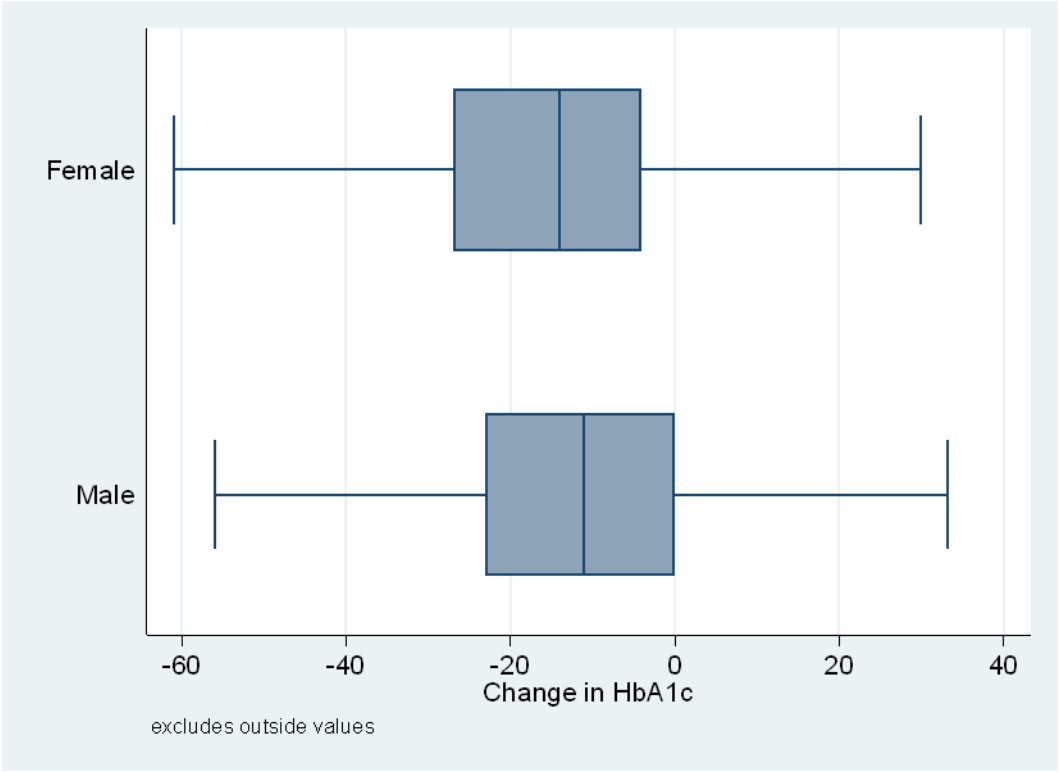


Figure 13ab. Median (IQR) change in HbA1c from baseline to closest to 12 months for the total cohort who had a decrease in HbA1c only (n=1324)

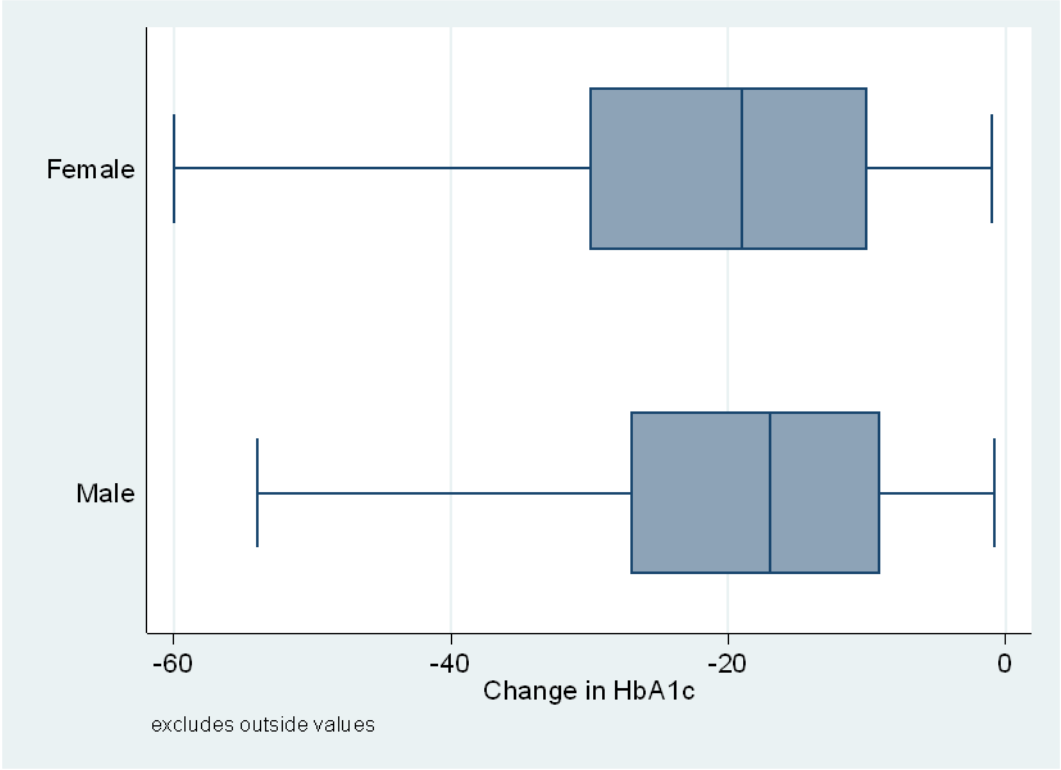
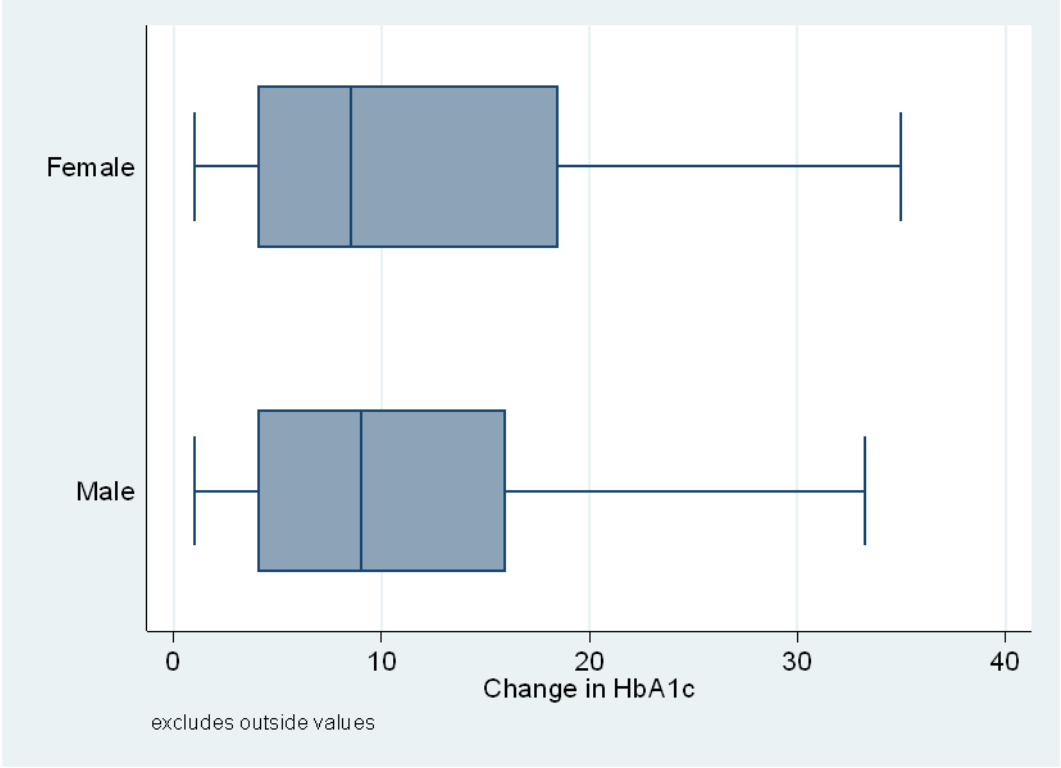


Figure 13ac. Median (IQR) change in HbA1c from baseline to closest to 12 months for the total cohort who had an increase in HbA1c only (n=369)



For exenatide naïve patients only, where change in HbA1c was calculable, HbA1c was reported to have decreased for 1030 patients (22.6% of exenatide naïve patients) and increased for 253 patients (5.6% of exenatide naïve patients).

Figure 13ba. Median (IQR) change in HbA1c from baseline to closest to 12 months for all exenatide naïve patients

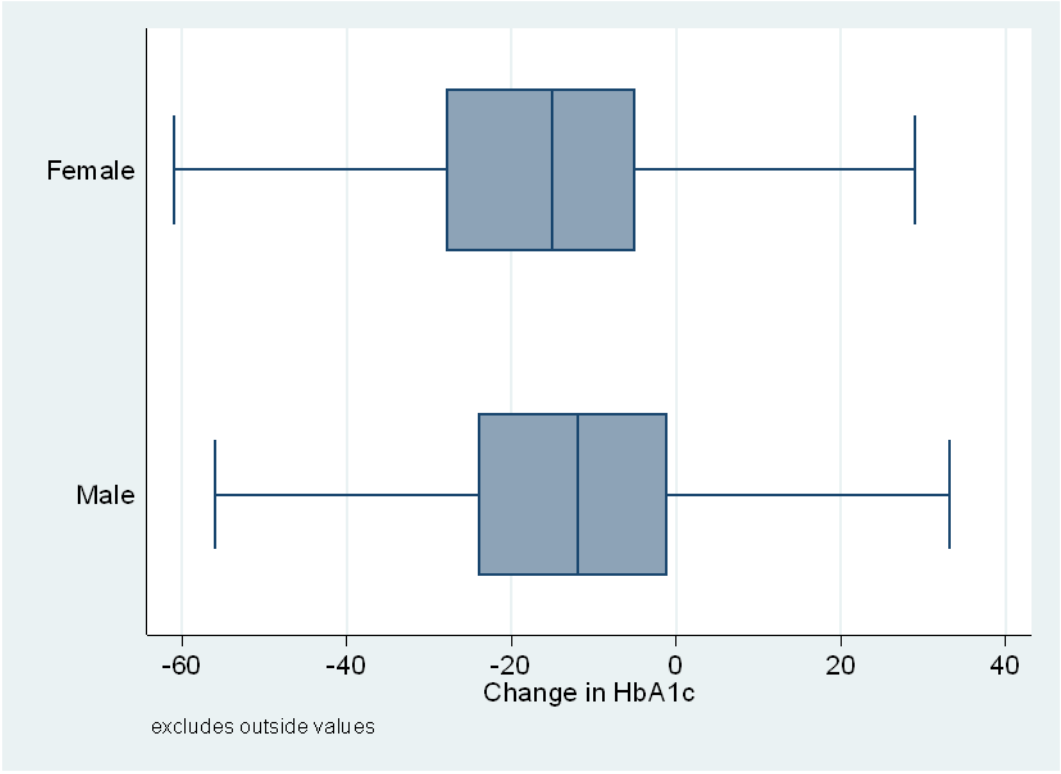


Figure 13bb. Median (IQR) change in HbA1c from baseline to closest to 12 months for exenatide naïve patients who had a decrease in HbA1c only (n=1030)

