



Medicines & Healthcare products
Regulatory Agency



MHRA
Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

GLUCOPHAGE SR 750 MG PROLONGED-RELEASE TABLETS (metformin hydrochloride)

UK Licence No: PL 11648/0066

Merck Serono Limited



LAY SUMMARY

Glucophage SR 750 mg prolonged release tablets (metformin hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Glucophage SR 750 mg prolonged release tablets (PL 11648/0066). It explains how the application for Glucophage SR 750 mg prolonged release tablets was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Glucophage SR 750 mg prolonged release tablets.

For practical information about using Glucophage SR 750 mg prolonged release tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Glucophage SR 750 mg prolonged release tablets and what are they used for?

The application for Glucophage SR 750 mg prolonged release tablets was submitted as a 'hybrid' application for a new strength of medicine. This means that Glucophage SR 750 mg prolonged release tablets are similar to a 'reference medicine' already authorised in the European Union (EU) called Glucophage SR 500 mg Film-Coated Tablets (PL 11648/0054).

Glucophage SR 750 mg prolonged release tablets are used together with diet and exercise to lower the risk of developing Type 2 diabetes in overweight adults, when diet and exercise alone for 3 to 6 months have not been enough to control blood glucose (sugar). People are at high risk of developing Type 2 diabetes if they have additional conditions like high blood pressure, age above 40 years, an abnormal amount of lipids (fat) in the blood or a history of diabetes during pregnancy.

This medicine is particularly effective if the patient is aged below 45 years, is very overweight, has high blood glucose levels after a meal or has developed diabetes during pregnancy.

Glucophage SR is also used for the treatment of Type 2 diabetes when diet and exercise changes alone have not been enough to control blood glucose.

How do Glucophage SR 750 mg prolonged release tablets work?

This medicine contains the active substance metformin hydrochloride. Metformin hydrochloride makes the body more sensitive to the hormone insulin and helps return to normal the way the body uses glucose. Insulin enables body tissues to take glucose from the blood and to use it for energy or for storage for future use. People with Type 2 diabetes do not make enough insulin in their pancreas or their body does not respond properly to the insulin it does make. This causes a build-up of glucose in the blood which can cause a number of serious long-term problems so it is important that patients continue to take their medicine, even though they may not have any obvious symptoms.

Glucophage SR Prolonged Release Tablets are made to release the drug slowly in the body.

How are Glucophage SR 750 mg prolonged release tablets used?

Glucophage SR 750 mg prolonged release tablets can only be obtained with a prescription.

Treatment will usually be started with 500 milligrams Glucophage SR daily. After the patient has been taking Glucophage SR for about 2 weeks, a doctor may measure their blood sugar and adjust the dose. The maximum daily dose is 2000 milligrams of Glucophage SR.

If the patient has reduced kidney function, a doctor may prescribe a lower dose.

Normally, the tablets should be taken once a day, with the evening meal. In some cases, a doctor may recommend that the tablets are taken twice a day. The tablets should always be taken with food.

This medicine should only be taken by adults aged 18 years and over.

What benefits of Glucophage SR 750 mg prolonged release tablets have been shown in studies?

Because the application for Glucophage SR 750 mg prolonged release tablets was submitted as a hybrid application, studies in people have been limited to tests to determine that the product is bioequivalent to an equivalent amount of the reference medicine, Glucophage SR 500mg Film-Coated Tablets (PL 11648/0054). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Glucophage SR 750 mg prolonged release tablets?

Like all medicines, Glucophage SR 750 mg prolonged release tablets can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Glucophage SR 750 mg prolonged release tablets, see section 4 of the package leaflet. For the full list of restrictions, see the package leaflet.

Why were Glucophage SR 750 mg prolonged release tablets approved?

It was concluded that, in accordance with EU requirements, Glucophage SR 750 mg prolonged release tablets have been shown to have comparable quality and to be bioequivalent to an equivalent amount of Glucophage SR 500mg Film-Coated Tablets (PL 11648/0054). Therefore, the MHRA decided that, as for Glucophage SR 500mg Film-Coated Tablets (PL 11648/0054), the benefits outweigh the identified risks and recommended that Glucophage SR 750 mg prolonged release tablets can be approved for use.

What measures are being taken to ensure the safe and effective use of Glucophage SR 750 mg prolonged release tablets?

Safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Glucophage SR 750 mg prolonged release tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Glucophage SR 750 mg prolonged release tablets

A Marketing Authorisation was granted in the UK on 21 February 2008.

