TITLE PAGE

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Title:	A cohort study to investigate the prescribing of albiglutide among women of child-bearing age who have type 2 diabetes

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Author(s):	[redacted]

PASS information

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Marketing authorisation holder(s)	GlaxoSmithKline
Joint PASS	No

Research question and objectives	**Research question** Prevalence of type 2 diabetes in women of child-bearing age is increasing. Apart from metformin, very little is known about the safety of oral hypoglycaemic agents in pregnancy but exposure to these could occur due to inadvertent use before pregnancy is recognised. Following the launch of albiglutide, an understanding of the characteristics and size of the at-risk population is needed in order to evaluate pregnancy related safety concerns. **Objectives** • To assess the proportion and characteristics of women with type 2 diabetes of child-bearing age who are prescribed albiglutide. • To assess the proportion and characteristics of women with type 2 diabetes who are prescribed albiglutide during pregnancy. • To summarise outcomes of women prescribed albiglutide during pregnancy including reported major congenital malformations, pregnancy losses, stillbirths and neonatal deaths.
Country(-ies) of study	UK
Author	Dr. [redacted] [redacted] United Kingdom [redacted]

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	GlaxoSmithKline Research & Development Limited 980 Great West Road Brentford Middlesex, TW8 9GS UK.
MAH contact person	[redacted]

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LIST OF ABBREVIATIONS

AE	Adverse Event
BMI	Body mass index
CPRD	Clinical Practice Research Datalink
EUROCAT	European Concerted Action on Congenital Anomalies and Twins
GLP-1	Glucagon-like protein-1
GSK	GlaxoSmithKline
GP	General Practitioner
GPRD	General Practice Research Database
i	Inhibitor
Met	Metformin
NICE	National Institute for Health and Care Excellence
PL/SQL	Procedural language / Structured query language
RA	Receptor agonists
SES	Socioeconomic status
SPARC	Scalable processor architecture
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
Su	Sulphonylurea
TZD	Thiazolidinediones
UK	United Kingdom

Trademark Information

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RESPONSIBLE PARTIES

Dr. [redacted]

[redacted]

[redacted]

[redacted]

[redacted] United Kingdom

[redacted]

SPONSOR SIGNATORY:

[redacted] 11/17/2015

Primary Author/ Project officer Date

[redacted] 17/11/2015

Therapy Area Leader Date

SPONSOR INFORMATION PAGE

WWEpi Project Identifier: PRJ2376

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Sponsor Contact Address

GlaxoSmithKline Research & Development Limited
1250 South Collegeville Road
Collegeville, PA 19426, USA
Telephone Number: [redacted]

Sponsor Medical Monitor Contact Information: N/A

Regulatory Agency Identifying Number(s): IND number 065177

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: Dr. [redacted]

_____

_____ _____

Investigator Signature Date

1. ABSTRACT

Title

A cohort study to investigate the prescribing of albiglutide among women of child-bearing age who have type 2 diabetes.

Rationale and background

The prevalence of type 2 diabetes is increasing and is being diagnosed in younger patients. There are a growing number of pregnancies where type 2 diabetes has been diagnosed before the start of pregnancy. The main recommendation for prescribing to treat type 2 diabetes during pregnancy is insulin or metformin. Given that the early weeks of pregnancy are when organogenesis occurs but could also be before pregnancy is recognised, there is the potential for inadvertent exposure to other anti-diabetic medications.

As presented in the product labelling in the EU, there are no or a limited amount of data regarding the use of albiglutide in pregnant women. Studies in animals have shown reproductive toxicity but the potential risk for humans is unknown. Albiglutide should not be used during pregnancy and is not recommended in women of child-bearing potential not using effective contraception. Albiglutide should be discontinued at least 1 month before a planned pregnancy due to the long washout period for albiglutide.

This study will describe the prescribing of albiglutide in women of child-bearing age in order to assess the size and characteristics of the at-risk population. Pregnancies that occur in the study population during the time period will be identified and described in terms of prescribing, patient characteristics and pregnancy outcomes in order to evaluate pregnancy related safety concerns with albiglutide.

Following the launch of albiglutide, an understanding of the characteristics and size of the at-risk population is needed in order to evaluate pregnancy related safety concerns.

Research question and Objective(s)

Primary objectives

- To assess the proportion and characteristics of women with type 2 diabetes of child-bearing age who are prescribed albiglutide.
- To assess the proportion and characteristics of women with type 2 diabetes who are prescribed albiglutide during pregnancy.

Secondary objective

- To summarise outcomes of women prescribed albiglutide during pregnancy including reported major congenital malformations, pregnancy losses, stillbirths and neonatal deaths.

Population

A cohort study will be used to investigate prescribing for type 2 diabetes in women of child-bearing age in the UK during the time period 1/1/2015 – 31/12/2019. A sub-group of women who have a pregnancy during the study period will also be identified. Patient characteristics will be described.

Prescriptions for medication used to treat diabetes will be identified and described for the overall cohort at study entry and where new medications are prescribed during the time period. Patient characteristics of those prescribed albiglutide will be compared to those prescribed other medications. For the sub-group of women who have a pregnancy during the study period, prescriptions received in the three months before the pregnancy start date and during pregnancy will be identified and compared between those receiving albiglutide and those receiving other medications. Data will be collated and reported on a semi-annual basis.

This study will use primary care data collected prospectively in the UK. In this study women who are permanently registered with their GP, aged between 11 and 49 years, who have at least two prescriptions for antidiabetic agents and a diagnosis of type 2 diabetes and at least one year of data available before study entry will be identified and included in the study.

Pregnancy outcomes will be identified and described. These will include major congenital malformations, pregnancy losses, livebirths, stillbirths and neonatal deaths. Prescriptions for anti-diabetes medication issued during the study period will be identified. These prescriptions will be grouped into classes of anti-diabetic medications in general and for albiglutide specifically. Patient characteristics used to describe the cohorts of patients will include age, smoking status, alcohol use, BMI, number of years since diagnosis of diabetes, diagnosis of microvascular and macrovascular comorbidities, and malignant neoplasms as recorded at study entry.

The UK Clinical Practice Research Datalink will be used for this study. This database contains primary care records for a representative sample of around 8% of the UK's population. The records include prescriptions issued in primary care, medical diagnoses, referral information, test data and other healthcare related information.

Previous work indicates that at least 10 000 women of child-bearing age with a diagnosis and prescribing for type 2 diabetes will be included in the study. The number of pregnancies that should be included for each year of the study will be at least 65.

Characteristics of the study population and the sub-group of patients with pregnancies occurring during the study period will be reported as counts and proportions. Existing prescribing will be described at cohort entry and new prescribing during the study period will be described by year in terms of incidence, prevalence and exposure rate by medication or group of medications. Comparisons of characteristics between those who receive prescriptions for albiglutide and those who receive prescriptions for other types of anti-diabetic medications will be made. Pregnancy outcomes will be collated and described in terms of patient characteristics and medication prescribed, if numbers are sufficient for this.

Milestones

An important milestone was the submission of this protocol to PRAC in September of 2014. An updated version addressing PRAC's comments was-submitted in February 2015. An updated version addressing PRAC's outstanding questions from MAH response to request for supplementary information was submitted in June 2015. The retrospective start of data "collection" will begin in January 2015 and end in December 2019. Interim reports will be generated every 6 months starting in 2016.

2. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
1	February 5, 2015	Various Sections	Updates marked in final tracked version	Address PRAC's comments and feedback received November 21, 2014
2	June 22, 2015	Section 6.6.3 Confounders and Effect Modifiers	Updates marked in final tracked version	Address PRAC's comments and feedback received April 28, 2015
3	November 27, 2015	Various Sections	Updates marked in green in final tracked version	Address PRAC's comments and feedback received October 24, 2015 and finalize protocol

3. MILESTONES

Milestone	**Planned date**
Start of data collection	January 1, 2015
End of data collection	December 31, 2019
<Interim report 1>	March 22, 2016
<Interim report 2>	September 21, 2016
<Interim report 3>	March 22, 2017
<Interim report 4>	September 21, 2017
<Interim report 5>	March 22, 2018
<Interim report 6>	September 21, 2018
<Interim report 7>	March 22, 2019
<Interim report 8>	September 21, 2019
Final report of study results	September 21, 2020
Final manuscript submitted	September 30, 2020

4. RATIONAL AND BACKGROUND

4.1. Background

The prevalence of type 2 diabetes worldwide is increasing dramatically (Sicree et al, 2014). In the UK, prevalence of type 2 diabetes increased from 2.47% in 1996 to 3.9% in 2005 (González et al, 2009) with incidence reported to be 515/100 000 people in 2010 (Holden et al, 2013).This trend is not limited to adults: increasing numbers of young people are being diagnosed with type 2 diabetes. A field study conducted in the UK reported an incidence rate of type 2 diabetes in children <17 years of 0.53/100 000/year (0.41-0.68) in 2004-05 with mean age of diagnosis of 13.3 ± 1.7 years in girls and 14.1 ± 2.0 years in boys (Haines et al, 2007). Numbers of women with type 2 diabetes who go on to have pregnancies have also increased over time which is thought to be due to the increasing levels of obesity and increasing age when women become pregnant (McGrogan et al, 2014).

Treatment of type 2 diabetes in the UK as recommended by the NICE guidelines indicates that exercise and dietary adjustments are not effective long term for most people; typically oral medication is recommended, which depending on the patient's other health needs, often starts with metformin with a sulphonylurea added if needed. If sufficient control has not been maintained then a thiazolidinedione or insulin can be introduced. Currently the guidelines recommend exenatide if a patient's BMI is > 35.0kg/m^2 or if use of this delays the requirement for insulin (National Institute for Health and Care Excellence, 2010).

Albiglutide is a glucagon-like protein-1 (GLP-1) receptor agonist that will be launched in the UK in 2015 for the treatment of type 2 diabetes. It is indicated as monotherapy where metformin is considered inappropriate and where adequate glycaemic control is not achieved with diet and exercise alone or as add-on combination therapy with other hypoglycaemic agents including basal insulin.

Optimum glycaemic control throughout pregnancy is vital in order to ensure the best possible maternal and foetal outcomes. In the UK, NICE recommend that women with type 2 diabetes who are planning to become pregnant should cease to use all oral hypoglycaemic agents apart from metformin and that insulin can be used if needed (NICE, 2008) . Preconception counselling is also recommended to all women with diabetes who are planning to become pregnant.

Recent reviews of diabetes medication in pregnancy reported that there is very limited data available on safety of medications for treating type 2 diabetes during pregnancy. While metformin can be recommended and there is some evidence for the use of glibenclamide later in pregnancy for gestational diabetes, no evidence is available for other oral hypoglycaemic agents.

Animal studies have indicated that GLP-1 receptor agonists should not be used during pregnancy due to reports of skeletal effects and growth retardation in rats and rabbits (Holt et al, 2014). At doses of up to 50mg/kg/day there were no effects on mating or fertility but reductions in oestrous cycles were observed. In the foetus there were effects

on embryo-foetal lethality and skeletal variations; offspring had reduced weight during the pre-weaning period, dehydration and coldness and a delay in balanopreputial separation. No effects were seen at 5mg/kg/day (exposures similar to clinical exposure).

In mice administered albiglutide at >1mg/kg/day during pregnancy or while nursing, reduced pre-weaning body weight was observed in F1 offspring but this reversed post-weaning with the exception of F1 females from dams treated perinatally (end of gestation to 10 days postpartum) at 5mg/kg/day. Trace levels of albiglutide were detected in plasma of offspring. It is unknown whether the reduced offspring effect was caused by a direct albiglutide effect on the offspring or secondary to effects on the dam.

There are no or limited amount of data from the use of albiglutide in pregnant women therefore the potential risk for humans is unknown. Albiglutide should not be used during pregnancy, and is not recommended in women of child-bearing potential not using effective contraception. Albiglutide should be discontinued at least 1 month before a planned pregnancy due to the long washout period for albiglutide.

Having previously investigated utilisation of medications in type 2 diabetes during pregnancy we found 179 pregnancies where oral hypoglycaemic medication other than metformin was prescribed in the three months before or during the first trimester of pregnancy (McGrogan et al, 2014). Given that this use may have been inadvertent, this indicates the need to better understand the benefits and risks associated with the use of this type of medication.

Studying medication safety during pregnancy is difficult: women of child-bearing age are usually excluded from clinical trials and sample sizes needed to investigate changes in risks of outcomes are large. Using electronic health care records can overcome these difficulties by including a larger sample of women who are representative of the general population. In terms of investigating the occurrence of congenital malformations, exposures at the beginning of pregnancy during the early part of the first trimester are crucial to understanding the impact on organogenesis but are difficult to capture accurately using studies that do not recruit until later on in pregnancy or that rely on women to recall their likely exposure.

The UK Clinical Practice Research Datalink (CPRD) has been proven to be a valuable tool in studying medication utilisation and safety during pregnancy due to the ability to link the mother's and baby's records to determine outcomes (McGrogan et al, 2014, Charlton et al, 2010b). It is possible to view records from before the start of pregnancy and early in the first trimester thus being able to capture potential exposures that occur early in pregnancy.

The proposed study will provide an overview of prescribing of albiglutide in women of child-bearing age and will describe in detail prescribing that occurs during pregnancy and related outcomes in the offspring. This will inform risk management planning and allow pregnancy related safety concerns to be evaluated.

4.2. Rationale

The purpose of the study is to provide information about the utilisation of albiglutide among women of child-bearing age and on the characteristics of these women compared with those prescribed other medication for type 2 diabetes. Prescribing that occurs immediately before or during pregnancy will be reported and the extent of this will be used to determine whether it is feasible to conduct a safety study of albiglutide in pregnancy.

5. RESEARCH QUESTION AND OBJECTIVE(S)

Research question

Prevalence of type 2 diabetes in women of child-bearing age is increasing. Apart from metformin, very little is known about the safety of oral hypoglycaemic agents in pregnancy but exposure to these could occur due to inadvertent use before pregnancy is recognised. Following the launch of albiglutide, an understanding of the characteristics and size of the at-risk population is needed in order to evaluate pregnancy related safety concerns.

Primary objectives

- To assess the proportion and characteristics of women with type 2 diabetes of child-bearing age who are prescribed albiglutide.
- To assess the proportion and characteristics of women with type 2 diabetes who are prescribed albiglutide during pregnancy.

Secondary objective

- To summarise outcomes of women prescribed albiglutide during pregnancy including reported major congenital malformations, pregnancy losses, stillbirths and neonatal deaths.

6. RESEARCH METHODS

6.1. Study Design

This descriptive study will use prospectively collected data to retrospectively identify a cohort of women aged between 11 and 49 years who have been prescribed treatment for type 2 diabetes. A descriptive cohort study is the most appropriate design to use given that we want to understand the prescribing patterns of this medication in women of child-bearing age and especially in pregnancy. This will allow us to describe pregnancy outcomes from potentially exposed pregnancies. This descriptive study will indicate if it is necessary and feasible in terms of potential safety signals identified and sample size of the cohort available to undertake a safety study of albiglutide in pregnancy.

Women will be included in the cohort from the start date of the study or when they meet all of the inclusion criteria, namely: age 11-49 years and have received at least two prescriptions for medication for type 2 diabetes and their data is of a standard suitable for research ("up to standard") and have at least one year of data available before entry to the study. The point when these criteria have been met and the patient joins the study is the index date. Up to standard data is assessed with reference to the presence of gaps in the data stream and the existence of an appropriate level of death recording. Women will remain in the cohort until they are aged 49 years or the study ends or the patient's record ends, whichever comes first. To be included in the cohort women must be permanently registered with their GP. One year of data is required before study entry in order that newly prescribed medications for diabetes can be identified. Women who only receive prescriptions for metformin and have records indicating poly-cystic ovary syndrome and no records indicating a diagnosis of diabetes will not be included in the study.