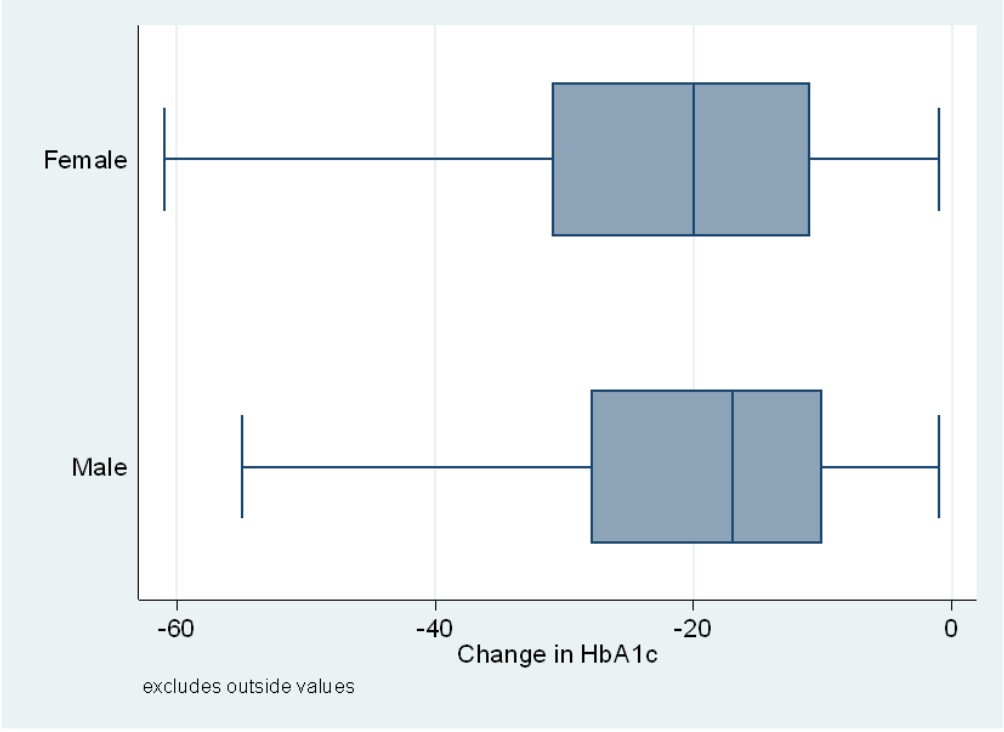
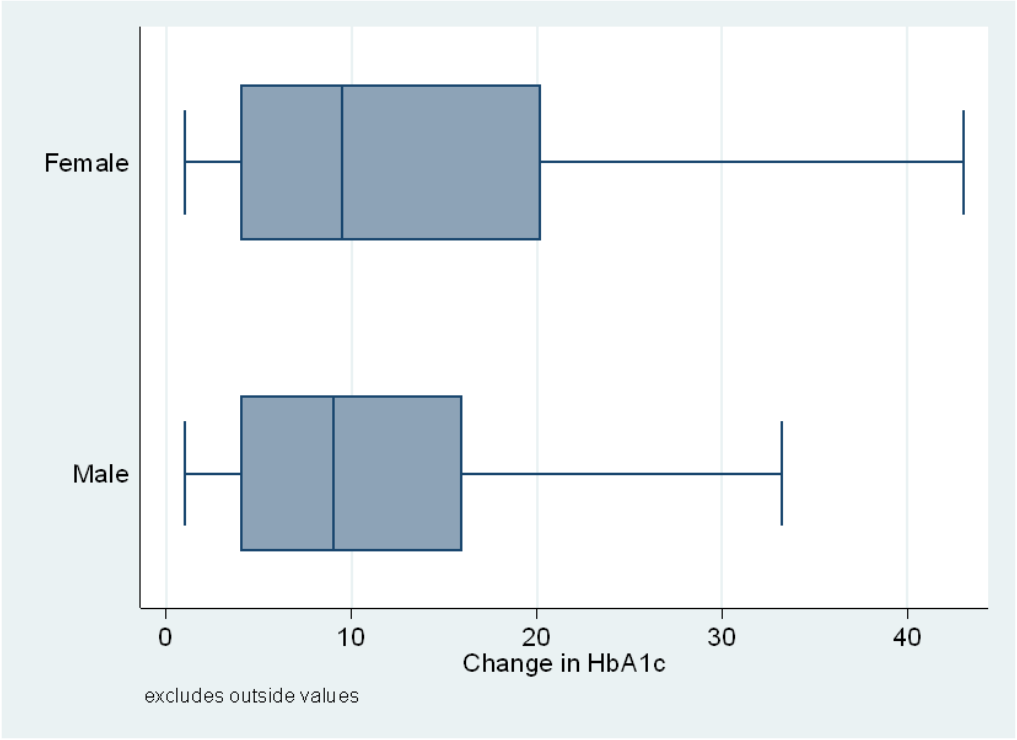


Figure 13bc. Median (IQR) change in HbA1c from baseline to closest to 12 months for exenatide naïve patients who had an increase in HbA1c only (n=253)



For previous Byetta® users, where change in HbA1c was calculable, HbA1c was reported to have decreased for 281 patients (17.2% of previous Byetta® users) and increased for 110 patients (6.8% of previous Byetta® users).

Figure 13ca. Median (IQR) change in HbA1c from baseline to closest to 12 months for all previous Byetta® users

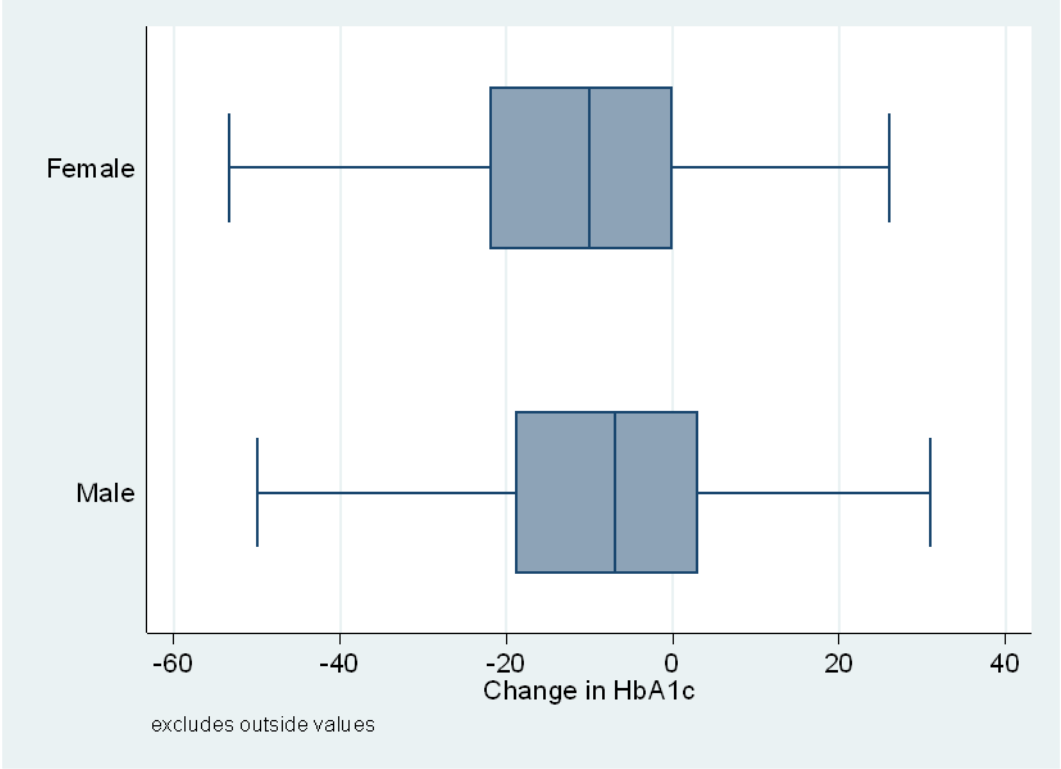


Figure 13cb. Median (IQR) change in HbA1c from baseline to closest to 12 months for previous Byetta® users who had a decrease in HbA1c only (n=281)