The full PAR for Glucophage SR 750 mg prolonged release tablets follows this summary. For more information about treatment with Glucophage SR 750 mg prolonged release tablets read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in June 2017.

SCIENTIFIC DISCUSSION

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I INTRODUCTION

The UK granted a Marketing Authorisation for the medicinal product Glucophage SR 750 mg prolonged release tablets (PL 11648/0066) to Merck Serono Limited on 21 February 2008. This product is a prescription-only medicine.

The application was submitted as an abridged hybrid national application, according to Article 10.3 of Directive 2001/83/EC, as amended. The applicant claims that Glucophage SR 750 mg is a line extension of the reference product Glucophage SR 500mg Film-Coated Tablets (PL 11648/0054), which was granted a Marketing Authorisation to Merck Serono Limited in 2003. Glucophage 500 mg film-coated tablets were first authorised in the UK on 21 September 1982 by Liplha Pharmaceuticals Limited and hence have been marketed in the EEA for at least 10 years.

Glucophage SR 750 mg prolonged release tablets are indicated as follows:

- Reduction in the risk or delay of the onset of type 2 diabetes mellitus in adult, overweight patients with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG), and/or increased HbA1C who are:
 - at high risk for developing overt type 2 diabetes mellitus and
 - still progressing towards type 2 diabetes mellitus despite implementation of intensive lifestyle change for 3 to 6 months

Treatment with Glucophage SR must be based on a risk score incorporating appropriate measures of glycaemic control and including evidence of high cardiovascular risk. Lifestyle modifications should be continued when metformin is initiated, unless the patient is unable to do so because of medical reasons.

- Treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control. Glucophage SR may be used as monotherapy or in combination with other oral antidiabetic agents, or with insulin.

This product contains the active substance metformin hydrochloride. Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via 3 mechanisms:

- reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
- and delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT).

The original application for the reference product was based on clinical data including single dose, steady state and fed state studies and clinical studies demonstrating effectiveness of the 500 mg modified release formulation in comparison to the immediate release preparations.

The current application is based on the same clinical studies but additional bioequivalence studies have been conducted to compare the pharmacokinetics of Glucophage 750 mg SR (2 tablets) and Glucophage 500 mg SR (3 tablets) under fed and fasted conditions. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of the product.

II QUALITY ASPECTS

II.1 Introduction

Glucophage SR 750 mg prolonged release tablets are white capsule-shaped, biconvex tablets, debossed on one side with '750' and on the other side with 'MERCK'. Each tablet contains 750 mg metformin hydrochloride corresponding to 585 mg metformin base.

Other ingredients consist of pharmaceutical excipients, namely sodium carboxymethylcellulose, hypromellose and magnesium stearate. Appropriate justification for the inclusion of each excipient has been provided.

The finished products are packaged in are packaged in polyvinylchloride/polyvinylidene chloride/aluminium blister strips in pack sizes of 14, 20, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120, 180 or 600 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food

II.2 Drug substance

Metformin hydrochloride

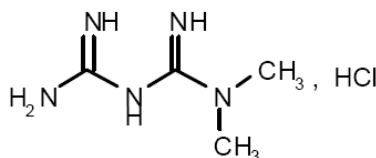
INN:

Metformin hydrochloride

Chemical name:

1-(diaminomethylidene)-3,3-dimethyl-guanidine

Structure



Chemical Formula

C₄H₁₁ClN₅

Molecular Weight

165.63

Appearance:

White crystalline appearance

Solubility:

Freely soluble in water. It is slightly soluble in alcohol and practically insoluble in acetone and in methylene chloride.

All aspects of the manufacture, in-process controls, validation and active substance specification are covered by a certificate of suitability for the active substance manufacturer.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active metformin hydrochloride is stored in appropriate packaging. The specifications and typical analytical test reports and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 5 years, when stored at appropriate storage instructions.

II.3 Medicinal Product Pharmaceutical Development

The objective of the development programme was to formulate a globally acceptable and stable product that could be considered a hybrid medicinal product of the reference product Glucophage SR 500 mg Film-Coated Tablets (PL 11648/0054).

A satisfactory account of the pharmaceutical development has been provided.

All excipients used comply with their respective European Pharmacopoeial monograph. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contains material of animal or human origin. There were no novel excipients used.

Dissolution and impurity profiles for the drug product were found to be similar to those for the reference product.

Manufacturing Process

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches. The results are satisfactory.

Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. The manufacturing process has been validated and appropriate in-process controls are applied.

