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

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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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EU PAS register number	ENCEPP/SDPP/7165
Active substance	albiglutide
Medicinal product	Tanzeum, Eperzan
Product reference	Eperzan (albiglutide, GSK716155)
Procedure number	EMA/H/C/2735
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
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MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	GlaxoSmithKline Research & Development Limited 980 Great West Road Brentford Middlesex, TW8 9GS UK.
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SPONSOR SIGNATORY SIGNATURE PAGE

I have read this report and confirm that to the best of my knowledge this report accurately describes the conduct and results of the study 201795.

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1.0 Abstract

Rationale and background
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.

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.

Study setting and design
The Clinical Practice Research Datalink (CPRD) was used for this study. This database contains UK general practice data for around 8% of the population. To determine the feasibility of carrying out this utilisation study, product details for albiglutide (and product names Eperzan and Tanzeum) were checked for in the product table of the CPRD for data recorded up to 31st January 2016.

Results
No details relating to albiglutide, Eperzan and Tanzeum were found in the product table of the CPRD which indicates that no prescriptions have been issued for this medication up to 31st January 2016.

2.0 List of abbreviations

CPRD	Clinical Practice Research Datalink
GPRD	General Practice Research Database
GLP-1	Glucagon-like protein-1
NICE	National Institute for Health and Care Excellence
UK	United Kingdom

3.0 Investigators

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4.0 Milestones

Milestone	Planned date	Actual date	
Start of data collection	January 1, 2015	TBD	Albiglutide has not been released in the UK therefore data collection has not commenced
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		

5.0 Rationale and 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 (NICE, 2008).

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 a 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, Campbell et al, 2013, Charlton et al, 2010). 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.

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.

6.0 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.

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.

7.0 Amendments and updates

An amendment to the reporting of results has been introduced owing to the delay in albiglutide being launched in the UK. This amendment requires six monthly feasibility reports to be made as outlined under 4.0 Milestones.

8.0 Research methods

The Clinical Practice Research Datalink (CPRD) is being used as the source of data for this study. This database contains information relating to medical diagnoses, issued prescription records, test results, referrals, patient characteristics and some lifestyle data, such as smoking status and body mass index for around 8% of the UK population (Campbell et al, 2013, Walley and Mantgani, 1997). For the prescription data, a reference table containing details of all the products for which a prescription could have been issued and recorded in the database is available. This table was searched to identify if albiglutide (and product names Eperzan and Tanzeum) had been included in the database up to 31st January 2016. This initial search was done to determine the feasibility of

carrying out the full study of utilisation of albiglutide in women of child-bearing age who had been diagnosed with type 2 diabetes.

9.0 Results

No details relating to albiglutide, Eperzan and Tanzeum were found in the product table of the CPRD which indicates that no prescriptions for this medication have been issued to patients in the CPRD up to 31st January 2016.

10.0 References

Campbell JDD, Eaton SC, Gallagher AM, Williams TJ. Is the CPRD GOLD population comparable to the U.K. population? Pharmacoepidemiology and Drug Safety 2013; 22:567.

Charlton RA, Weil JG, Cunnington MC, de Vries CS. Identifying major congenital malformations in the UK General Practice Research Database (GPRD): a study reporting on the sensitivity and added value of photocopied medical records and free text in the GPRD. Drug Saf 2010b; 33:741-50.

González ELM, Johansson S, Wallander M-A, Rodríguez LAG. Trends in the prevalence and incidence of diabetes in the UK: 1996–2005. Journal of Epidemiology and Community Health 2009; 63:332-6.

Haines L, Wan KC, Lynn R, Barrett TG, Shield JP. Rising incidence of type 2 diabetes in children in the U.K. Diabetes Care 2007; 30:1097-101.

Holden SH, Barnett AH, Peters JR, Jenkins-Jones S, Poole CD, Morgan CL, et al. The incidence of type 2 diabetes in the United Kingdom from 1991 to 2010. Diabetes Obes Metab 2013; 15:844-52.

Holt RI, Lambert KD. The use of oral hypoglycaemic agents in pregnancy. Diabet Med 2014; 31:282-91.

McGrogan A, Snowball J, de Vries CS. Pregnancy losses in women with Type 1 or Type 2 diabetes in the UK: an investigation using primary care records. Diabet Med 2014; 31:357-65.

NICE clinical guideline 63. Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period. . 2008 [3/9/2012]; Available from: http://www.nice.org.uk/nicemedia/pdf/CG063Guidance.pdf.

Sicree R, Shaw J, Zimmet P, Institute BIHaD. The Global Burden: Diabetes and Impaired Glucose Tolerance. International Diabetes Federation; [28/6/2014]; Available from: https://www.idf.org/sites/default/files/The_Global_Burden.pdf.

Walley T, Mantgani A. The UK General Practice Research Database. Lancet 1997; 350:1097-9.

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