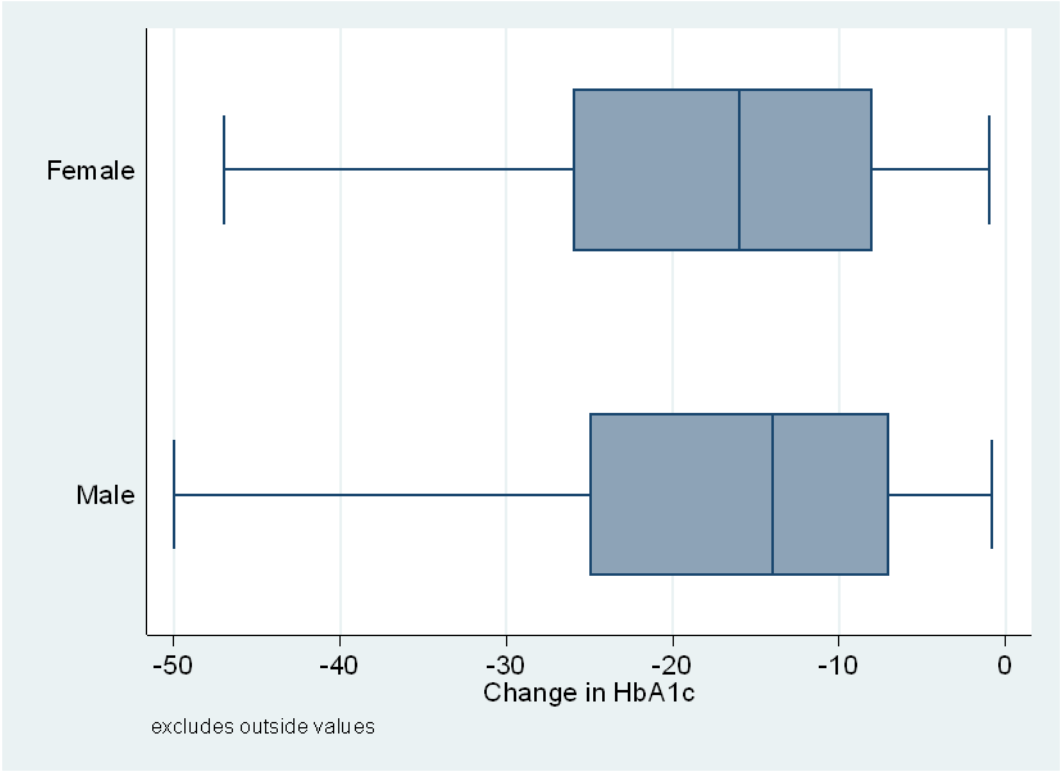
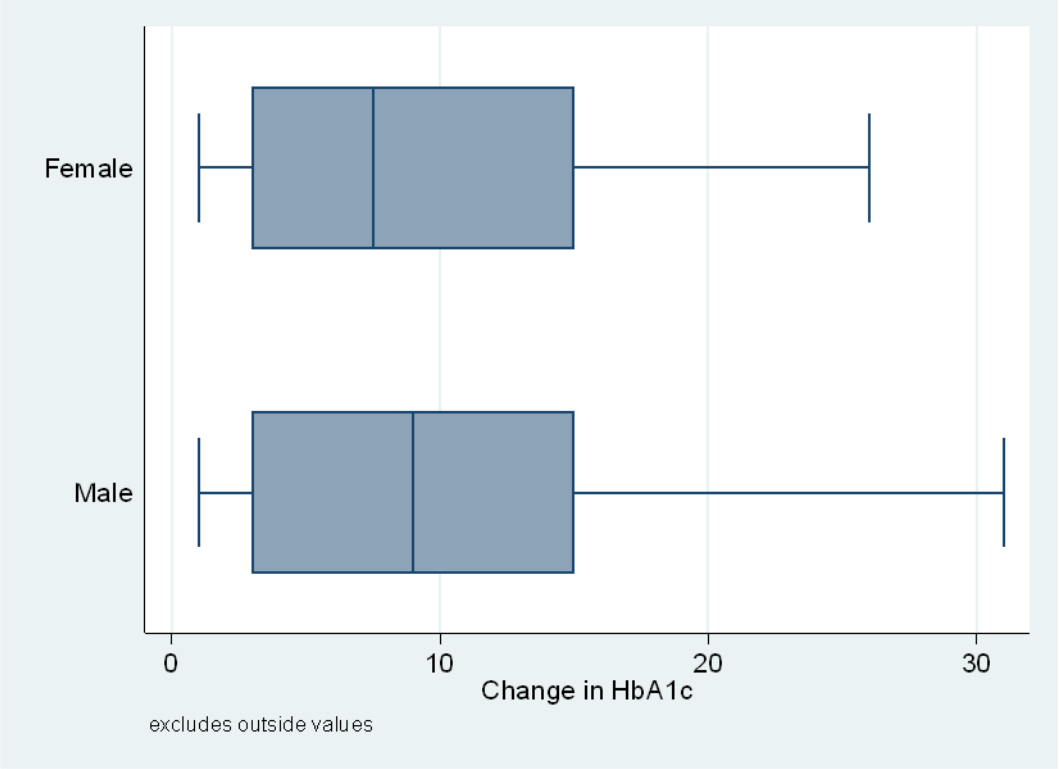


Figure 13cc. Median (IQR) change in HbA1c from baseline to closest to 12 months for previous Byetta® users who had an increase in HbA1c only (n=110)



10.5.1.5 Potentially clinically significant changes in health profile

10.5.1.5.1 Weight loss reported as free text

The number of patients for whom the GP reported weight loss as a free text event[33] have been summarised in Table 43. These counts have been derived from the MedDRA preferred terms 'abnormal loss of weight', 'weight decreased' or 'body mass index decreased'.

In the total cohort, there were 53 patients (0.8% of cohort; 95% CI [0.6, 1.1]) for whom the GP reported weight loss on treatment (plus the 10-week washout period) during the 12-month observation period. For 23 patients (0.4% of cohort) a loss in weight was reported as a free text event during treatment with Bydureon® (plus the 10-week washout period) and for 33 patients (0.5% of cohort) this was reported as a reason for stopping. Note, a GP may have reported weight loss as both a free text event in the event section of the 12-month questionnaire and as a reason for stopping, so these counts are not mutually exclusive.

The cumulative incidence of weight loss was similar for exenatide naïve patients and previous Byetta® users; weight loss was reported for 42 patients in the exenatide naïve group (0.9%; 95% CI [0.7, 1.2]) and for 11 patients who were previous Byetta® users (0.7%; 95% CI [0.3, 1.2]).

[33] Derived from the event sections and/or reasons for stopping on the 12-month questionnaire

Table 43. Number of patients reporting free text events of weight loss[a] during treatment with Bydureon® and as a reason for stopping within the 12- month observation period and cumulative incidence estimates (+95% CI)

	Exenatide Naïve (N=4556)			Previous Byetta® users (N=1629)			Total Cohort (n=6294)		
	n	%	95% CI	n	%	95% CI	n	%	95% CI
Weight loss reported as a free text event during Bydureon®	19	0.4	0.3, 0.7	4	0.2	0.1, 0.6	23	0.4	0.2, 0.5
Weight loss reported as a reason for stopping Bydureon®	25	0.5	0.4, 0.8	8	0.5	0.2, 1.0	33	0.5	0.4, 0.7
Weight loss (Total)	42	0.9	0.7, 1.2	11	0.7	0.3, 1.2	53[a]	0.8	0.6, 1.1

[a] Derived from MedDRA preferred terms 'abnormal loss of weight', 'weight decreased' or 'body mass index decreased'
[b] Three patients had weight loss reported as both a free text event and a reason for stopping

For these patients, where reported, weight and/or BMI measurements at baseline and closest to 12 months (according to the rule base defined in Section 10.5.1) have been summarised separately from the cohort. Tables and figures (in the form of box plots) for these results are presented in Appendix 25a and changes in weight/BMI are summarised in the narrative below.

Results suggest that all patients experienced a decrease in weight/ BMI or there was no change from the values they reported (Appendix 25a).

In the total cohort, for those patients with reported weight loss and for whom a potential change in BMI could be calculated[34], the mean (SD) of the differences in BMI from baseline to closest to 12 months was -3.9 (3.4) kg/m^2 and the median (IQR) of the differences in BMI was -3.6 (-4.7, -1.8) kg/m^2. After stratifying by prior exenatide use, the mean and median of the differences in BMI from baseline to closest to 12 months was greater for exenatide naïve patients than for previous Byetta® users. The respective mean (SD) and median (IQR) of the differences were -4.3 (4.3) kg/m^2 and -4.1 (-4.5, -1.7) kg/m^2 for exenatide naïve patients and -3.3 (1.5) kg/m^2 and -3.0 (-4.9, -1.9) kg/m^2 for previous Byetta® users. Seven patients for whom the GP reported weight loss fulfilled the criteria for a potentially clinically significant reduction in BMI (defined as ≥1 kg/m^2 change in BMI from index); four patients were in the exenatide naïve group and three were previous Byetta® users. Box plots for the changes in BMI (kg/m^2) have been presented in Figures 1a-1f, Appendix 25a.

In the total cohort, for those patients with reported weight loss and for whom a potential change in weight could be calculated[35], the mean (SD) of the differences in weight from baseline to closest to 12 months was -10.1 (8.3) kg and the median (IQR) of the differences in weight was -8.0 (-15.0, -5.2) kg. After

[34] Calculable potential change in BMI for patients with reported weight loss: exenatide naïve (n=5), previous Byetta® users (n=3), total cohort (n=8)

[35] Calculable potential change in weight for patients with reported weight loss: exenatide naïve (n=7), previous Byetta® users (n=3), total cohort (n=10)

stratifying by prior exenatide use, the mean and median of the differences in weight from baseline to closest to 12 months was fairly similar between the exenatide naïve and previous Byetta® user groups. The respective mean (SD) and median (IQR) of the differences was -10.3 (9.7) kg and -8.0 (-15.0, -5.2) kg for exenatide naïve patients and -9.8 (5.6) kg and -8.0 (-16.0, -5.3) kg for previous Byetta® users. Nine patients for whom the GP reported weight loss fulfilled the criteria for a potentially clinically significant reduction in weight (defined as ≥3% change in weight (kg) from index); six patients were in the exenatide naïve group and three were previous Byetta® users. Box plots for the changes in weight (kg) have been presented in Figures 2a-2f, Appendix 25a.

10.5.1.5.2 Potentially clinically significant changes in health profile measurements

Appendix 25b (Table 1) also summarises the number of patients meeting the following specific criteria:

- Potentially clinically significant weight loss (defined as ≥3% change in weight (kg) from index)
- Potentially clinically significant BMI reduction (defined as ≥1 kg/m^2 change in BMI from index)
- Potentially clinically significant systolic blood pressure (SBP) increase (defined as ≥5 mmHg increase in SBP from index)
- Potentially clinically significant systolic blood pressure (SBP) decrease (defined as ≥ 5mmHg decrease in SBP from index)

The results from Table 1 in Appendix 25b have been summarised below. Note, a potentially clinically significant change in weight/BMI analyses (derived from changes in weight/BMI measurements) may or may not include patients for whom weight loss was also reported as free text (as reported in Table 43 above).

In the total cohort, 639 patients (44.8% where change in weight calculable for the total cohort, 10.2% of cohort) had a potentially clinically significant reduction in weight. A higher proportion of patients in the exenatide naïve group fulfilled the criteria of a ≥3% reduction in weight (kg) from index; 511 exenatide naïve patients had potentially clinically significant weight loss (48.1% where change in weight calculable for exenatide naïve patients, 11.2% of exenatide naïve patients) and 125 patients who were previous Byetta® users had a potentially clinically significant reduction in weight (35.5% where change in weight calculable for previous Byetta® users, 7.7% of previous Byetta® users).