Finished Product Specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Stability of the product

Stability studies were performed on three commercial batches of the finished product and in the packaging proposed for marketing, in accordance with current guidelines. All results from stability studies were within specified limits. These data support a shelf-life of 3 years, with no specific storage conditions.

II.4 Discussion on chemical, pharmaceutical and biological aspects

It is recommended that a Marketing Authorisation is granted for Glucophage SR 750 mg prolonged release tablets.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

The SmPC, PIL and labels are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website.

The approved labelling is shown below:





III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of metformin hydrochloride are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

III.2 Pharmacology

No new pharmacology data are required for this application and none have been submitted.

III.3 Pharmacokinetics

No new pharmacokinetic data are required for this application and none have been submitted.

III.4 Toxicology

No new toxicology data are required for this application and none have been submitted.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)

As the product is intended for generic substitution of products that are already marketed, no increase in environmental exposure to metformin hydrochloride is anticipated. Thus the absence of an ERA is accepted.

III.6 Discussion of the non-clinical aspects

It is recommended that a Marketing Authorisation is granted for Glucophage SR 750 mg prolonged release tablets.

IV. CLINICAL ASPECTS

IV.1 Introduction

This is a national application for a line extension of an existing modified release form of metformin (Glucophage SR). The current MAH (Merck Serono Limited) seek a further strength of 750 mg. Metformin (Gluophage) has been in use for a number of years and the 500 mg modified release formulation was authorised in September 2003 (PL 11648/0054).

The original application was based on clinical data including single dose, steady state and fed state studies and clinical studies demonstrating effectiveness of 500 mg modified release formulation in comparison to the immediate release preparations.

The current application is for a further strength of the modified release preparation based on the same clinical studies but in addition studies demonstrating bioequivalence between the Glucophage 750 mg SR (2 tablet) and Glucophage 500 mg SR (3 tablets) have been submitted. The applicant has submitted the following;

1. Bioequivalence studies between Glucophage 750 mg SR (2 tablets) and Glucophage SR 500 mg (3 tablets) after single oral administrations in healthy volunteers in the fasted and fed state.
2. A comparison of Glucophage SR 750 mg tablets from two manufacturing sites
2. The original studies of 500 mg modified release formulation
3. A satisfactory clinical overview

IV.2 Pharmacokinetics

The bioequivalence studies submitted are summarised in the table below:

Table 2.7.1.1 Summary of bioavailability studies

Study Ref. No.	Study Objective	Study Design	Treatment: (Dose, Dosage Form, Route) [Product ID]	Subjects (No) Type	Pharmacokinetic parameters:										Study Report Location
					C _{max} (ng/mL)		AUC(INF) (ng.h/mL)		AUC(0-T) (ng.h/mL)		T _{max} (h)		T _{1/2} (h)		
					Geometric mean (%C.V.) Adjusted geometric mean	Geometric mean (%C.V.) Adjusted geometric mean	Geometric mean (%C.V.) Adjusted geometric mean	Geometric mean (%C.V.) Adjusted geometric mean	Median (Min, Max)	Mean (S.D.)					
1. BE of 2x 750 mg Glucophage SR tablets vs. 3x 500 mg Glucophage SR tablets in fed subjects. 2. Safety of Glucophage SR and Glucophage SR formulations administered with food.	Open-label, randomized, single-dose, two treatment, two-period, crossover.	500mg, Prolonged-release tablet, oral [500 mg] 750 mg, Prolonged-release tablet, oral [750 mg]	23 Healthy volunteers - fed	500 mg	750 mg	500 mg	750 mg	500 mg	750 mg	500 mg	750 mg	500 mg	750 mg	Mod 5, sec 5.3.1	
				1104 (16) 1105	1193 (17) 1197	14622 (15) 14651	14607 (16) 14642	14219 (14) 14245	14209 (16) 14243	5.0 (3.0, 12.0)	5.0 (4.0, 12.0)	4.6 (0.76)	4.8 (0.84)		
1. BE of 2x 750 mg Glucophage SR tablets vs. 3 x 500 mg Glucophage SR tablets in fasting subjects. 2. Safety of Glucophage SR and Glucophage SR formulations.	Open-label, randomized, single-dose, two treatment, three period, optimally-designed replicate crossover. (ABB or BAA)	500mg, Prolonged-release tablet, oral [500 mg] 750 mg, Prolonged-release tablet, oral [750 mg]	20 Healthy volunteers - fasting	500 mg	750 mg	500 mg	750 mg	500 mg	750 mg	500 mg	750 mg	500 mg	750 mg	Mod 5, sec 5.3.1	
				1321 (31) 1315	1400 (32) 1392	9063 (30) 9087	8293 (26) 9254	8293 (32) 8343	8552 (28) 8429	3.0 (1.0, 5.0)	3.0 (2.0, 5.0)	9.5 (4.8)	9.7 (6.0)		
1. BE of Glucophage SR 750 mg tablets manufactured in Humacao, Puerto Rico, vs. Glucophage SR 750 mg tablets manufactured in Evansville. 2. Safety of Glucophage SR 750 mg tablets.	Open-label, randomized, two-period, two-treatment, crossover.	750 mg, Prolonged-release tablet, oral – Evansville [Ev.] 750 mg, Prolonged-release tablet, oral – Humacao [Hu.]	23 Healthy volunteers - fasting	750 mg Ev.	750 mg Hu.	750 mg Ev.	750 mg Hu.	750 mg Ev.	750 mg Hu.	750 mg Ev.	750 mg Hu.	750 mg Ev.	750 mg Hu.	Mod 5, sec 5.3.1	
				835 (39) 834	798 (34) 798	6264 (34) 6266	5861 (32) 5860	5738 (36)	5500 (34)	4.0 (2.0, 5.0)	4.0 (2.0, 5.0)	8.9 (7.5)	7.8 (3.9)		