Medications prescribed for the treatment of type 2 diabetes to those in the study cohort will be identified and described at study entry. Where new treatments are received during the study period these will be identified and reported on a 6-monthly basis. Patient characteristics will be compared between those who receive prescriptions for albiglutide and those who do not.

Women who, while present in the study cohort have a pregnancy will be identified and their characteristics, prescribing patterns of diabetes medication and outcomes of their pregnancies will be reported on. Aggregated pregnancy outcomes will be reported in terms of number of losses and number of major malformations; if possible, these will be verified at the end of the study.

6.2. Setting

The Clinical Practice Research Datalink (CPRD), previously the General Practice Research Database (GPRD) will be used for this study. This database holds longitudinal primary care records for approximately 8% of the UK population including medical diagnoses, prescription records, test results and other patient characteristics. The CPRD has been used by this group at the [redacted] and others in studying cohorts of patients with type 2 diabetes (Mulnier et al, 2006a, Mulnier et al, 2006b, Mulnier et al,

2008). A previous study conducted by this group reported pregnancy outcomes for women with diabetes during pregnancy (McGrogan et al, 2014).

Advantages of using the CPRD for pregnancy studies include that it is possible to identify prescriptions issued during pregnancy, tests or referrals received and link the maternal record to her offspring who can then also be followed up for identification of major malformations. Should a pregnancy end in termination, records can be checked to determine possible reasons for this for example due to major malformations in the foetus (Charlton et al, 2014b).

The results from this study are expected to be generalizable to the rest of the UK and to other countries where the prescribing guidelines are similar.

Female patients classified as being permanent patients (i.e. not temporary patients, for example those on holiday) within the CPRD and whose general practice contributes data to the CPRD that is 'up to standard' will be eligible to join the study once they have received two prescriptions for medication for type 2 diabetes and will remain in the cohort while they are aged between 11 and 49 years inclusive. The study period where prescribing of medication for type 2 diabetes will be described will be from 1/1/2015 until 31/12/2019.

Women with type 2 diabetes will be identified using an algorithm that uses diagnosis codes for type 2 diabetes, prescription data, test data such as HbA1c, receipt of home monitoring kits and fasting glucose tests. Women must have at least three diabetes related records to be included in the cohort with at least two of these being for medication. Prescribing for diabetes is required in order to identify those who have a true diagnosis rather than those for whom diabetes is considered as a diagnosis but is not confirmed.

While type 2 diabetes can be managed initially with diet and exercise or for mild cases of diabetes, it was decided to only include those who receive medication for diabetes in the study as this study addresses prescribing of antidiabetic medications among women of child-bearing age and will give a more comparable cohort of patients. Prescriptions for relevant medication also provide verification of the medical diagnosis made in patients' records in the CPRD hence requiring two prescriptions for relevant medications.

In order to determine whether patients have type 1or type 2 diabetes a number of checks will be made: type 2 diabetes will be assumed for those with diabetes related records who are also older than 35 years at first diabetes record or who have a high BMI or who receive oral medication for more than 12 months or who have at least 12 months between first diagnosis of diabetes and first prescription of insulin or a specific medical diagnosis for type 2 diabetes. Where the diagnosis is unclear, we will use the patient record browser to review records for a sample of patients. This browser, written in-house, allows us to review records in chronological order in the way that a GP would view these so for example diagnoses, prescribing, referrals and/or test results made in the same consultation can be viewed and patterns of prescribing can be identified. This can aid in interpretation of a patient's history.

An algorithm (Snowball et al, 2007,Charlton et al, 2014), previously developed at the [redacted] will be used to identify dates of any pregnancies that occur during the

study for all of the women who are included in the cohort. The pregnancy algorithm identifies all pregnancy related codes in the CPRD. The codes used include all antenatal, neonatal and postnatal care, pregnancy, childbirth and termination related information found from medical diagnoses, referrals, tests and maternity data in the CPRD. From these, pregnancy start and end dates are derived and if there is not sufficient information in the records, default time periods of 40 weeks gestational age for a delivery and 10 weeks for a termination are used.

Records relating to pregnancy outcomes will be identified and categorised as delivery (livebirth, stillbirth, neonatal death) or loss (induced termination, miscarriage). Where a livebirth is recorded, the medical records of mothers and babies are linked using the mother's family number to link with an infant(s) with a corresponding family number who has a date of birth within ±62 days of the mother's delivery date.

As this is a descriptive study and we are interested in the utilisation of albiglutide during pregnancy, for the primary objective, all pregnancies identified during the study period will be included, even if the pregnancy end date occurs after the study end date. These pregnancies will be truncated at the study end date with prescribing until the study end date reported. For the secondary objective, only pregnancies where the mother's record for the three months before the pregnancy start date, the entire pregnancy and where the pregnancy ended during the study period will be included.

The study will run from the anticipated launch of albiglutide in the UK in January 2015 until 31/12/2019, in order to give sufficient time to achieve a reasonable market penetration. Annual reports from the study cohort will be made for each calendar year of the study. Patient characteristics, prescribing of diabetes medication and pregnancy outcomes will be identified and reported.

6.3. Variables

6.3.1. Outcome definitions

Pregnancy outcomes including major congenital malformations, stillbirth, neonatal death and pregnancy loss will be identified and reported. The pregnancy algorithm uses medical codes to determine whether a pregnancy ends with a delivery or loss. Pregnancy losses are defined as those that occur before 24 weeks of gestation and are classed as spontaneous (miscarriage), ectopic, due to hydatiform mole, terminations for medical reasons (including for major malformations), terminations for other reasons and terminations for unknown reasons. Pregnancy losses occurring from 25 weeks are classed as stillbirths and recorded as deliveries by the algorithm. Counts of these outcomes will be aggregated for the individual years of the study. If necessary, further information will be requested from GPs using questionnaires; this requirement will be assessed at the end of the study.

Records of major congenital malformations as defined by EUROCAT, 2014 will be identified in the medical records of the offspring for the year following birth. This is because not all malformations are evident at birth and there may be a delay in the diagnosis being recorded in the patient's medical record. For those pregnancies that end

during the final year of the study, only outcomes identified during the study period will be reported.

Major congenital malformations will be identified using medical diagnoses and other supporting codes indicative of a malformation (e.g. a code relating to surgery for repair of a cleft palate) that are available on the CPRD. To do this, distinct medical codes for all the offspring identified will be reviewed by a researcher and any codes for malformations or related treatment will be identified. All babies with possible malformations will be checked using the patient record browser to view related hospital referrals, test results, discharge information and records indicating corrective surgery. Infants with at least two different medical codes that identify the outcome, for example a code for the malformation and a code indicating surgery to correct the malformation, will be taken as having a true malformation. Those with only a single record will be categorised as a 'possible malformation' case.

While codes recorded on the CPRD can provide useful information and some validation of major malformations, it may also be necessary to request further supporting information from general practitioners by sending out questionnaires; information regarding any family history of congenital malformations will also be requested if deemed necessary. In a study using the GPRD, Charlton et al. reported that 86% of malformations identified were verified by requesting extra information recorded by the GP in written or freetext records (Charlton et al, 2010b). While freetext is no longer available for new CPRD data, it is possible to send GPs questionnaires requesting further information about diagnoses. The need for this will be assessed at the end of the study.

Major congenital malformations will be reported in aggregated counts in order to maintain anonymity. Where possible a breakdown by type of medication will be given but this will depend on the numbers identified. Chromosomal defects, malformations of a genetic origin and those not thought to be drug induced (for example positional talipes) will be excluded and not reported on. Advice on the coding of major malformations will be sought from experienced colleagues with a clinical background, where necessary.