For BMI, 619 patients in the total cohort (46.9% where change in BMI calculable for the total cohort, 9.8% of cohort) had a potentially clinically significant reduction in BMI. Similar to the weight analyses above, a higher proportion of patients in the exenatide naïve group fulfilled the criteria of a 1kg/m^2 change in BMI from index. Four hundred and eighty seven patients had a potentially clinically significant BMI reduction (48.9% where change in BMI calculable for exenatide naïve patients, 10.7% of exenatide naïve patients) and 129 patients who were previous Byetta® users had a potentially clinically significant reduction in BMI (40.8% where change in BMI calculable for previous Byetta® users, 7.9% of previous Byetta® users).

A potentially clinically significant increase in SBP was observed in a total of 487 patients (29.3% where change in SBP calculable for the total cohort, 7.7% of cohort). A higher proportion of previous Byetta® users fulfilled the criteria of a ≥5 mmHg increase in SBP from index; 148 patients with prior Byetta® use had a potentially clinically significant increase (33.6% where change in SBP calculable for previous Byetta® users, 9.1% of previous Byetta® users) and 333 patients who were exenatide naïve had a potentially clinically significant increase in SBP (27.7% where change in SBP calculable for exenatide naïve patients, 7.3% of exenatide naïve patients).

In contrast, more than twice the number of patients fulfilled the criteria for a potentially clinically significant decrease in SBP (n=984, 59.2% where change in SBP calculable for the total cohort, 15.6% of cohort). Similarly, a slightly higher proportion of previous Byetta® users fulfilled the criteria of a ≥5 mmHg decrease in SBP from index; 274 patients with prior Byetta® use had a potentially clinically significant decrease (62.3% where change in SBP calculable for previous Byetta® users, 16.8% of previous Byetta® users) and 698 patients who were exenatide naïve had a decrease in SBP considered as potentially clinically significant (58.0% where change in SBP calculable for exenatide naïve patients, 15.3% of exenatide naïve patients).

10.5.2 Smoking/Alcohol status

Information on the patients' smoking and alcohol intake was requested from GPs on the 12-month questionnaire. Results for smoking and excessive alcohol consumption prior to or present at start of treatment with Bydureon® are shown in Table 44. Excessive alcohol consumption was defined on the 12-month questionnaire as the consumption of greater than 21 units of alcohol per week for males and greater than 14 units of alcohol per week for females. Prior to treatment with Bydureon®, 257 patients (4.1 % of cohort) were reported to have consumed excessive amounts of alcohol. Prior history of excessive consumption was slightly more common for exenatide naïve patients as compared to previous Byetta® users (4.4% vs. 3.2%, respectively). In contrast to alcohol consumption, a prior history of smoking was reported in a significantly greater proportion of the cohort (n=2025, 32.2% of cohort). Similar to prior alcohol consumption history, prevalence of smoking prior to or at present at start of treatment with Bydureon® was slightly higher for exenatide naïve patients (33.8%) as compared to previous Byetta® users (28.2%).

Table 44. Smoking and excessive alcohol consumption[a] prior to or present at start of Bydureon®

	Exenatide Naïve (N=4556)						Previous Byetta® users (N=1629)						Total Cohort (N=6294)					
	Yes		No		Non-response		Yes		No		Non-response		Yes		No		Non-response	
	n	%	n	%	n	%	n	%	n	%	n	%	N	%	n	%	n	%
Excessive alcohol consumption[a]	202	4.4	4278	93.9	76	1.7	52	3.2	1543	94.7	34	2.1	257	4.1	5899	93.7	138	2.2
Smoking	1540	33.8	2927	64.2	89	2.0	459	28.2	1127	69.2	43	2.6	2025	32.2	4111	65.3	158	2.5

[a] Excessive alcohol consumption was defined as: male >21 units/week and female>14 units/week

The 12-month questionnaire also requested the GP to provide a date of when smoking was stopped if the patient was an ex-smoker. Prescriber reported information suggests that a date of stopping smoking was provided for a total of 623 ex-smokers (30.8% of prior smokers). Of these, the highest proportion of patients had stopped smoking less than 10 years prior to starting Bydureon® (n=455, 73.0% of patients for whom information on date when smoking was stopped was provided) (Table 45). However, due to the question posed it is not possible to ascertain the number of current smokers and ex-smokers.

Table 45. Time between smoking cessation and start of treatment with Bydureon® for patients who have stopped smoking

	Exenatide Naïve		Previous Byetta® users		Total cohort	
Duration (years)	**n**	**%**	**n**	**%**	**N**	**%**
<1	60	12.9	12	7.8	73	11.7
1-4	151	32.5	44	28.8	196	31.5
5-9	130	28.0	54	35.3	186	29.9
10-20	85	18.3	29	19.0	115	18.5
>20	39	8.4	14	9.2	53	8.5
Total (N)[a]	465	100.00	153	100.0	623	100.0

[a] Number of patients for whom information on date when smoking was stopped was provided

The prevalence of excessive alcohol consumption and smoking during treatment with Bydureon® was much lower than a prior history of these patient behaviours. During treatment with Bydureon®, 99 patients (1.6% of cohort) were reported to have consumed excessive amounts of alcohol and 797 (12.7% of cohort) were reported to have smoked (Table 46). Prevalence of excessive alcohol consumption was similar for exenatide naïve patients (1.7%) and previous Byetta® users (1.3%), whereas smoking was slightly higher for exenatide naïve patients as compared to previous Byetta® users (13.2% vs. 11.2%, respectively).

Table 46. Number of patients who smoked/consumed excessive alcohol[a] whilst taking Bydureon®

	Exenatide Naïve (N=4556)						Previous Byetta® users (N=1629)						Total Cohort (N=6294)					
	Yes		No		Non-response		Yes		No		Non-response		Yes		No		Non-response	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Excessive alcohol consumption[a]	75	1.7	3490	76.6	991	21.8	21	1.3	1307	80.2	301	18.5	99	1.6	4860	77.2	1335	21.2
Smoking	608	13.4	3092	67.9	856	18.8	182	11.2	1159	71.2	288	17.7	797	12.7	4313	68.5	1184	18.8

[a] Excessive alcohol consumption was defined as: male >21 units/week and female>14 units/week

10.5.3 Non-compliance/Adherence issues

The 12-month questionnaire requested information from GPs on patient non-adherence or compliance regarding Bydureon® therapy. The GPs were asked if they were aware of the patient having treatment compliance (adherence) problems with Bydureon®. The responses to this question are provided in Table 47.

A response to treatment compliance/adherence was provided for 6005 patients (95.4% of cohort) and a total of 899 patients (14.3% of cohort, 15.0% where specified) were reported to have non-adherence or compliance issues with Bydureon®. The proportion of patients with compliance/adherence issues was slightly higher in the exenatide naïve group (n=659, 14.5% of exenatide naïve patients) as compared to the previous Byetta® user group (n=224, 13.8% of previous Byetta® users).

Table 47. Number of patients prescribed Bydureon® for whom the GP was aware of patient non-adherence or compliance

Awareness of non-adherence/compliance	Exenatide naïve (N=4556)		Previous Byetta® users (N=1629)		Total cohort (N=6294)	
	N	%	n	%	n	%
Yes	659	14.5	224	13.8	899	14.3
No	3687	80.9	1355	83.2	5106	81.1
Non-response	210	4.6	50	3.1	289	4.6
Total (N)	4556	100.0	1629	100.0	6294	100.0

If the patient was reported to experience treatment compliance/adherence problems, the GP was requested to further indicate the type of problem through pre-specified tick box responses (Table 48). More than one treatment compliance/adherence issue could be reported so counts are not mutually exclusive. A response to the type of treatment compliance/adherence issue was provided for 699 patients (77.8% of patients for whom the GP was aware of these issues). In total, of those patients from whom the GP reported adherence/compliance issues (n=899), 'non-compliance with Bydureon® regimen' and 'non-adherence to lifestyle modification programme' were reported in similar proportions (46.2% and 45.6% of patients for whom the GP was aware of these issues, respectively). 'Missed appointments with GP/nurse' was reported for 322 patients (35.8% of patients for whom the GP was aware of these issues). In addition, for 279 patients the GP ticked 'other' and were further requested to specify the type of treatment/compliance problem. These have been listed as reported by the GP in Appendix 26; for two patients the GP had ticked 'other' and not specified the type of problem.

After stratifying by prior exenatide use, it can be seen that 'non-adherence to lifestyle modification programme' was slightly more frequently reported as compared to 'non-compliance with Bydureon® regimen' in previous Byetta® users (50.9% vs. 47.8%, respectively). The reverse findings are seen in the exenatide naïve group, in addition to a higher proportion of patients having 'missed appointments with GP/nurse' in exenatide naïve patients as compared to previous Byetta® users (36.4% vs. 33.0%, respectively).

Table 48. Type of non-adherence/compliance issues reported by the prescribing GP

Non-adherence/ compliance issue	Exenatide naïve n	Exenatide naïve % of patients for whom the GP reported awareness of adherence/compliance issues (N=659)	Previous Byetta® users n	Previous Byetta® users % of patients for whom the GP reported awareness of adherence/compliance issues (N=224)	Total cohort n	Total cohort % of patients for whom the GP reported awareness of adherence/compliance issues (N=899)
Non-compliance with Bydureon® regimen	303	46.0	107	47.8	415	46.2
Non-adherence to lifestyle modification programme	288	43.7	114	50.9	410	45.6
Missed appointments with GP/nurse	240	36.4	74	33.0	322	35.8
Other[a]	208	31.6	63	28.1	279	31.0
Non-response[b]	146	22.2	48	21.4	200	22.2

[a] All other non-adherence/compliance issues as reported by the GP have been listed in Appendix 26.

[b] Patients for whom the GP has ticked 'Yes' to adherence/compliance problems but have not specified the type of problem

10.6 Adverse Events/Adverse Reactions

Modified-PEM data has been derived through secondary use of medical records information as abstracted onto study specific questionnaires by GPs in England and aggregate event data has been collated during the course of this study. Since the clinicians are prescribing a licensed product it is their responsibility to report any suspected adverse reactions (including serious adverse drug reactions) to the company and/or to the MHRA using Yellow Cards as they would normally do in their practice. Reports received by the DSRU in error are forwarded to the MHRA and/or the MAH as appropriate.

The DSRU will continue to review and process additional questionnaires received up until one year after the production of this final report. The numbers of such reports are expected to be small as they are reports who are sent late by doctors. If any signal/concern emerges from the review of questionnaires returned late, this will reported by the DSRU to the MAH.