The protocol defines acceptance criteria of 0.8 – 1.25 for both AUC and C_{max}. This is satisfactory. The duration of sampling following dosing and sampling frequency around T_{max} is considered adequate.

The Washout period, Randomisation scheme and method of data analysis are considered acceptable.

Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:

	Fed	Fasted
C _{max} (ng/mL)	1.083 (1.032- 1.137)	1.058 (0.949- 1.181)
AUC _t (ng.h/mL)	1.00 (0.969 – 1.032)	1.010 (0.911 – 1.121)
AUC _∞ (ng.h/mL)	0.99 (0.967 – 1.033)	1.018 (0.920 – 1.127)

The standard pharmacokinetic parameters suggest that the two formulations dose per dose fall within the conventional definitions of bioequivalence with 90% CI between 80-125% for all. It is interesting to note that the 90% CI are narrower in the fed state although the results are well within the limits.

The study design is adequate although the number of subjects are few. This however was based on statistical power calculations using pilot data and it is not surprising that the estimates were a good fit suggesting that the two formulations do not significantly differ in release and absorption profiles.

Based on the studies submitted, the two dose formulations (dose per dose) could be considered bioequivalent. This permits substitution for dose per dose but no alterations in posology would be possible based on these studies.

IV.3 Pharmacodynamics

The pharmacodynamics of metformin (Glucophage) are well established using the immediate release and the 500 mg SR formulations. The kinetics of the 750 mg SR tablets are similar (dose per dose) to

500 mg SR formulations. It is therefore possible to conclude that 750 mg SR could be a replacement for 500 mg SR tablets at equivalent dose (dose per dose). The pharmacodynamics of 750 mg tablets have not been tested in the clinical setting directly although in one study a starting dose of 750 mg was utilised. However it is unclear if these were metformin naïve patients or those who were already had some exposure to metformin but had shown an inadequate response. Therefore, further extrapolations of the pharmacodynamic effect would not be based on evidence.

Hence based on the current dataset, 750 mg SR would be useful primarily as a replacement for the 500 mg tablets at specified dose and posology and the SmPC should remain identical.

IV.4 Clinical efficacy

The application was based on bioequivalence between 2 x 750mg vs 3 x 500mg SR tablets. Therefore the efficacy and safety of a 1500 mg dose of metformin administered as two different formulations could be considered similar and further clinical studies are not required to establish this.

The applicant has not provided any data to suggest that the safety / efficacy profile of 750 mg is similar to any other formulation (strength). Hence the risk:benefit of 750 mg tablets when administered at doses different to those achieved by any combination of 500 mg SR tablets has not been established. Any claims for reduced gastrointestinal side effects or increased efficacy of 750 mg over 500 mg SR [or any other formulation of metformin (glucophage)] is not established in the absence of specific clinical data.

IV.5 Clinical Safety

No new data on safety have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications.