6.3.2. Exposure definitions

All prescriptions for medications used to treat diabetes within three months of study entry and during the study period will be identified for the patient cohort. Coding of medications in the CPRD follows the structure of the British National Formulary, 2014. These will be categorised as: albiglutide and oral agent, albiglutide and insulin, albiglutide and oral agent and insulin, other GLP-1 receptor agonists, metformin alone, sulphonylurea alone, metformin and sulphonylurea, insulin alone, thiazolidinedione alone, oral combination, oral and insulin combination, DPP-4 inhibitor alone, other monotherapy.

During the study period, all medications newly prescribed to the patient will be reported on. A newly prescribed medication is one that the patient has not been prescribed previously in their record at all. Where a patient receives more than one diabetes medication over the same time period, this will be defined as a combination treatment; if one or more treatments are stopped and another started this will be a switch in treatments. Where the information is available, prescription length in days will be found from either

the duration recorded or from the quantity and daily dose recorded. If the information is not available then this will be imputed either by using similar prescriptions in the patient's record where the duration is recorded or by using the median duration for that medication and dose from the entire cohort. Dose information will be found from the prescription records.

Where pregnancies are identified, all prescribing for diabetes in the three months before the pregnancy start date and for each trimester of pregnancy will be reported on. Prescribing will also be described by numbers and proportions of patients who receive different treatments in terms of their characteristics including age, BMI, presence of comorbidities and length of time since initial diagnosis of diabetes. While data on medication uptake is not available, where repeat prescriptions are issued during pregnancy this will be taken as an indicator of intended use. Where women receive prescriptions for other medications known to be associated with congenital malformations for example sodium valproate, isotretinoin, methotrexate, ACE inhibitors and HMGCoA reductase inhibitors, these will be will also be identified.

6.3.3. Confounders and effect modifiers

In order to describe the group who receive prescriptions for albiglutide and to compare this with the rest of the study population, a number of patient characteristics will be identified:

- Age at study entry: defined in five year age bands (11-17, 18-24, 25-29 etc.)
- BMI at study entry: captured in the year before cohort entry and defined in five point brackets (<20, 20-24, 25-29 etc.) and determined from height and weight records in the CPRD. Where these are not available and records indicate that the patient is overweight then the BMI category assumed will be 25-30 kg/m^2 and where records indicate that the patient is obese the category 30-35 kg/m^2 will be used. The time between the recording of BMI being made and the index date for the patient will be indicated.
- Smoking status at study entry: captured in the year before cohort entry and defined as smoker, non-smoker, ex-smoker or unknown depending on the records available closest to the patient entering the study cohort. The time between the recording of smoking status being made and the index date for the patient will be indicated.
- Alcohol use defined at study entry: captured in the year before cohort entry and categorised as current drinker, current teetotaller, ex-drinker or heavy drinker. Heavy drinker is defined where the patient has codes indicating heavy or problem drinker or that they are being prescribed alcohol dependence therapy or where the units of alcohol consumed each week is greater than 31. This status remains for each patient until a further record is made that conflicts with the information for example units consumed per week changes to be within 'current drinker' guidelines. The time between the recording of alcohol use being made and the index date for the patient will be indicated.
- Recreational drug use will be reported, where this is recorded.

- Duration of diabetes: determined using the first record identified on the database for the diagnosis or treatment of diabetes; where the first record is within 12 months of the patient joining the database, this will be classed as unknown since it is likely that this will be a pre-existing diagnosis.
- Macrovascular comorbidities including coronary artery disease, peripheral arterial disease, stroke, acute coronary artery syndrome, heart failure, stable angina, hyperlipidaemia, coronary revascularisation, hypertension and renal impairment will be identified, where possible, using medical diagnosis codes.
- Microvascular comorbidities including diabetic nephropathy, neuropathy and retinopathy will be identified using medical diagnosis codes.
- Severity of diabetes: the microvascular and macrovascular complications as well as the use of combination antidiabetic agents will serve as a proxy for the severity and progression of type 2 diabetes.
- Malignant neoplasms
- Practice level socioeconomic status
- Oral contraceptives prescribed, injections given or contraceptive devices fitted.

For those who have a pregnancy identified during the study period, prescriptions received in the three months before and/or during pregnancy known to be associated with congenital malformations will also be identified for example sodium valproate, isotretinoin, methotrexate, ACE inhibitors, HMGCoA reductase inhibitors, nitrates, beta blockers, calcium channel blockers, diuretics, antiplatelet agents, angiotensin II receptor blockers, fibrates, NSAIDs and folic acid. Other chronic medical conditions recorded and previous pregnancy outcomes (livebirths, spontaneous losses, stillbirths, congenital malformations) will also be reported. Where the pregnancy algorithm has allocated a default length to the pregnancy (40 weeks for a delivery, 10 weeks for a termination), this will be reported. If records are available, family history of congenital malformations will also be identified.

6.4. Data sources

The CPRD, formerly known as the General Practice Research Database (GPRD) will be used for this study. This database contains information about the patients' diagnoses, prescribing, laboratory test results, referral requests, immunisations, pregnancies, symptoms and deaths recorded within general practice. The CPRD receives patients' records from contributing general practices that are paid for including their data in the database. Data is recorded by general practitioners in the form of READ codes. Where required, further information about patient records can be obtained providing the patient is still registered with the same practice. This can be done either by asking their GP to complete a questionnaire or by requesting a copy of the patient's anonymised medical records.

The CPRD has been found to be generally representative of the UK population in terms of the age distribution, geographical distribution of practices and mortality rates (Campbell et al, 2013, Lawson et al, 1998, Charlton et al, 2014a). It has been shown that the recording of prescriptions issued in primary care on the CPRD is in good agreement

with dispensing data (Walley et al, 1997). A number of studies have been undertaken to verify different outcomes on the GPRD and two reviews record the high validity found (Herrett et al, 2010, Khan et al, 2010). Previous studies using the GPRD indicate that the prevalence of type 2 diabetes found is similar to that recorded in field studies (Mulnier et al, 2006a). The algorithm that will be used to identify pregnancies and their outcomes on the CPRD has been developed over a number of years with samples of individual cases checked for accuracy (Snowball et al, 2007, Charlton et al, 2010a) and a sample of major congenital malformations have been validated in a previous study (Charlton et al, 2010b). Work investigating pregnancy loss in patients with diabetes using the GPRD reported very similar patient characteristics to the Confidential Enquiry into Maternal and Child Health field study also conducted in the UK (McGrogan et al, 2014).

6.5. Study size

This is a descriptive study and will include all women who are eligible to join the study cohort therefore a sample size calculation is not required. However, previous work has indicated that there should be at least 10 000 women of child-bearing age with pharmacologically treated type 2 diabetes on the CPRD in the study period. In 2005 we identified around 67 pregnancies that occurred in women diagnosed with type 2 diabetes: we expect, given the increasing prevalence of type 2 diabetes and the increase in the number of general practices contributing data to the CPRD that this number will be higher for the study period being considered. The size of the population prescribed albiglutide will be dependent on market penetration in the UK.

6.6. Data management

The data for this study will be extracted from the CPRD. At the moment we use flat file CPRD data however during the course of the project it is planned that the CPRD will move to online data only, therefore with this in mind use of both flat file and online Gold data are anticipated.

The data will be loaded on to the department's dedicated Oracle database in the university datacentre from full text files supplied by the CPRD on an encrypted drive or from online downloads. The department will be migrating from Oracle 11g to Oracle 12c running on a SPARC T5 server during 2014. The database is backed up to secure storage with high availability and consistency checking. Once the source data is loaded, verified and indexed the dataset is set to read only to ensure data integrity. Each dataset release has full version control, currently by using separate schemas. Scripts (SQL and PL/SQL), code lists and other files are stored in the department projects folder on servers which are securely backed up by the university IT department.

In years one and five of the study, flat file data if it is still available in this form will be loaded and used for the extraction of the data for the study. In years two, three and four, online data will be used from the CPRD's GOLD system as this makes the data more readily available but it is more difficult to obtain complete datasets for large cohorts. Using the flat files will allow full patient characteristics to be obtained and described.