11 Discussion

This final study report summarises data on patients prescribed Bydureon® in the primary care setting in England conducted as a Post-Authorisation Safety Study (PASS) in the EU. This study uses a M-PEM cohort design that is defined as a pharmacoepidemiological method to understand the post-marketing safety of medicines. Patients in the study included exenatide naïve patients and previous Byetta® users who were prescribed Bydureon® between January 2012 and September 2016. A total of 24760 unique patients prescribed Bydureon® were identified from 283523 Bydureon® prescriptions. The study used a specific design which aimed to capture information on drug utilisation, patient characteristics and events based on GP reporting on questionnaires sent at ≥12-months after index. Of the 20860 eligible patients for whom a 12-month questionnaire was sent to prescribing GPs, 7752 patients had a 12-month questionnaire returned, giving a response rate of 37.2%. Ten of these 12-month questionnaires were returned after data-lock (28th February 2018), thus only 7742 questionnaires were eligible for inclusion in the analysis of this report. After exclusion of the 12-month questionnaires which were non-evaluable (n=1448), 6294 remained available for study analysis (81.3% of 12-month questionnaires returned prior to data-lock, 30.2% of 12-month questionnaires sent). Exclusion criteria included patients for whom an off-label indication (i.e., type 1 diabetes mellitus) was provided (n=16, 0.2% of 12month questionnaires returned prior to data-lock) and patients for whom a diagnosis of type 2 diabetes mellitus was reported post index (n=8, 0.1% of 12-month questionnaires returned prior to data-lock). Thus, all patients in this final evaluable cohort were considered to be taking Bydureon® for an indication of type 2 diabetes mellitus, which was diagnosed prior to or at the time of starting Bydureon®.

11.1 Key results

The primary objective of the study was to estimate the cumulative incidence of acute pancreatitis in the first 12 months after starting treatment with Bydureon®. Secondary objectives included describing the baseline

health profile of patients on treatment with Bydureon®, the treatment regimen received and describing the risk profile of events. In addition, exploratory objectives included describing the characteristics of patients with acute pancreatitis, pancreatic cancer and thyroid neoplasms. There is a relatively large body of literature looking at the safety of Bydureon®, both from clinical trials and observational research. The results from this M-PEM study, which is part of the full PASS program for Bydureon®, have been considered alongside other research results. Incidence estimates provided in this discussion from this M-PEM study include events occurring on treatment with Bydureon® or during the 10-week washout period after stopping within 12-months after index, unless otherwise specified.

Prior Byetta® use

Stratification of the cohort between exenatide naïve and past users has been performed throughout the report. The majority of patients did not have previous exposure to Byetta® (n=4556, 72.4% of cohort) and were therefore classified as 'exenatide naïve'. Approximately one-quarter of patients (n=1629, 25.9% of cohort) contributed to the 'previous Byetta® user' group and for 109 patients (1.7% of cohort) previous exposure to exenatide (Byetta®) was not known from the information available.

Acute pancreatitis

In this M-PEM study, the cumulative incidence of acute pancreatitis over the 12-month observation period was 0.2% (95% CI [0.1, 0.4]; n=14); only two of the 14 patients had a prior history. Cumulative incidence of acute pancreatitis was the same for both exenatide naïve patients (0.2% (95% CI [0.1, 0.4]); n=10) and previous Byetta® users (0.2% (95% CI [0.0, 0.5]); n=3). Incidence rate of acute pancreatitis was observed to be low; for the total cohort the 12-month incidence rate was 2.5 per 1000 person-years (95% CI [1.5, 4.3]). After stratifying by previous exenatide use, incidence rate was slightly higher for exenatide naïve patients as compared to previous Byetta® users ((2.5 per 1000 person-years; 95% CI [1.4, 4.6]) vs. (2.1 per 1000 person-years; 95% CI [0.7, 6.4], respectively). However, overlapping 95% confidence intervals indicate no statistically significant difference in the incidence rate between the two user groups.

In addition to the above analysis, time-to-first acute pancreatitis analyses was performed to explore the risk of having the event over time. For the total cohort, more than 50% of cases (n=10) occurred during the first 120 days of treatment. Results suggest that there is no clear pattern in the hazard function (time to onset) of acute pancreatitis over time within this study.

For 12 of the 14 patients, Bydureon® was stopped as a result of the acute pancreatitis. Pancreatic complications of necrosis and pseudocyst were reported for one patient and a fatal outcome in another.

The low incidence of acute pancreatitis in this M-PEM study (0.2%) is comparable or lower than that observed in clinical trials. Single counts of pancreatitis were reported in the shorter pivotal DURATION clinical trials for patients taking Bydureon® (<1.0%). (3-10) Similar findings were observed in the DURATION extension trials; only one case of acute pancreatitis was reported during six years of follow-up

(0.7%; annual rate 0.001 events/year) in an uncontrolled open-label extension of the DURATION-1 trial and no further cases were reported beyond 26 weeks in the 84-week extension of the DURATION-3 trial. (12, 36) However, in a randomised controlled trial investigating the effects of Bydureon® on cardiovascular outcomes in patients with type 2 diabetes mellitus (EXSCEL trial) including 7356 patients randomised to the Bydureon® arm and 7936 to the control group, the incidence of acute pancreatitis was 0.4% (n=26) and 0.3% (n=22), respectively. Note, follow up in this trial (median duration 3.2 years) was longer than that of this M-PEM study (12 months). (19) In addition, the cumulative incidence of acute pancreatitis in this M-PEM study is lower than that reported in an open-label randomised controlled trial comparing the GLP-1 agonist semaglutide with exenatide once-weekly over 56 weeks in 813 subjects with type 2 diabetes mellitus; three cases of confirmed (treatment emergent) mild acute pancreatitis occurred in patients taking exenatide, providing an incidence estimate of 0.7%. (37)

The majority of evidence of acute pancreatitis within observational studies is based on exenatide use prior to Bydureon® marketing authorisation, however, results are comparable with our study findings. In a retrospective cohort study of a large US medical and pharmacy claims database including 6545 patients taking exenatide and followed up for a mean duration of 0.6 years, the risk of acute pancreatitis was 0.3% (n=22) with a corresponding rate of 569.9 cases/100, 000 patient years. However, after adjustment for multiple confounders there was no evidence of an increased risk with exenatide as compared to the control (a new sulphonylurea, biguanide or thiazolidinedione); the adjusted hazard ratio was 0.9 (95% CI [0.6, 1.5]). (38) In this M-PEM study, only unadjusted estimates have been provided. A further retrospective cohort analysis including 13, 791 patient years of exenatide use in patients with employer provided health insurance from 2007-2009 in the US revealed an annual risk of hospitalisation for acute pancreatitis of 0.2% (n=27). However, the difference in risk of hospitalisation for acute pancreatitis between exenatide users and non-users was not statistically significant after adjustment for potential confounders (adjusted OR 0.93; 95% CI [0.63, 1.36]). (39) A similar low incidence of acute pancreatitis was observed in a cohort study including 25, 719 patients taking exenatide between June 2005 and December 2007 where 40 cases (0.2%) of acute pancreatitis were reported in the exenatide treatment arm. (40)

Despite reporting of acute pancreatitis on treatment with Bydureon® in this M-PEM study, inference of causality is not clear. In 2013-2014, the FDA and EMA undertook comprehensive evaluations of post-marketing safety reports of acute pancreatitis in patients taking incretin-based therapies, including exenatide. Both agencies concluded that the current knowledge and data did not lead to conclusive results regarding a causal relationship between incretin based therapies and acute pancreatitis. The inherent limitations of establishing causality were noted, including the evaluation of events with a high background rate and possible confounding by indication. (22) In a large US retrospective cohort study enrolling patients for at least 12 months to assess the risk of acute pancreatitis and biliary disease in patients with type 2 diabetes mellitus, the incidence of acute pancreatitis overall was higher than in this M-PEM study (0.8% vs. 0.2%, respectively) and patients with type 2 diabetes were shown to have a 2.83-fold (95% CI [2.61, 3.96]) greater risk of acute pancreatitis than the non-diabetic cohort. (18) Overall, the incidence of acute

pancreatitis during the 12-month M-PEM study period was not higher than that seen from other studies in both the pre-marketing phase and post-marketing.

Other targeted events

An additional aim in this study relating to secondary and exploratory objectives was to examine the risk of the following events; pancreatic cancer, thyroid neoplasm, gallstones, biliary colic or cholecystitis, acute renal failure, allergic reactions (type 1 hypersensitivity), and cardiac events.

Pancreatic cancer

There were four cases (0.1%) of pancreatic cancer reported to occur on treatment with Bydureon® (plus the 10-week washout period) during the 12-month observation period. The overall median (IQR) time to event was 146.5 (72.5, 199) days. Two of these cases were reported in exenatide naïve patients, one patient was a previous Byetta® user and for the remaining patient, previous Byetta® use was not known. Risk factors included smoking history for two patients. For three of the four patients the information reported on the 12-month and supplementary questionnaire confirms that the patient had pancreatic cancer and a fatal outcome was reported in all three of these patients. However, for the remaining patient the GP reported that the patient stopped Bydureon® due to 'possible pancreatic cancer risk' and no further information was provided. There was also an additional case of pancreatic cancer diagnosed more than 12-months after index and beyond the 10-week washout period after stopping Bydureon®.

In this M-PEM study, any inference on the incidence of pancreatic cancer cannot be made, as the study length and size has not been designed for this. However, in the US retrospective cohort analysis including 13,791 patient years of exenatide (described above), it was shown that pancreatic cancer was rarer than hospitalisations for acute pancreatitis. The incidence of pancreatic cancer in patients amongst exenatide users was 0.081%. Results also suggest that pancreatic cancer was not significantly associated with exenatide use as compared to non-use (OR 1.543; 95% CI [0.489, 4.869]). (39) In the six-year extension to the DURATION-1 trial, only one case of pancreatic carcinoma was reported and it was noted that this was not considered related to treatment but did lead to withdrawal of Bydureon®. (12) However, the incidence of pancreatic cancer in the EXSCEL trial with a median follow up of 3.2 years was the same for both exenatide naïve patients (0.2%; n=15) and the placebo group (0.2%; n=16). (19)

However, a survey of adverse outcomes reported to the Food and Drug Administration from 2004-2009 revealed a 2.9-fold increase in the incidence of pancreatic carcinoma among exenatide users, compared with that seen with other antidiabetes medications. (41) The FDA and EMA subsequently assessed the safety of incretin based therapies with respect to pancreatic cancer and concluded that a causal relationship is not supported by the data. (22) The long latency period and a higher background rate of pancreatic cancer amongst diabetic patients means that any inference is difficult. A meta-analysis of 36 observational studies examining the association between type 2 diabetes and pancreatic cancer showed an 80% increase in risk of pancreatic cancer with type 2 diabetes mellitus (OR 1.82; 95% CI [1.66–1.89]).