IV.6 Pharmacovigilance System

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

V. USER CONSULTATION

The package leaflet has been evaluated in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that it contains.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with metformin hydrochloride is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

Annex 1 Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/non approval	Assessment report attached
To bring the SmPC in line with other Glucophage licences by updating section 5.1 with the phrase “In clinical studies, the major non glycaemic effect of metformin is either weight stability or modest weight loss.” The PIL is updated consequentially.	PL 11648/0066 - 0015	SmPC PIL	09/06/2011	22/06/2011	Approval	Y
To add a new indication: prediabetes. Consequential updates to sections 4.2, 4.4, 4.6 and 5.1 of the SmPC, to the PIL and to the RMP	PL 11648/0066 - 0039	SmPC PIL	23/03/2016	16/05/2017	Approval	Y

Annex 1

Reference: PL 11648/0066-0015
Product: Glucophage SR 750 mg prolonged release tablet
Marketing Authorisation Holder: Merck Serono Ltd
Active Ingredient(s): Metformin hydrochloride

Reason

To bring the SmPC in line with other Glucophage licences by updating section 5.1 (Pharmacodynamic properties) with the phrase “In clinical studies, the major non glycaemic effect of metformin is either weight stability or modest weight loss.” The PIL is updated consequentially.

Evaluation

Satisfactory updated SmPC fragment and PIL were submitted in support of the variation application.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website.

Conclusion

Approved on 22 June 2011

Annex 2

Reference:	PL 11648/0066-0039
Product:	Glucophage SR 750 mg prolonged release tablet
Marketing Authorisation Holder:	Merck Serono Ltd
Active Ingredient(s):	Metformin hydrochloride

1. Reason

To add a new indication: prediabetes. Consequential updates to sections 4.2, 4.4, 4.6 and 5.1 of the SmPC, to the PIL and to the RMP.

2. Background

Diabetes is a chronic disease characterised by an inability to regulate blood glucose concentrations. Type 2 diabetes mellitus (T2DM) is due primarily to reduced secretion of insulin (reduced beta-cell function and mass) and peripheral resistance to the action of insulin.

Prediabetes or prediabetic hyperglycaemia is defined as increased serum glucose levels that are however below the threshold for the diagnosis of overt diabetes. Although progression to overt diabetes is not inevitable (indeed the term "prediabetes" is not universally used), progression is expected in patients with higher risk factors, around 10% of individuals with impaired glucose tolerance progress to overt diabetes on an annual basis.

As discussed further in this assessment, prediabetic hyperglycaemia is associated with specific micro-vascular alterations, such as retinopathy and neuropathy, and it is suggested that prediabetes is associated with an increased risk of adverse macro-vascular outcomes. The therapeutic rationale of intervening in prediabetes is therefore to delay the progression to overt T2DM and improve long term outcomes.

Prediabetes initially presents as impaired glucose tolerance (IGT), in which postprandial glucose control is impaired, and/or impaired fasting glucose (IFG) which is characterised by a chronic elevation of fasting plasma glucose (FPG).

The current definition of prediabetic hyperglycaemia according to the American Diabetic Association is at least one of the following:

- Impaired fasting glucose of 100-125mg/dl (5.6-6.9mmol/l)
- HbA1C of 5.7-6.4 %
- Impaired glucose tolerance defined by plasma glucose of 140-199mg/dl (7.8-11.0mmol/l) 2 hours after a 75 mg glucose challenge

For all three tests, the risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.

There are some variations on the definition of prediabetes, in particular the World Health Association (2006) use a different definition for the lower level of FPG in the definition of IFG (110mg/dl, 6.1 mmol/l) and this is the definition used in the current CHMP guideline on diabetes therapies. The WHO definition of IGT is identical to that proposed by the American Diabetic Association.

The UK NICE guidance from 2012 proposes slightly different cut-offs for risk of progression to type 2 diabetes: fasting plasma glucose of 5.5–6.9 mmol/l or an HbA1c level of 6.0–6.4%. However, the guidance recognises that there is a continuum of risk, and that people with an HbA1c below 6.0% may also be at risk.

It is well known that the prevalence of T2DM in the UK is increasing, and it follows that the prevalence of prediabetes is increasing, as the risk factors are the same. According to NICE figures in 2012, an

estimated 850,000 people in England may have had undiagnosed diabetes. Many more may have blood glucose levels above the normal range, but not high enough for a diabetes diagnosis. According to a 2014 publication using Health Survey for England data and based on the above ADA prediabetes HbA1c criterion alone, the prevalence increased from 11.6% to 35.3% from 2003 to 2011. In the 2001 data, 50.6% of the population who were overweight (BMI >25) and ≥ 40 years of age had prediabetes. Clearly, even with a second-line indication in high risk patients not responding to intensive lifestyle changes, extension of the Glucophage licence to prediabetes could mean a significant increase in its usage.

In the high-risk individual with IGT, there are several studies demonstrating that lifestyle modification, based on modest weight loss and increased physical activity, prevents or delays progression - there is consensus that this is the first line intervention.