6.6.1. Data handling conventions

Any missing data for example smoking status and alcohol use will be defined as such and recorded separately. Major congenital malformations will be coded in line with EUROCAT definitions (EUROCAT, 2014). Pregnancy losses will be coded according to the evidence available in the medical codes recorded for each patient.

Loss to follow up: For the secondary objective where pregnancy outcomes will be reported on, the minimum contribution period will be that the mother will have needed to be in the study cohort for the three months before her pregnancy start date until the end date of the pregnancy. For pregnancies where the offspring does not have one year of follow up following birth, this information will be recorded, for example outcomes identified at 3, 6, 9 and 12 months.

6.6.2. Resourcing needs

The main resources needed for this project are the CPRD data and research staff time. We hold a licence for the CPRD and we regularly receive new full extracts of all the data held in the form of flat files. These however are time consuming to load onto the servers and therefore this will be used at the start and end of the project. For the intermediate years, online CPRD data from GOLD will be used. CPRD have indicated that flat file data will cease to be available in the near future therefore if this is the case then the data extraction in year five will also use GOLD data rather than the flat files as indicated.

The majority of the work on this project will be undertaken by [redacted] who is the database manager and who has 12 years' experience in loading and managing CPRD data, in writing complex algorithms for example to identify pregnancies and in providing support to research projects by extracting datasets and coding data.

Support will be provided by Dr. [redacted] who has extensive experience (7 years) of drug safety in pregnancy work using the CPRD and other databases. Dr. [redacted] will provide input into updating code lists, reviewing test cases for validation and pregnancy outcomes and in writing the reports.

Dr. [redacted] has 8 years' experience working with CPRD data on a number of projects but most recently undertaking a utilisation and outcomes study of the treatment of diabetes before and during pregnancy. Dr. [redacted] will contribute to and review code lists, test cases, write the reports and manage the project.

Dr. [redacted] and [redacted] hold research fellow contracts that are ongoing, providing research funding is available. Dr. [redacted] holds a permanent academic contract.

6.6.3. Timings of Assessment during follow-up

Data will be extracted from the CPRD twice a year for five years, commencing in January 2016. The algorithms and coding lists will be updated semi-annually in order to account for any changes in the data and coding conventions. Every six months the algorithms will be run on the entire dataset from the start date of the project in order that

full information can be provided in each interim report. This will also take into account any retrospective changes that are made to the data.

Interim reports will be provided twice a year (March 2016, September 2016, March 2017, September 2017, March 2018, September 2018, March 2019, September 2019) with the final report submitted in August 2020.

6.7. Data analysis

The analysis undertaken for this study will be descriptive. The study objectives will be addressed through the presentation of counts and proportions of women of child-bearing age who have type 2 diabetes and receive prescription(s) for albiglutide and other antidiabetic agents.

6.7.1. Essential analysis

Primary objective: To assess the proportion and characteristics of women with type 2 diabetes of child-bearing age who are prescribed albiglutide.

The characteristics of all women in the cohort will be described by counts and proportions of the total women in the cohort. These characteristics will include age, BMI, smoking, alcohol use, duration since diagnosis of type 2 diabetes, macrovascular comorbidities, microvascular comorbidities and contraception use at cohort entry. Characteristics will be described at cohort entry for each patient in terms of the medication prescribed for diabetes within three months of cohort entry (Table 1). Characteristics will also be described according to new medication for diabetes that is prescribed during the study period (Table 2).

Incidence, period prevalence and days exposed to different medications will be calculated for each year of the study and for the overall study period. These statistics will only include new medications prescribed while patients are contributing time to the study cohort and will not include any existing treatment that they are receiving when they join the study. The denominator used for the prevalence calculation will be the number of patients in the cohort at the end of each year of the study period being considered. For incidence, person time will be used as the denominator and incident prescriptions of each medication will be defined where the patient has not been prescribed that medication previously in their record (Table 3).

Sensitivity analysis will be used to determine the effect of the duration since the first record of diabetes and any effect of limiting the time between diagnosis and first prescription of anti-diabetic medications from 12 months to 6 months.

Primary objective: To assess the proportion and characteristics of women with type 2 diabetes who are prescribed albiglutide during pregnancy.

Women who have a pregnancy during the study period will be identified and their pregnancy start and end dates will be determined. All prescriptions for diabetes medications received during the 3 months before pregnancy start date and each trimester of pregnancy will be tabulated. Patient characteristics at the start date of the pregnancy

and prescribing received in the three months before the pregnancy start date will be tabulated as counts and percentages (Table 4). Numbers of patients receiving each class of medication will be described by three month period and outcome (Table 5). Comparisons will be made between the group receiving prescriptions for albiglutide during pregnancy and those receiving other medications, providing the sample sizes are large enough.

Secondary objective: To summarise outcomes of women prescribed albiglutide during pregnancy including reported major congenital malformations, pregnancy losses, stillbirths or neonatal deaths.

Outcomes of women identified to have a pregnancy during the study period will be described by counts and proportions (Table 6). For pregnancy losses and major congenital malformations, all prescribing for diabetes received in the three months before the pregnancy start date and the first trimester will be described as these are the relevant exposures for these outcomes. For deliveries (livebirths, stillbirths and neonatal deaths), prescribing throughout pregnancy will be described.

Foetal outcomes will be compared (where numbers permit) between the different treatment combinations received by mothers during and/or in the three months before pregnancy and those whose mothers only received metformin during pregnancy and/or in the three months before pregnancy.

While all of the possible prescribing categories are given in the shell Table 1- Table 6, these may need to be grouped once the results are collated, to maintain patient anonymity.

6.7.2. Exploratory analysis

Not applicable.

6.7.3. General considerations for data analyses

This study will be descriptive therefore no adjustments will be made for potential confounders.

6.8. Quality control

All scripts and code lists will be reviewed by a second researcher. In addition a set of test cases will be generated for the first extraction of data. At each subsequent extraction the test dataset will be validated (occasionally records are deleted or practices are merged between CPRD versions) and new test cases added to include a sample of patients with new codes, if applicable. Any discrepancies between the test cases and results will be accounted for and rectified.

Data submitted to the CPRD undergoes quality checks before the general practice is deemed to be contributing data that is up to a standard appropriate for research. Individual patient records are identified as acceptable providing that data on sex, age, event recording and registration details are consistent (Khan et al, 2010).

Pregnancy outcomes have been validated in previous work by this group: a sample of congenital malformations have been validated against printed records and free text (Charlton et al, 2010b); pregnancy losses were compared with national statistics in writing the pregnancy algorithm (Charlton et al, 2010a) and in subsequent studies losses have been checked against free text entries in the CPRD (McGrogan et al, 2014).

In this study, a series of test cases will be identified to validate the algorithms being used for patient identification and coding purposes.

For the diabetes algorithm, a sample of patients with the following characteristics will be identified for validation purposes. Those who are diagnosed with type 2 diabetes at:

1. Age > 35 years and receive oral antidiabetic prescribing or insulin or both
2. Age > 35 years with a high BMI and receive oral antidiabetic prescribing or insulin or both
3. Age < 35 years and receive oral antidiabetic medication
4. Age < 35 years and receive insulin and oral antidiabetic medication
5. Age < 35 years with a high BMI and receive oral antidiabetic prescribing or insulin or both
6. Age < 35 years and receive insulin
7. Age < 25 years and receive oral antidiabetic prescribing or insulin or both

For the group of women with pregnancies, test cases will be created using the following criteria:

Exposure permutations

1. Exposure during time periods: 3 months before pregnancy start date, trimester 1, trimester 2/3, other period within study.
2. Prescriptions during time period: albiglutide alone, other diabetes prescription alone, albiglutide and other diabetes prescription, no prescribing.

Pregnancy outcome permutations

Identify a sample of cases where the outcome of the pregnancy is a

1. Loss: spontaneous or induced for medical reason or induced for non-medical reasons or ectopic or hydatiform mole (if any identified).
2. Delivery: where the mother's records are linked with the baby's records including neonatal death or major congenital malformation if any occur.
3. Delivery: where the mother's records could not be linked with the baby's records, including stillbirths if any occur.