Patients who had been diagnosed for less than four years had a 50% greater risk of pancreatic cancer compared with individuals who had diabetes for more than four years (OR 2.1 vs. 1.5; p=0.005). (42) This potentially supports the hypothesis of reverse causality, whereby diabetes itself may be an early manifestation of the cancer. However, all cases of pancreatic cancer in this M-PEM study were reported to occur more than five years after the diagnosis of type 2 diabetes mellitus.

Thyroid neoplasm

There were no cases of thyroid neoplasm reported within or beyond the 12-month observation period. This is in keeping with evidence from clinical trials whereby thyroid neoplasms have very rarely been reported. The pooled analysis of eight clinical trials revealed a rate of 0.2 per 100 patient-years and none of these cases were considered to be malignant. (13) Similarly, occurrence of medullary thyroid cancer in the EXSCEL trial of longer duration (median follow up of 3.2 years) was low (<0.1% for both Bydureon® and placebo arms) and all cases had elevated calcitonin levels at baseline. (19)

Gallstones, biliary colic or cholecystitis

The incidence of the composite outcome 'gallstones, biliary colic or cholecystitis' during the 12-month observation period on treatment with Bydureon® (plus the 10-week washout period) was 0.6% (95% CI [0.4, 0.8]). The cumulative incidence was observed to be nearly twice as high for previous Byetta® users (0.9%; 95% CI [0.5, 1.4]) as compared to patients who were exenatide naïve (0.5%; 95% CI [0.3, 0.8]), however overlapping of the 95% CIs indicates no statistically significant difference between the two prior exenatide user groups. In addition, a large proportion had a prior history of this composite outcome. Findings are consistent with the known profile of patients with type 2 diabetes, who are known to be at increased risk of biliary disease. Results from a retrospective cohort study using a large US health care claims database including patients enrolled for at least 12 months showed that patients with type 2 diabetes had a 1.91-fold (95% CI [1.84, 1.99]) increased risk of biliary disease (cholelithiasis, acute cholecystitis, or cholecystectomy) than patients without type 2 diabetes; the incidence of biliary disease in the type 2 diabetic cohort (2.5%) was also higher than in our M-PEM study. (18)

Acute renal failure

In this M-PEM study, the cumulative incidence of acute renal failure was low (0.5%; 95% CI [0.3, 0.7]) and was similar between exenatide naïve patients and previous Byetta® users. It is important to note that 'acute renal failure' in this study was defined by the narrow scope MedDRA SMQ of 'acute renal failure', which also includes non-specific terms such as dialysis. Thus, there is potential for over-estimation of cases of acute renal failure in this M-PEM study.

However, results are comparable with clinical trial evidence. In the DURATION-7 trial comparing Bydureon® with placebo in patients on insulin glargine (plus/minus metformin) one case of acute renal failure related adverse event was reported in the exenatide treatment arm, yielding an incidence of 0.4%, in keeping with these M-PEM study results. (9) Furthermore, a retrospective cohort study of a large medical and pharmacy

claims database evaluating whether the risk of acute renal failure increases with exenatide and sitagliptin in 2355 patients revealed an unadjusted incidence of acute renal failure of 0.5%. Rate of acute renal failure was also higher overall for diabetic patients as compared to non-diabetic patients (HR 1.51 (95% CI [1.26, 1.81]); p<0.001), thus these findings support the concept of diabetes itself potentially contributing to the risk of acute renal failure. (43) Overall, the incidence of acute renal failure during the 12-month M-PEM study period was in line with existing study results.

Allergic reactions (type 1 hypersensitivity)

The cumulative incidence for hypersensitivity (type 1 reactions) in this M-PEM study was 0.7% (95% CI [0.5, 0.9]). Cumulative incidence for exenatide naïve patients was slightly lower than for previous Byetta® users (0.6% vs. 0.9%, respectively), however the 95% CIs overlapped indicating no statistically significant difference between the two prior exenatide user groups. Incidence of this outcome is slightly higher than clinical trial evidence, though it should be noted for some cases in this M-PEM study it was not possible to definitively confirm whether the events were true type 1 hypersensitivity reactions; this could potentially explain the observed higher incidence. In the pivotal DURATION trials, a single case of 'hypersensitivity' and 'lip swelling' were reported in the exenatide group in the DURATION-8 trial and DURATION-3 trials, respectively; both results yielded an incidence of 0.4%. (5, 10) In this M-PEM study, there was only one case where the GP themselves reported 'anaphylaxis' on treatment within the 12-month observation period and two cases of reported 'angioedema' (one of which was noted as 'hereditary angioedema'); these cases alone yield an incidence of <0.1%. Results from this M-PEM study do not infer causality and it should be noted that type 1 hypersensitivity reactions may have occurred due to other exposures.

Cardiac events

In this M-PEM study, the cumulative incidence of events reported within the MedDRA system organ class 'cardiac disorders' was 3.6% (95% CI [3.2, 4.1]). The cumulative incidence of cardiac events was slightly higher for previous Byetta® users (4.2%; 95% CI [3.3, 5.3]) as compared to exenatide naïve patients (3.4%; 95% CI [2.9, 3.9]), but with overlapping 95% CIs. Note, that this outcome includes cardiac diagnoses, signs and symptoms. The most commonly reported event was 'dizziness' followed by 'chest pain'. In terms of the most frequently reported clinical diagnoses, there were 26 events which fulfilled the criteria of acute coronary syndrome.

In the EXSCEL clinical trial investigating the effect of Bydureon® on cardiovascular outcomes in patients with type 2 diabetes, the primary composite outcome (first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke) occurred in 11.4% of exenatide patients as compared to 12.2% of the placebo group (HR 0.91; 95% CI [0.83, 1.00]). Results demonstrated that Bydureon® was non-inferior to placebo with respect to safety (p<0.001), however, in terms of efficacy was not superior to placebo (p=0.06). Furthermore, incidence of fatal or non-fatal myocardial infarction in the exenatide group was 6.6% and was comparable to the placebo arm (HR 0.97; 95% CI [0.85, 1.10]. Incidence of myocardial

infarction appears to be higher than that reported in this M-PEM study, however, the EXSCEL clinical trial had a longer period of observation (median 3.2 years vs. 12 months, respectively). (19)

In this M-PEM, although data on heart rate was not specifically collected, there were four events of 'tachycardia' and 18 reports of 'palpitations' on treatment with Bydureon® during the 12-month observation period (all included in the composite outcome of cardiac events). Incidence of these events was therefore low in the M-PEM study. Overall, the incidence of cardiac events reported during the 12-month M-PEM study observation period was not higher than reported in other studies.

Weight loss

At baseline, the majority of patients had a weight of ≥90 kg (80.7% where weight specified) and a BMI of ≥30 kg/m^2 (91.7% where BMI specified). This raises the possibility of channelling by prescribers to those diabetics who are obese, with the purported benefits of Bydureon® in weight loss in mind. For those patients where a potential change in weight or BMI could be calculated, the mean (SD) of the differences in weight or BMI from baseline to closest to 12 months was -3.0 (7.6) kg and -1.0 (4.7) kg/m^2, respectively. These results are comparable to clinical trial evidence from the pivotal DURATION studies where patients who received Bydureon® for 24-30 weeks had a mean weight loss of 1.5-3.7 kg. (3-10) Results from this M-PEM study are also similar to the 52-week and six-year extension to the DURATION-1 study; at 52 weeks the mean change in weight for Bydureon® patients was -4.1 (95% CI [-5.3, -2.9]) kg and at six years it was sustained at -4.2 (95% CI [-5.8, -2.6]) kg. (12, 44)

Changes in weight in this M-PEM cohort are also overall similar to those observed from observational data. In a real-world retrospective cohort study (CIBELES project) conducted in Spain, the average reduction in weight and BMI after six months of treatment with Bydureon® was -3.9 (95% CI [-4.8, -2.9]) kg and -1.41 (95% CI -1.77, -1.05]) kg/m^2, respectively and weight reductions were sustained in the subset of patients with one year of follow up. (45) Results from a further retrospective study identifying patients from the Clinical Practice Research Datalink in the UK between 2009 and 2014 were also consistent with findings in this M-PEM study. Mean change in weight for Bydureon® patients at six months was -3.7 kg and at 12-24 months, mean weight change was -3.2 kg. (46)

Of note within this M-PEM study is that a greater reduction in weight for exenatide naïve patients than for previous Byetta® users was observed (-3.5 kg vs -1.4 kg). A potential explanation for this observation is that patients had already begun to lose weight while taking Byetta® and so their weight loss on Bydureon® was not as pronounced. Reductions in body weight are known to be similar between patients taking Bydureon® and Byetta®. (3) Numbers within the prior Byetta® user group were also far smaller than in the exenatide naïve group, so patients with weight increases in this group may have masked the extent of weight reductions in patients who lost weight. Examination of box plots of median weight change among those with weight decrease only supports this explanation, since there is little difference between exenatide naïve patients and prior Byetta® users.

In the total cohort, there were 53 patients (0.8% of cohort) for whom the GP reported weight loss as a free text outcome on treatment (plus the 10-week washout period) during the 12-month observation period. For those patients for whom a potential change in BMI or weight could be calculated, the mean (SD) of the differences in BMI or weight from baseline to closest to 12 months was -3.9 (3.4) kg/m^2 and -10.1 (8.3) kg. These changes are much greater than those summarised above, however, these measurements are only for a small subset of patients for whom the GP themselves reported weight loss as a clinical outcome and for whom changes could be calculated (n≤10 for each parameter). This would be expected as the weight loss was significant enough for the GP to record it as an event in the patients' medical record.

In addition, 44.8% of the cohort for whom change in weight was calculable had a potentially clinically significant reduction in weight (defined as ≥3% reduction from baseline) on treatment with Bydureon®. In the observational CIBELES study, 53.1% of patients lost ≥3% of weight at six months. (45) Prevalence of weight loss ≥3% was higher over a shorter duration in CIBELES than for this M-PEM study, however, it is important to note that changes in weight were not calculable for a significant proportion of the M-PEM cohort. Thus, comparisons are difficult.