A 2007 meta-analysis by UK authors included 17 trials which quantified the effectiveness of pharmacological and lifestyle interventions to prevent or delay T2DM in people with impaired glucose tolerance. These included trials of lifestyle interventions, various pharmacological interventions vs. lifestyle intervention [of which, the DPP study discussed below was the biggest] and trials of pharmacological or herbal interventions with no lifestyle intervention control group. From the meta-analyses the pooled hazard ratios for progression to T2DM were 0.51 (95% CI 0.44 to 0.60) for lifestyle interventions v standard advice, 0.70 (0.62 to 0.79) for oral diabetes drugs vs. control and 0.44 (0.28 to 0.69) for orlistat vs control.

Recently (March 2016) the NHS Diabetes prevention program was presented for England. The announcement highlighted the latest data: "There are currently 5 million people in England at high risk of developing Type 2 diabetes. If current trends persist, one in three people will be obese by 2034 and one in ten will develop Type 2 diabetes. However, evidence exists which shows that many cases of Type 2 diabetes are preventable."

The figure of 5 million people at risk in England comes from Public Health England and its National Cardiovascular Health Intelligence Network, August 2015.

Prediabetes is accepted as a potential therapeutic target from a regulatory point of view, indeed in 2008 the lack of guidance on this in the previous CHMP diabetes guideline was noted, which was one of the drivers for the current revised guideline.

3. Supporting Evidence

This is a bibliographic submission for which an appropriate literature search strategy has been outlined by the Marketing Authorisation Holder. Although 7 studies met the inclusion criteria of controlled clinical trials using metformin in prediabetic hyperglycaemia with the primary target parameter of risk reduction of conversion to overt T2DM, the focus is on the 2 largest studies - the DPP (Diabetes Prevention Program) and its follow-up, DPPOS (Diabetes Prevention Program Outcome study). Additional supportive references are included for background and safety aspects.

3.1 Clinical practice guidelines

NICE guidance from 2012 advises that FPG or HbA1c should be done in adults with high risk scores, or those aged 25 and over of South Asian or Chinese descent whose body mass index (BMI) is greater than 23 kg/m².

NICE recommends (whilst recognizing it is currently not licensed in this setting) metformin should be considered in adults at high risk whose blood glucose measure shows they are still progressing towards type 2 diabetes, despite their participation in an intensive lifestyle-change programme, or adults at high risk who are unable to participate in lifestyle-change programmes because of a disability or for medical reasons. It advises to start with a low dose (for example, 500 mg once daily) and then increase gradually as tolerated, to 1500–2000 mg daily. If the person is intolerant of standard metformin, modified-release

metformin should be considered. An initial treatment period of 6–12 months is recommended, monitoring fasting plasma glucose or HbA1c levels at 3-month intervals and stopping metformin if no effect is seen.

Other available guidelines for the management of prediabetic hyperglycaemia from Europe and the US also consider lifestyle interventions preferentially over pharmacologic therapy, and support the use of pharmacologic therapy (especially metformin) as a second-line intervention.

3.2 Clinical efficacy

The Marketing Authorisation Holder has submitted seven controlled clinical trials using metformin to treat prediabetes, with the target parameter of risk reduction of conversion to overt diabetes. The most important clinical trials are the diabetes prevention program (DPP) and an extension of this study called the diabetes prevention program outcome study (DPPOS).

The DPPOS study is still currently on-going, with the main endpoint in the 3rd phase (years 13 to 22) to look at macrovascular outcomes.

Both the DPP and DPPOS are prospective investigator sponsored trials, with investigators from the US National Institute of Diabetes and Digestives and Kidney Diseases, using Glucophage IR (immediate-release metformin). The methods for the DPP were published in 1999 and the main results were published in 2002. Many subsequent publications dealing with various secondary endpoints and further analyses from DPP and DPPOS have been published.

3.2.1 DPP Study

Study protocol:

The DPP recruited patients aged >25 years, with BMI of >24 (>22 in Asians), with FPG of 5.3-6.9 mmol/l and values of 7.8-11.0 two hours after a 75-g oral glucose load. Eligible participants were randomly assigned to either:

- Standard lifestyle recommendations plus Glucophage IR
- Standard lifestyle recommendations plus placebo twice daily
- An intensive program of lifestyle modification - with a goal of ≥ 150 min/week of activity and $\geq 7\%$ weight loss

A fourth group were assigned to treatment with troglitazone, but this treatment arm was discontinued prematurely due to concerns of liver toxicity.