Other

1. Include a sample of patients not meeting the study criteria to ensure that they are correctly excluded from the study.

For all sets of test cases, patients' records will be viewed in the medical records browser and manually coded for lifestyle factors, comorbidities, time since diagnosis, pregnancy dates and pregnancy outcomes. These results will be compared with the algorithm results and any discrepancies will be fixed or accounted for. The identification of the test patients and manual coding will be done independently by a different researcher from the person who writes the algorithms for the study.

6.9. Limitations of the research methods

There are a number of limitations that need to be considered when reviewing the results of this study. These refer either to the recording of the data or the interpretation of what this represents.

1) Exposure data

Some patients may receive referrals to secondary care for assessment or treatment: this information, particularly any prescribing data may not be available on the CPRD. However the majority of repeat prescribing will be carried out within primary care and will be captured in the database. Risk level: LOW.

The prescription data available within the CPRD refers to the scripts that have been issued: no information is available on dispensing or compliance with this medication. Diabetes is a chronic disease and receipt of repeat prescriptions should therefore provide a good proxy for patient compliance with medication for the majority of the population in the study. For patients who have a pregnancy during the study, glycaemic control will need to be maintained but once pregnancy is recognised, use of medication may change. We will investigate any changes in prescribing by looking at individual trimesters and using repeat prescribing as an indication of continuing use of that medication. Risk level: LOW.

This study will report on the prescribing of albiglutide and other antidiabetic agents in women of child-bearing age with type 2 diabetes and a sub-group of women with pregnancies during the study period. While we can speculate the likely market

penetration of the new medication, until it is launched onto the market we do not know how accurate these projections will be. This will have a low impact since the study is descriptive and therefore any sample size achieved will be valid to report on. Risk level: LOW.

2) Missing data

In terms of data integrity the CPRD provides data covering many areas however in previous work with the database we have noted that while codes are present to indicate that tests have been taken, results are not always available for example HbA1c recording. It could be that a bias exists towards the recording of non-normal results that need further investigation. In this study, while the availability of HbA1c results during pregnancy would be useful in describing the glycaemic control of patients, this is not essential. Risk level: LOW.

Smoking status and BMI are well recorded in the CPRD but these records are not complete: previous work indicates that 99.2% of women with type 2 diabetes and at least one pregnancy had some records for smoking data in the CPRD; for BMI 89.2% had records available. Missing data will be coded to reflect this. Risk level: LOW.

It can be difficult to match mothers with their offspring, for example if outcomes are reported after the end of the project or if patients move to a different GP practice soon after their pregnancy ended. Using the pregnancy algorithm we can match around 80% of mothers to babies: this statistic will be reported for the study population considered. While it is possible that families may move away from the area we expect that this will not happen very frequently. For any pregnancies that complete in the final year of the study, the follow up time for capturing malformations will be limited but this will only affect a small number of the pregnancies in the study. Risk level: LOW.

3) Distinguishing between type 1 and type 2 diabetes

For some patients, especially younger patients who receive some insulin, it may be difficult to distinguish between those who have type 1 and those who have type 2 diabetes. We recognise this difficulty and will therefore ensure that the test cases are reviewed carefully and will also review patient records in the medical browser where necessary. If a small number of patients with type 1 diabetes were inadvertently included in this study population or a small number of patients who were prescribed insulin were excluded from the study this will not have a large effect on the main results of the study regarding the utilisation of albiglutide since this is contraindicated in patients with type 1 diabetes. Proportions of pregnancy losses and major congenital malformations in patients with pre-existing type 1 or type 2 diabetes are similar. Risk level: LOW.

4) Identifying pregnancies

For some patients identifying pregnancy start dates can be difficult either due to complex history of multiple pregnancies, conflicting data or due to a lack of data being recorded. Where this is the case default pregnancy periods are used: 40 weeks for a pregnancy ending in a normal (i.e. not pre-term) delivery and 10 weeks for a pregnancy ending with a loss. If the pregnancy duration is incorrectly estimated this has the potential to result in

errors in the precise timing of exposure however, as diabetes is a chronic condition and patients are likely to be prescribed medication on a long term basis, the impact of this is expected to be low. Risk level: LOW.

5) Identifying pregnancy outcomes

In terms of identifying pregnancy outcomes, we have found in previous work that while many pregnancy outcomes are well coded and detailed information can be obtained from the CPRD data, some discrepancies do occur for example miscarriages being incorrectly coded as stillbirths. Also if terminations are induced for medical reasons such as a malformation this information may not be apparent from the medical codes and further details may be needed. If following the identification of these outcomes and reviewing of the coded information in the medical records browser the reported outcomes cannot be confirmed, we will request further information from the patient's GP. Risk level: LOW.

6) Data availability

GSK are not in control of the data collection therefore if CPRD data becomes unavailable to the researchers or collection is stopped, only the data collected up until that point can be used. Collection of general practice data in the UK commenced in 1987 and its use in research, linkage to other data and the amount of practices enrolled continues to increase. It is therefore expected that the CPRD data will continue to be available for the duration of this study. The pharmacoepidemiology group conducting this work have used the database since 1998 and have a number of other ongoing studies that use this data: it is expected that the researchers will continue to maintain their access to this data. Risk level: LOW.

7) Strengths

There are a number of strengths to this study design: the CPRD dataset is large and representative of the UK population which will make it possible to identify a large cohort of women of child-bearing age and a reasonable number of pregnancies affected by type 2 diabetes. This will enable comparisons to be made of those who are prescribed different medications for the treatment of their type 2 diabetes. Within the CPRD it is also possible to capture all types of pregnancy outcome, including those that end in a spontaneous pregnancy loss or termination of pregnancy. Our extensive work with the CPRD has enabled us to develop a complex algorithm to identify women with pregnancies in the database and link their medical records to those of their offspring thus enabling adverse pregnancy outcomes to be identified and reported on.

The data held by the CPRD is collected prospectively, during the normal course of primary care patient management. Prescription data that forms the exposure measurement is recorded before the pregnancy outcome is known which prevents any potential problems with patient recall bias; similarly the study population is unlikely to suffer from selection bias. As a woman's entire pregnancy record can be captured, potential exposures from early on in pregnancy can be identified; these are the exposures that are most likely to affect organogenesis and are difficult to capture in other study types such as field studies.

Apart from metformin and insulin there is very little information available about the utilisation and safety of medications for type 2 diabetes during pregnancy. The results from this study will provide valuable information about how type 2 diabetes is treated in the UK during pregnancy and how albiglutide, a newly launched medication, is prescribed in women of child-bearing age.

6.9.1. Study closure/uninterpretability of results

Not applicable.

6.10. Other aspects

Not applicable.

7. PROTECTION OF HUMAN SUBJECTS

7.1. Ethical approval and subject consent

All observational studies using the CPRD have ethics approval from the [redacted] Individual studies are required to obtain approval from the [redacted] and this approval will be sought prior to the commencement of the study.

7.2. Subject confidentiality

All data contributed to the CPRD is anonymised before being received by researchers. Results from the study will be reported as aggregated data in order that individual patients cannot be identified. The data providers require that no data is described for categories where there are fewer than five patients. It is possible that this may occur for example where different types of malformation are identified. If this does then categories will be broadened to maintain anonymisation.

8. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Will be carried out according to standard operating procedure SOP-BMD-3003 Safety Reporting from Epidemiology Studies and Analyses of Epidemiology Databases. This SOP applies to all GSK-sponsored observational studies and analyses of epidemiology data with safety-related primary objectives. It outlines the process and responsibilities with respect to global reporting of safety-related results of GSK-sponsored non-interventional, observational studies and is in compliance with Good Pharmacovigilance Practice (GVP) guidelines. It outlines the roles and responsibilities of the epidemiologist/study manager as it relates to PASS studies as well as individual adverse event case reports.

9. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

9.1. Target Audience

The results from this study will be submitted to GSK twice a year with the final report written up for presentation at the International Conference of Pharmacoepidemiology. A manuscript will also be written and submitted for publication in a peer-reviewed journal.

The results will be disseminated externally via regulatory submission, manuscripts and abstracts.

ENCEPP and STROBE guidelines will be followed as appropriate.

9.2. Study reporting and publications

Plans for dissemination of the results of the study are given in Table below.

Timetable of reports and publications

Milestone	Target Date
Interim report 1 to GSK (draft)	February 2016
Interim report 1 to GSK (final)	March 2016
Interim report 2 to GSK (draft)	August 2016
Interim report 2 to GSK (final)	September 2016
Interim report 3 to GSK (draft)	February 2017
Interim report 3 to GSK (final)	March 2017
Interim report 4 to GSK (draft)	August 2017
Interim report 4 to GSK (final)	September 2017
Interim report 5 to GSK (draft)	February 2018
Interim report 5 to GSK (final)	March 2018
Interim report 6 to GSK (draft)	August 2018
Interim report 6 to GSK (final)	September 2018
Interim report 7 to GSK (draft)	February 2019
Interim report 7 to GSK (final)	March 2019
Interim report 8 to GSK (draft)	August 2019
Interim report 8 to GSK (final)	September 2019

Milestone	Target Date
Draft of final report to GSK	August 2020
Final report to GSK	September 2020
Final manuscript submitted	September 2020

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ANNEX 1.LIST OF STAND-ALONE DOCUMENTS

Tables Annex 1:Shell tables

Table 1 Characteristics of women (counts [N] and proportion [%]) of child-bearing age with type 2 diabetes with respect to prescribing for diabetes at study entry identified in the CPRD between 1/1/2015 and 31/12/2019

Age (years)[1]	Albiglutide alone	Albiglutide + oral	Albiglutide + insulin	Albiglutide +oral +insulin	Albiglutide overall	Other GLP-1RA	Met alone	Su alone	Met + Su	Insulin alone	TZD alone	Oral combination	Oral + insulin	DPP-4i alone	Other
11-17 18-24 25-29 30-34 35-39 40-44 45-49															
BMI[1] <20 20-24 25-29															

Age (years)[1]	**Albiglutide alone**	**Albiglutide + oral**	**Albiglutide + insulin**	**Albiglutide +oral +insulin**	**Albiglutide overall**	**Other GLP-1RA**	**Met alone**	**Su alone**	**Met + Su**	**Insulin alone**	**TZD alone**	**Oral combination**	**Oral + insulin**	**DPP-4i alone**	**Other**
30-34 35-39 ≥40 Unknown															
Smoking status Smoker Non-smoker Ex-smoker Unknown															
Alcohol use Drinker Teetotal Ex-drinker Unknown															

Age (years)[1]	Albiglutide alone	Albiglutide + oral	Albiglutide + insulin	Albiglutide +oral +insulin	Albiglutide overall	Other GLP-1RA	Met alone	Su alone	Met + Su	Insulin alone	TZD alone	Oral combination	Oral + insulin	DPP-4i alone	Other
Recreational drug use															
Practice SES quintile 1 2 3 4 5															
Diabetes duration < 1 year 1 -4 years 5-9 years 10-14 years ≥ 15 years Unknown															

Age (years)[1]	**Albiglutide alone**	**Albiglutide + oral**	**Albiglutide + insulin**	**Albiglutide +oral +insulin**	**Albiglutide overall**	**Other GLP-1RA**	**Met alone**	**Su alone**	**Met + Su**	**Insulin alone**	**TZD alone**	**Oral combination**	**Oral + insulin**	**DPP-4i alone**	**Other**
Microvascular comorbidity Diabetic nephropathy Neuropathy Retinopathy															
Macrovascular comorbidity Coronary artery disease Peripheral artery disease Stroke															
Contraception Prescribed Injection Other															

Notes: [1]Table categories will be combined where there are fewer than five patients contributing to any individual cell in order to maintain patient anonymity. Met = metformin; Su = sulphonylurea; TZD = thiazolidinedione; SES = socioeconomic status; RA = receptor agonists; I = inhibitor.

Table 2 Characteristics of women (counts [N] and proportion [%]) of child-bearing age with type 2 diabetes with respect to the prescribing of new diabetes medication received during each the study period. Women may be counted in more than one column of the table, where they receive more than one new category of medication

	Albiglutide alone	Albiglutide + oral	Albiglutide + insulin	Albiglutide +oral +insulin	Albiglutide overall	Other GLP-1RA	Met alone	Su alone	Met + Su	Insulin alone	TZD alone	Oral combination	Oral + insulin	DPP-4i alone	Other
Age[1] 11-17 18-24 25-29 30-34 35-39 40-44 45-49															
BMI[1] <20 20-24 25-29 30-34															
35-39 ≥40 Unknown															
Smoking status Smoker Non-smoker Ex-smoker Unknown															
Alcohol use Drinker Teetotal Ex-drinker Unknown															
Recreational drug use															
Practice SES quintile															
1 2 3															

	Albiglutide alone	Albiglutide + oral	Albiglutide + insulin	Albiglutide +oral +insulin	Albiglutide overall	Other GLP-1RA	Met alone	Su alone	Met + Su	Insulin alone	TZD alone	Oral combination	Oral + insulin	DPP-4i alone	Other
4 5															
Diabetes duration < 1 year 1 -4 years 5-9 years 10-14 years ≥ 15 years Unknown															
Microvascular comorbidity Diabetic nephropathy Neuropathy Retinopathy															
Macrovascular comorbidity Coronary artery disease Peripheral artery disease Stroke															
Contraception Prescribed Injection Other															

Notes: [1]Table categories will be combined where there are fewer than five patients contributing to any individual cell in order to maintain patient anonymity. Met = metformin; Su = sulphonylurea; TZD = thiazolidinediones; RA = receptor agonists; I = inhibitor.

Table 3 Period prevalence, incidence and exposed days of prescribing of diabetes medication by time period. Each patient can be counted in more than one column if they receive new treatments that are under different categories during the year being considered

	Albiglutide alone	Albiglutide + oral	Albiglutide + insulin	Albiglutide + insulin + oral	Albiglutide overall	Other GLP-1RA	Met alone	Su alone	Met + Su	Insulin alone	TZD alone	Oral combination	Oral + insulin	DPP-4i alone	Other
Time period	**Period prevalence (prevalent users/1000 person years)**														
2015															
2016															
2017															
2018															
2019															
2015-2019															
	Incidence (incident users/1000 person years)														
2015															
2016															

	Albiglutide alone	Albiglutide + oral	Albiglutide + insulin	Albiglutide + insulin + oral	Albiglutide overall	Other GLP-1RA	Met alone	Su alone	Met+ Su	Insulin alone	TZD alone	Oral combination	Oral + insulin	DPP-4i alone	Other
2017															
2018															
2019															
2015-2019															
	Exposed days (exposed days/1000 person years)														
2015															
2016															
2017															
2018															
2019															
2015-2019															

Notes: Met = metformin; Su = sulphonylurea; TZD = thiazolidinediones; RA = receptor agonists ; I = inhibitor.