Deaths

In total, 43 patients were reported to have died have died during the 12-month observation period, with 25 deaths (0.4% of cohort) occurring on treatment with Bydureon®. The incidence of death on treatment was similar for exenatide naïve patients and previous Byetta® users (0.4% vs. 0.5%, respectively). Where specified, the most frequently reported cause of death was 'cardiac failure', 'pneumonia' or 'pneumonia aspiration'. Results are in keeping with clinical trial evidence, in which the incidence of death was reported as 0.4% with Bydureon®. (4, 10) Incidence of death in this M-PEM study is also much lower than that reported in the EXSCEL trial of longer duration, in which the incidence of death from any cause was 6.9% for the exenatide treatment arm and 7.9% for the placebo arm (HR 0.86; 95% CI [0.77, 0.97]). (19) This is not unexpected given the shorter duration of the M-PEM study.

Given the similar incidence of deaths in the M-PEM study compared to clinical trial data, the incidence of death in this M-PEM study is unlikely to have been influenced by differential reporting by GPs. This remains a possibility though, since GPs may have been more likely to complete and return questionnaires for patients who had experienced events such as death as compared patients who did not experience safety or effectiveness events. Information on deaths or other outcomes for the patients for whom the GP did not respond is not known.

Pregnancies

In total there were nine patients with a pregnancy reported after index in the study. Eight of these patients had a pregnancy confirmed to occur within the 12-month observation period; for one patient the pregnancy was confirmed to occur outside the 12-month observation period. For five of the pregnancies reported

within the 12-month observation period, Bydureon® was thought to have been taken during the first trimester based on the information available. The following outcomes were reported for the pregnancies; live birth (n=3), spontaneous abortion (n=1), congenital abnormalities (n=1[36]) and outcome unknown (n=3).

It is known that the estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with an HbA1c >7 and has been reported to be as high as 20-25% in women with HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognised pregnancies is 2-4% and 15-20%, respectively. (47) In addition to maternal diabetes, both patients for whom congenital abnormalities was reported had risk factors of smoking and morbid obesity.

Results from this study are difficult to compare due to lack of adequate data from other studies and should be considered as part of the broader literature on safety of Bydureon®. Furthermore, the possibility of preferential reporting of cases with anomalies in this M-PEM study cannot be excluded.

Patient characteristics and determinants of prescribing

The secondary focus of this study was to advance the understanding of the patient population prescribed Bydureon® in the primary care setting.

Age and sex distribution

In summary, there were 3475 (55.2%) males and 2819 (44.8%) females in the cohort and the median (IQR) age of the total cohort was 57 (50-65) years. These findings are consistent with the average age of patients with type 2 diabetes mellitus suggesting that the cohort is representative of the population treated in clinical practice. (48) In this M-PEM study, as expected, use in the elderly (≥75 years) was more common (n=291, 4.6% of cohort) than use in young (<18 years) patients (n=2). The latter constitutes to off-label prescribing.

Prior medical history

The prevalence of a prior history of acute pancreatitis was low. This was reported in 0.6% of the total cohort. This is in keeping with the SmPC recommendations of caution for use in patients with a history of pancreatitis. (1) The most frequently reported disorder category at the time of starting Bydureon® was 'gastrointestinal disorder' (14.8% of cohort), with 'gastro-oesophageal reflux disease' the most common. As expected in patients with type 2 diabetes mellitus, 'hepatic steatosis' was the most prevalent prior disorder specified under the 'hepatic disorder' category. There was also a single case of a prior history of 'thyroid cancer'. In the US, Bydureon® is not recommended for use in patients with a personal or family history of medullary thyroid carcinoma. (11)

[36] A further case of congenital abnormality is discussed in Appendix 24; this pregnancy occurred outside of the 12-month observation period.

In addition, in this M-PEM study, use of Bydureon® was reported in 16 patients with type 1 diabetes mellitus at index; these patients were excluded from the evaluable cohort as this constitutes to off-label prescribing. Although, to date the majority of studies have investigated the use of Byetta® in patients with type 1 diabetes, there are studies evaluating the use of Bydureon® in type 1 diabetic patients for which the results are yet to be published. (11) Overall, the prevalence of off-label prescribing in this study related to prior medical history was low.

Prescribing decisions

In this study, Bydureon® was most frequently initiated in primary care (51.9% of cohort), which reflects the usual clinical management of type 2 diabetes mellitus in England. The major determinant of prescribing for all patients was 'specialist decision', followed by 'GP clinical decision'. This is in keeping with an increased likelihood of treatment of type 2 diabetes mellitus being shared between primary and secondary care, in particular for patients with inadequate glycaemic control. It is possible that GPs are more reliant on the specialist knowledge and advice of the secondary care specialist with respect to prescribing decisions for Bydureon®, thus reflecting the hierarchical nature of prescribing decisions in the NHS. In particular NICE recommends that a GLP-1 agonist in combination with insulin should only be initiated with specialist care advice and ongoing support from a consultant-led multidisciplinary team. (34)

Treatment regimen

Nearly all patients (94.4% of cohort) were prescribed Bydureon® as recommended at index, as a 2mg once weekly subcutaneous injection. In terms of line of therapy, Bydureon® was most frequently initiated as 'triple therapy' (61.6% of cohort). These study results indicate that Bydureon® was more commonly prescribed for patients where alternative antidiabetes treatment had not provided adequate control; this is in accordance with the product label and guidance from NICE. (1, 34) Metformin was the most frequently reported concomitant antidiabetes medication at index (81.5% of cohort) and in keeping with NICE recommendations, sulphonylureas were also commonly prescribed (45.0% of cohort). Approximately one-fifth of patients (24.3% of cohort) were taking at least one insulin based therapy at index; this potentially reflects the high level of input from specialist care in this M-PEM study (as described above). In summary, the majority of patients in the cohort were prescribed Bydureon® according to the licensed dose and treatment regimen.

Treatment cessation

Approximately 30% of patients were reported to have stopped Bydureon® within the 12 months after index. These results are similar to discontinuation rates in the one year real-world observational study evaluating exenatide once weekly added to basal insulin, in which 32% of Bydureon® users stopped therapy. (49) In this M-PEM study, the three most frequently reported reasons for stopping were 'drug ineffective', 'therapy change', and 'nausea'. These results are as expected as nausea is commonly reported with Bydureon®.

Other events

In keeping with the known safety profile of Bydureon®, 'nausea and vomiting symptoms' were frequently reported (5.4% of cohort) and 'injection site reactions' were also very common (3.0% of cohort). Hypoglycaemia was reported in 0.6% of the cohort; prolonged-release exenatide is known to have a common frequency of occurrence of hypoglycaemia when used in combination with a sulphonylurea or insulin. (1) Hypoglycaemia incidence in this M-PEM study is, however, lower than that observed in propensity-matched electronic health data cohort study comparing exenatide-once weekly with basal insulin, in which the incidence in exenatide patients followed up for an average of 1.5 person-years was 7.4%. (50) The incidence of nausea or vomiting was also observed to be higher (16.9% of exenatide patients) than this M-PEM study.

General health parameters

At index, approximately one-third of patients had an HbA1c≥59 mmol/mol (≥7.5%); of these 66.0% had an HbA1c of ≥75 mmol/mol (≥9.0%) indicating very poor control of their diabetes. These cohort characteristics are thought to reflect the characteristics of long-term type 2 diabetic patients, where treatment with other anti-diabetes medications may have been unsuccessful in glycaemic control.

For those patients where a potential change in HbA1c could be calculated, the mean (SD) difference in HbA1c from baseline to closest to 12 months was -13.2 (19.6) mmol/mol, equivalent to -3.4 (-3.9)%. Change in HbA1c is slightly higher than that observed in the pivotal clinical trials. The DURATION 1-8 studies have shown that exenatide once-weekly (Bydureon®) resulted in HbA1c reductions of 1.0-1.9% over 24-30 weeks. (3-10) However, results are more comparable to the SUSTAIN-3 trial in which the mean HbA1c decreased by 10 mmol/mol with exenatide once weekly at 56 weeks. (37)

Change in HbA1c in this M-PEM study is also higher than that observed in a real-world observational study evaluating exenatide once weekly added to basal insulin. After one year of therapy the mean change in HbA1c from baseline was -0.7% in patients taking exenatide once weekly. (49) In the CIBELES study, HbA1c decreased by -1.1% (95% CI [-1.39, -0.81]) at six months, and similar changes were observed for patients who had 12 months of follow up. (45) While the possibility for over reporting of positive changes in HbA1c remains (due to the small number of patients for which HbA1c values were reported), our results indicate that on average patients experienced improvements in HbA1c during treatment with Bydureon®.

An average decrease in systolic blood pressure was also observed for patients for whom a change could be calculated. The mean (SD) of the differences in SBP from baseline to closest to 12 months was -2.6 (15.9) mmHg for the total cohort. Results are similar to the findings from the DURATION-7 trial (-2.6 (-4.4, -0.7) mmHg) and the CIBELES observational study in which the mean (SE) change in SBP at 12 months was observed as -2.5 (1.9) mmHg. (9, 45) Overall, the findings from this study regarding blood pressure are in line with the existing literature.

11.2 Limitations

All observational epidemiological studies have the potential for bias from various sources. Within questionnaire based studies like the M-PEM design, there are several recognised potential sources of bias in the study which are also mentioned in Section 9.6. (31)

A potential source of bias in any questionnaire based study is non-response bias. In this M-PEM study prescribers and patients are identified from prescription data and GPs were requested to participate in the study by means of responding to a questionnaire on the identified patient based on medical records review. The response rate for the 12-month questionnaire was 37.2%. This is comparable with other recent M-PEM studies conducted by the DSRU for which the average response rate is approximately 45%. The response rate for this M-PEM study is also comparable to response rates reported elsewhere for UK GP postal surveys, for which 31-32% of GPs responded. (51, 52) There may be a number of possible reasons for a low response rate including increasing GP work demands, complexity of the questionnaires, and GP opinion on the reimbursement amount for completion of the questionnaires. However, it is not known whether the responding GPs were systematically different to non-responding GPs. Bias would only arise if a systematic difference was present. In addition, our results show a well-distributed response from GP practices across England.