Treatment with metformin was initiated at an initial starting dose of 850 mg once daily. After one month, the dose of metformin was increased to 850 mg twice daily, unless gastrointestinal symptoms warranted a longer titration period. Initiation with half a tablet (425mg daily) was optional in patients with gastrointestinal intolerance. Adherence was assessed quarterly on the basis of pill counts and structured interviews.

The "standard lifestyle recommendations" for the medication groups were provided in the form of written information and an annual 20 to 30 minute individual session that emphasised the importance of a healthy lifestyle. Participants were encouraged to follow prevailing US guidelines on healthy eating and the equivalent of the US National Cholesterol Education Program Step 1 diet, to reduce their weight, and to increase their physical activity.

The goals for the participants assigned to the "intensive lifestyle intervention" were to achieve and maintain a weight reduction of at least 7% of initial body weight through a healthy low-calorie, low-fat diet and to engage in physical activity of moderate intensity, for at least 150 minutes per week. A 16-lesson curriculum covering diet, exercise, and behaviour modification was designed to help the participants achieve these goals. The curriculum, taught by case managers on a one to one basis during the first 24 weeks after enrolment, was flexible, culturally sensitive, and individualised. Subsequent individual sessions (usually monthly) and group sessions with the case managers reinforced the

behavioural changes. Participants in the lifestyle arm met with a case manager 16 times over the first 6 months and then generally monthly thereafter. They made telephone contact at least monthly. Group courses on exercise and weight loss lasting 4–6 weeks were offered every 3 months. Also, two supervised exercise sessions were offered each week. Moreover, anyone having difficulty achieving or maintaining the study's goals for loss or exercise were offered incentives, such as exercise tapes or equipment, free enrolment in exercise facilities, free low-calorie foods, more structured eating plans, and home visits for encouragement and counselling.

3234 study participants were randomly assigned to one of the three interventions - 1082 to placebo, 1073 to metformin, and 1079 to the intensive lifestyle intervention. Participants were followed for an average of 2.8 years (range, 1.8 to 4.6). At the close of the study, 99.6 percent of the participants were alive, of whom 92.5 percent had attended a scheduled visit within the previous five months.

Baseline data:

Groups were balanced for blood pressure (BP) and lipid parameters at baseline. The average baseline FPG in mmol/L units was 5.9 mmol/L, and 9.2 respectively after OGTT.

Table 1: Main baseline characteristics, DPP study

CHARACTERISTIC	OVERALL (N= 3234)	PLACEBO (N= 1082)	METFORMIN (N= 1073)	LIFESTYLE (N= 1079)
Sex — no. (%)				
Male	1043 (32.3)	335 (31.0)	363 (33.8)	345 (32.0)
Female	2191 (67.7)	747 (69.0)	710 (66.2)	734 (68.0)
Race or ethnic group — no. (%)				
White	1768 (54.7)	586 (54.2)	602 (56.1)	580 (53.8)
African American	645 (19.9)	220 (20.3)	221 (20.6)	204 (18.9)
Hispanic	508 (15.7)	168 (15.5)	162 (15.1)	178 (16.5)
American Indian	171 (5.3)	59 (5.5)	52 (4.8)	60 (5.6)
Asian†	142 (4.4)	49 (4.5)	36 (3.4)	57 (5.3)
Family history of diabetes — no. (%)	2243 (69.4)	758 (70.1)	733 (68.3)	752 (69.8)‡
History of gestational diabetes — no. of women (%)	353 (16.1)	122 (16.3)	111 (15.7)‡	120 (16.3)
Age — yr	50.6±10.7	50.3±10.4	50.9±10.3	50.6±11.3
Weight — kg	94.2±20.3	94.3±20.2	94.3±19.9	94.1±20.8
Body-mass index	34.0±6.7	34.2±6.7	33.9±6.6	33.9±6.8
Waist circumference — cm	105.1±14.5	105.2±14.3	104.9±14.4	105.1±14.8
Waist-to-hip ratio	0.92±0.09	0.93±0.09	0.93±0.09	0.92±0.08
Plasma glucose — mg/dl§				
In the fasting state	106.5±8.3	106.7±8.4	106.5±8.5	106.3±8.1
Two hours after an oral glucose load	164.6±17.0	164.5±17.1	165.1±17.2	164.4±16.8
Glycosylated hemoglobin — %	5.91±0.50	5.91±0.50	5.91±0.50	5.91±0.51
Leisure physical activity — MET-hr/wk¶	16.3±25.8	17.0±29.0	16.4±25.9	15.5±22.1

Outcomes:

The predefined primary outcome was diabetes, according to the 1997 criteria of the ADA: FPG >7.0mmol/l or OGTT >11.1mmol/l. This was diagnosed by annual oral glucose-tolerance tests and 6 monthly fasting plasma glucose tests, with additional tests prompted by symptoms suggestive of DM. If the FPG or OGTT results met these criteria, a second FPG or OGTT was performed within 6 weeks. If both tests were diagnostic of diabetes, the participant was considered to have reached the primary outcome. Since the start of the study, these threshold values were not changed, although an additional criterion was added, patients with HbA1c of ≥6.5%.