Table 4 Characteristics and prescribing to women with type 2 diabetes at pregnancy start date. Data are reported as counts (percentages %)[1]

	Albiglutide + oral	Albiglutide + insulin	Albiglutide + oral + insulin	Albiglutide overall	Other GLP-1RA	Met alone	Su alone	Met+ Su	Insulin alone	TZD alone	Oral combination	Oral + insulin	DPP-4i alone	Other
Pregnancy outcome Livebirth (trimester 2) Livebirth (trimester 3) Stillbirth (trimester 2 or 3) Loss (trimester 1) Loss (trimester 2)														
Age [1] 11-17 18-24 25-29 30-34 35-39 40-44														

	Albiglutide + oral	Albiglutide + insulin	Albiglutide + oral + insulin	Albiglutide overall	Other GLP-1RA	Met alone	Su alone	Met+ Su	Insulin alone	TZD alone	Oral combination	Oral + insulin	DPP-4i alone	Other
45-49														
BMI [1]														
<20														
20-24														
25-29														
30-34														
35-39														
≥40														
Unknown														
Smoking status														
Smoker														
Non-smoker														
Ex-smoker														
Unknown														

	Albiglutide + oral	Albiglutide + insulin	Albiglutide + oral + insulin	Albiglutide overall	Other GLP-1RA	Met alone	Su alone	Met+ Su	Insulin alone	TZD alone	Oral combination	Oral + insulin	DPP-4i alone	Other
Alcohol use Drinker Teetotal Ex-drinker Unknown														
Practice SES quintile 1 2 3 4 5														
Diabetes duration < 1 year 1 -4 years 5-9 years 10-14 years														

	Albiglutide + oral	Albiglutide + insulin	Albiglutide + oral + insulin	Albiglutide overall	Other GLP-1RA	Met alone	Su alone	Met+ Su	Insulin alone	TZD alone	Oral combination	Oral + insulin	DPP-4i alone	Other
≥ 15 years Unknown														
Microvascular comorbidity Diabetic nephropathy Neuropathy Retinopathy														
Macrovascular comorbidity Coronary artery disease Peripheral artery disease Stroke														
Other chronic medical condition														
Other co-prescribing during pregnancy														

	Albiglutide + oral	Albiglutide + insulin	Albiglutide + oral + insulin	Albiglutide overall	Other GLP-1RA	Met alone	Su alone	Met+ Su	Insulin alone	TZD alone	Oral combination	Oral + insulin	DPP-4i alone	Other
Previous pregnancy outcome Livebirth Stillbirth, neonatal death Major malformation Spontaneous loss														

Notes: [1]Table categories will be combined where there are fewer than five patients contributing to any individual cell in order to maintain patient anonymity. Met = metformin; Su = sulphonylurea; TZD = thiazolidinediones; RA = receptor agonists; I = inhibitor.

Table 5 Delivery outcomes of all patients with a pregnancy included in the study population. Data are reported as numbers (percentages %)[1]

Deliveries (livebirths)	**Albiglutide + oral**	**Albiglutide + insulin**	**Albiglutide + oral + insulin**	**Albiglutide overall**	**Other GLP-1RA**	**Met alone**	**Su alone**	**Met + Su**	**Insulin alone**	**TZD alone**	**Oral combination**	**Oral + insulin**	**DPP-4i alone**	**Other**
3 months before pregnancy start date Trimester 1 Trimester 2 Trimester 3														
Deliveries (stillbirths)														
3 months before pregnancy start date Trimester 1 Trimester 2 Trimester 3														

Deliveries (livebirths)	**Albiglutide + oral**	**Albiglutide + insulin**	**Albiglutide + oral + insulin**	**Albiglutide overall**	**Other GLP-1RA**	**Met alone**	**Su alone**	**Met + Su**	**Insulin alone**	**TZD alone**	**Oral combination**	**Oral + insulin**	**DPP-4i alone**	**Other**
Losses 3 months before pregnancy start date Trimester 1 Trimester 2														

Notes: [1] Table categories will be combined where there are fewer than five patients contributing to any individual cell in order to maintain patient anonymity. Met = metformin; Su = sulphonylurea; TZD = thiazolidinediones; RA = receptor agonists; I = inhibitor.

Table 6 Outcomes of women who have a pregnancy during the study period and who are prescribed medication for type 2 diabetes. For pregnancy losses and congenital malformations prescribing in the three months before the pregnancy start date and the first trimester will be described; for deliveries, prescribing throughout the pregnancy will be described[1]

Outcomes	Albiglutide + oral	Albiglutide + insulin	Albiglutide + oral + insulin	Albiglutide overall	Other GLP-1RA	Met alone	Su alone	Met + Su	Insulin alone	TZD alone	Oral combination	Oral + insulin	DPP-4i alone	Other
Major congenital malformations														
Pregnancy losses Spontaneous Ectopic Hydatiform mole Induced for medical reasons Induced for other reasons														

Outcomes	Albiglutide + oral	Albiglutide + insulin	Albiglutide + oral + insulin	Albiglutide overall	Other GLP-1RA	Met alone	Su alone	Met + Su	Insulin alone	TZD alone	Oral combination	Oral + insulin	DPP-4i alone	Other
Deliveries Livebirths Stillbirths and neonatal deaths														

Notes: [1]Table categories will be combined where there are fewer than five patients contributing to any individual cell in order to maintain patient anonymity. Met = metformin; Su = sulphonylurea; TZD = thiazolidinediones; RA = receptor agonists; I = inhibitor.

ANNEX 2.FOR PASS STUDIES ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Section 1: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the formulation of the research question clearly explain:				
1.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	18
1.1.2 The objectives of the study?	☒	☐	☐	18
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	19
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
1.2.3 if applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Is the source population described?	☒	☐	☐	19
2.2 Is the planned study population defined in terms of:				

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.2.1 Study time period?	☒	☐	☐	19
2.2.2 Age and sex?	☒	☐	☐	20
2.2.3 Country of origin?	☒	☐	☐	20
2.2.4 Disease/indication?	☒	☐	☐	20
2.2.5 Co-morbidity?	☒	☐	☐	20
2.2.6 Seasonality?	☐	☐	☒	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	19

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	21
3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	19
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.4 Is sample size considered?	☒	☐	☐	25
3.5 Is statistical power calculated?	☐	☐	☒	

Comments:

This study is descriptive therefore counts and percentages will be reported but measures of effect will not be calculated. Statistical power for the study has not been calculated as this is a descriptive study and all patients meeting the criteria will be included in the study.

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	☒	☐	☐	22
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc)	☒	☐	☐	21
4.1.3 Covariates?	☒	☐	☐	23

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	22
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	21
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	23
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	22
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☒	☐	☐	21
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	22
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	22
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	22
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	23
5.4 Is exposure classified based on biological mechanism of action?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	21
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	22

Comments:

Section 7: Biases and Effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address: 7.1.1 Selection biases? 7.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒ ☒	☐ ☐	☐ ☐	 30 30
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	23
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	23
7.4 Does the protocol address other limitations?	☒	☐	☐	30

Comments:

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☒	☐	☐	27
8.2 Is the choice of statistical techniques described?	☒	☐	☐	27
8.3 Are descriptive analyses included?	☒	☐	☐	27
8.4 Are stratified analyses included?	☒	☐	☐	27
8.5 Does the plan describe the methods for identifying:				

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.5.1 Confounders?	☐	☒	☐	
8.5.2 Effect modifiers?	☐	☒	☐	
8.6 Does the plan describe how the analysis will address:	☐	☒	☐	
8.6.1 Confounding?	☐	☒	☐	
8.6.2 Effect modification?				

Comments:

This study is descriptive, no associations are being tested and therefore potential confounders and/or effect modifiers will not be formally evaluated. These will be described in the overview of patient characteristics.

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	25
9.2 Are methods of quality assurance described?	☒	☐	☐	28
9.3 Does the protocol describe quality issues related to the data source(s)?	☒	☐	☐	28
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	25

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.5 Does the protocol specify timelines for				
9.5.1 Start of data collection?	☒	☐	☐	15
9.5.2 Any progress report?	☒	☐	☐	15
9.5.3 End of data collection?	☒	☐	☐	15
9.5.4 Reporting? (i.e. interim reports, final study report)	☒	☐	☐	15
9.6 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	15
9.7 Are communication methods to disseminate results described?	☒	☐	☐	34
9.8 Is there a system in place for independent review of study results?	☒	☐	☐	34

Comments:

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	33
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
10.3 Have data protection requirements been described?	☒	☐	☐	33

Comments:

Name of main author of study protocol: [redacted]

Date:

Signature: _____