A further consideration for selection bias is if patients of GPs who returned the questionnaire were systematically different to patients of those GPs who did not return the questionnaire. Given the response rate, it is possible that patients included in the study by GPs were systematically different to patients not included. (53) It is difficult to make an assumption of any difference in the severity of illness, degree of adherence to medication, or access to primary care for these patients as compared to patients for whom we have evaluable information. Patient were included in this study at least 12 months after treatment initiation with Bydureon®, thus it is possible that GPs may have enrolled patients who had outcome events preferentially to uneventful patients. It may have been that GPs were more likely to participate if their patient experienced an event that was considered to be possibly related to the drug of interest. (28) This could have resulted in an over-estimate of the frequency and incidence of outcome events. It is not possible to ascertain the extent to which selection bias exists nor the impact it may have had on the results, as information on the patients not included in the study was not collected.

There was also a further potential bias where GPs may under-report or differentially report particular events in particular patients. It is possible that GPs may have had incomplete information on medical history and outcomes associated with current treatment especially if these had resulted in hospitalisation. Patients may have also reported some events of interest to other doctors or health organisations without informing their GPs. Under-reporting of events is possible in M-PEM including under-reporting of serious events with fatal outcomes.

Conversely, as mentioned above, there was potential for overestimation; GPs may have paid more attention and thus more frequently reported those cases which experienced an event as compared to cases where treatment was successful and without complication. It is not possible to quantify the degree of this potential bias without information on non-participating patients.

Misclassification is also possible. There may have been conflicting information reported for the same event on both the 12-month and the corresponding supplementary questionnaire. In these circumstances, where applicable, supplementary data was used to update information on the 12-month questionnaire. Additionally, different GPs may interpret the questions differently leading to some ”noise” in the analyses. This may apply to the pre-specified event questions on the 12-month questionnaire; for other events the GP was requested to report any other events recorded in the patient’s medical notes.

In this M-PEM study, exposure was based on dispensed prescription data. These data are more accurate than exposure data based solely on written prescriptions. However, as with many observational studies, the degree of patient compliance in taking the prescribed medication cannot be fully ascertained. While it is not possible to be sure that the patient used the medication, it is almost certain that the patient received it. Furthermore, repeat prescriptions indicate that the patient continued to obtain the medication.

In this study, patients were grouped according to if they had previous Byetta® exposure or not (i.e., exenatide naïve). From the data available, it was evident that there was some confusion between Byetta® and Bydureon® by some GPs, which resulted in conflicting data. An example of this is where the GP reported a Bydureon® index date prior to the marketing authorisation date and provided a Byetta® dose. In these circumstances, it was inferred that the patient did receive Bydureon® but also had prior exposure to Byetta®. Specific rules were applied in the analysis (described in Section 10.2.1) to account for different scenarios where the GP had reported a Byetta® start or stop dose.

A further potential source of misclassification was in relation to information on concomitant and prior antidiabetes medications. There was some evidence of conflicting data between the line of therapy (i.e., monotherapy, dual therapy, triple therapy) and the number of antidiabetes medications reported as part of the co-therapy. In these circumstances, the number of reported antidiabetes medications was used to allocate the patient to the line of therapy. In addition, there was a potential for under-estimation of prior antidiabetes medication exposure time. This is because in circumstances where only one date was provided for a medication that was reported twice, the specified date was used to calculate the median duration of therapy; it was considered appropriate to use the provided date in favour of having missing information. Furthermore, where two different antidiabetes medications within the same ATC class were provided with different prior dates, only the earliest dated medication was analysed and reported to provide an estimate of exposure of that particular class of antidiabetes medication. However, if the GP reported multiple prior antidiabetes medications within the same ATC class but only provided one date, both

medications were analysed and presented, as it was not possible to infer which was started first from the available information.

Information was collected on cases of selected events including pancreatic cancer, thyroid neoplasms and other medical conditions. It is acknowledged that these conditions may have been present prior to commencing Bydureon®, as specific information was not collected regarding baseline screening for these events prior to starting therapy on the 12-month questionnaire. However, supplementary information was requested for targeted events of interest, which included questions on prior history and these events have been described in case narratives and/or case series format in order to support generation of hypotheses for further evaluation.

Standardised definitions (e.g. Standardised MedDRA Queries) were used to capture specific events reported as free text. For some cases, it was not possible to definitively confirm whether the events met the outcome criteria (e.g. type 1 hypersensitivity, acute renal failure) based on the information available; however, these events were included as potential cases according to the rule base for capturing specific events. For completeness, a list of the reported preferred terms were provided for each event definition. In addition, although it was possible to report the degree of weight loss in this M-PEM study, the rate of weight loss could not be calculated and thus it was not possible to infer if the loss of weight met the criteria for rapid weight loss (>1.5 kg/week) as reported in the SmPC. (1)

A key factor of interest for targeted events was the temporal relationship with treatment. New onset events that developed within the first 12 months of drug treatment may be suggestive of a possible causal relationship; however, individual drug-relatedness assessments were not performed. Often multiple risk factors existed, placing the patient at an elevated risk independent of drug exposure, which made individual assessment being performed to determine relatedness challenging. In addition, this M-PEM study has only been able to characterise any cases of pancreatic cancer and thyroid neoplasm. This study cannot provide inference on the incidence of these neoplasms in the M-PEM cohort, as the study length and size was not designed for this.

Information on relevant confounders in the estimates of risk may be missing or incomplete since data abstracted from patient medical records held by GPs may not have contained complete information on events and variables that were relevant to the study. However, the study asked GPs to provide data where available and report events affecting all body systems, without making any prior assessment on relatedness.

Another important consideration that could have introduced bias is that the M-PEM cohort was a group comprised of both antidiabetes medication naïve and prior antidiabetes medication users. Selection bias could have arisen because patients who failed to respond or could not tolerate other antidiabetes medications (e.g. metformin) were prescribed Bydureon®. The estimates of incidence and reasons for

treatment withdrawal (through depletion of susceptibles) may differ between these two groups. In acknowledgement of this important source of bias, this M-PEM study was designed to capture information on prior use of antidiabetes medications in Bydureon® users because of the complex treatment patterns for patients requiring glycaemic control, for the purposes of further exploration of possible safety signals. Confounding by severity is also possible, as is treatment switching of multiple-drug therapy. However, the analyses conducted are unadjusted and so results need to be viewed with caution.

Another potential source of bias would occur if there is any time differential between switching patients from Byetta® to Bydureon®. Protopathic bias, another methodological limitation of observational research, may result because the antidiabetes treatment has been prescribed for early symptoms of an event of interest. (54)

For further information on M-PEM limitations and potential for bias please refer to the protocol (Appendix 1).

11.3 Interpretation

This final report summarises drug utilisation and safety data for patients prescribed Bydureon® in the primary care setting in England from a post-authorisation safety study. This study uses a M-PEM cohort design with a specific data collection questionnaire sent at 12 months after index, which aimed to capture information on drug utilisation, patient characteristics and events based on GP reporting from medical records.

Overall, the majority of patients in this M-PEM study were being prescribed Bydureon® according to its licensed indication in primary care in England; event incidences appear to be generally in line with known information about the product and no new safety issues have been identified in this study.

11.4 Generalisability

This study aimed to identify patients prescribed Bydureon® from both urban and rural areas in primary care in England. As a result of the large cohort number and widespread geographical distribution of the GP practices included in the study, there is no reason to believe that the evaluable cohort is likely to be systematically different to the population in England treated with Bydureon® in primary care, therefore, results of this study can be considered generalisable to the population of England. However, this study is part of a broader literature in the safety of Bydureon®, and any conclusions on safety should be put into context with results from other post-marketing studies for the product.

12 Other Information

None.

13 Conclusion

The M-PEM study design provides a framework suitable to evaluate the safety of newly marketed medicines in the primary care setting. The results of this M-PEM study data show that Bydureon® is largely being prescribed to populations in accordance with prescribing recommendations and national clinical guidelines. Baseline characteristics of patients prescribed Bydureon® are in keeping with the profile of patients with type 2 diabetes mellitus.

In terms of the primary outcome of acute pancreatitis, the estimates of risk were overall low and consistent with those estimated from clinical trial data. No unexpected findings warranting further investigation were identified from the results. This study is part of a broader literature on the safety of Bydureon® and any conclusions on safety should be put into context with results from other post-marketing studies for the product.

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15 Appendices

Annex 1. List of stand-alone documents

None.

Annex 2. Additional information

Appendix 1: Study protocol

Appendix 2: Study questionnaire

Appendix 3: Statistical Analysis Plan (SAP)

Appendix 4: Summary of 12-month questionnaires returned after data lock

Appendix 5: Summary of patients for whom an off-label indication was reported

Appendix 6: Summary of patients with a type 2 diabetes mellitus date of diagnosis reported after the index date

Appendix 7: Other ethnicities reported

Appendix 8a: All specified events for pre-specified prior disorder categories reported prior to or present on start of treatment

Appendix 8b: All other specified events reported prior to or present on start of treatment

Appendix 9: Other settings where treatment initiated

Appendix 10: Other supporting reasons for prescribing

Appendix 11: Other doses reported on starting treatment

Appendix 12: All concomitant antidiabetes medications and non-antidiabetes medications

Appendix 13a: All reasons for stopping treatment during the 12-month observation period

Appendix 13b: All reasons for stopping treatment after 12-month observation period

Appendix 14: Other doses reported on stopping treatment during the 12-month observation period

Appendix 15: Case narratives for acute pancreatitis events

Appendix 16: Sensitivity analysis of cumulative incidence and rate of acute pancreatitis during treatment with Bydureon® within the 12-month observation period excluding the 10-week washout period

Appendix 17: Weibull parametric model plots and parameters for the total cohort and exenatide naïve patients for acute pancreatitis within the 12-month observation period

Appendix 18: Time-to-first acute pancreatitis events occurring within the 12-month observation period (excluding the 10-week washout period)

Appendix 19: Case narratives for pancreatic cancer

Appendix 20: Reported preferred terms for type 1 hypersensitivity events, acute renal failure and cardiac events

Appendix 21: Targeted events reported on treatment within the 12-month observation period excluding the 10-week washout period, reported with missing event date and

reported on treatment after 12-month observation period

Appendix 22: All general events reported

Appendix 23: All deaths on treatment within the 12-month observation period (minus the 10-week washout period) and after the 12-month observation period

Appendix 24: Congenital abnormalities signal report

Appendix 25a: Changes in weight and BMI for patients with free text reported weight loss

Appendix 25b: Potentially clinically significant changes in weight, BMI and SBP

Appendix 26: Other reported treatment/compliance problems