Secondary endpoints included include cardiovascular risk profile and disease, B-cell function, insulin sensitivity, renal function, body composition, physical activity and nutrient intake, and health-related quality of life. Cardiovascular risk profile was assessed by cardiovascular history and symptoms, an

electrocardiogram, smoking history, C-reactive protein, fibrinogen, tissue plasminogen activator and lipoprotein profile. Cardiovascular disease was assessed by carotid intimal wall thickness, blood pressure, and ankle: brachial systolic blood pressure.

Main efficacy results:

The blinded treatment phase was terminated 1 year early after an average follow-up of 2.8 years (range 1.8 to 4.6) following advice of the data monitoring board, on the basis of data obtained through March 31, 2001. This corresponded to 65% of the planned person-years of observation. To maintain a type I error level of 0.05 for significance in pairwise comparisons of the risk of diabetes between groups, with adjustment for repeated interim analyses, the group-sequential log-rank test required a P value of less than 0.0159. For pairwise comparisons of other outcomes, a Bonferroni-adjusted criterion of $P < 0.0167$ was used.

84 % percent of those taking metformin were given the full dose of one tablet (850 mg in the case of metformin) twice a day; the remainder were given one tablet a day to limit side effects.

The cumulative incidence of diabetes was lower in the metformin and lifestyle-intervention groups than in the placebo group throughout the follow-up period. The crude incidence was 11.0, 7.8, and 4.8 cases per 100 person-years for the placebo, metformin, and lifestyle-intervention groups, respectively

The incidence of diabetes was 31% lower (95% CI 17-43) in the metformin group than in the placebo group.

The incidence of diabetes was 58 % lower (95% CI 48-66) in the intensive lifestyle-intervention group than in the placebo group

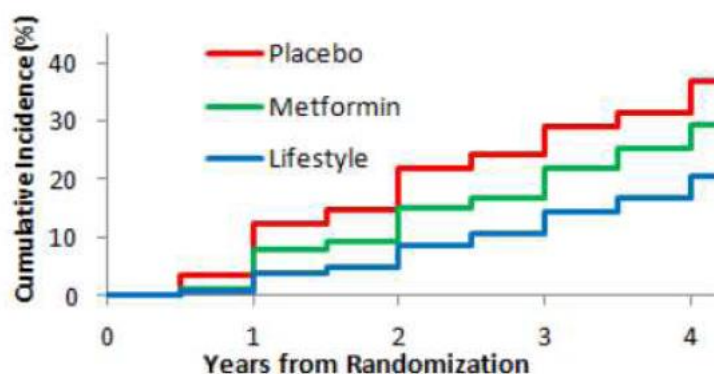
The incidence of diabetes was 39 % lower (95% CI 24-51) in the intensive lifestyle-intervention group than the metformin group.

The incidence of diabetes differed significantly among the three groups ($P < 0.001$ for each comparison) - none of these results were materially affected by adjustment for base-line characteristics.

The estimated cumulative incidence of diabetes at three years was 28.9 percent, 21.7 percent, and 14.4 percent in the placebo, metformin, and lifestyle-intervention groups, respectively.

In a later post-hoc analysis, diabetes incidence defined by $HbA1C > 6.5\%$ was reduced by 44% in the metformin group and by 49% in the intensive lifestyle group, vs. placebo.

Figure 1: Cumulative incidence of diabetes throughout DDP study



Fifty percent of the participants in the lifestyle intervention group had achieved the goal of weight loss of 7 percent or more by the end of the curriculum (at 24 weeks), and 38 percent had a weight loss of at least 7 percent at the time of the most recent visit; the proportion of participants who met the goal of at

least 150 minutes of physical activity per week (on the basis of logs kept by the participants) was 74 percent at 24 weeks and 58 percent at the most recent visit. Dietary change was assessed only at one year. Daily energy intake decreased by a mean (\pm SE) of 249 ± 27 kcal in the placebo group, 296 ± 23 kcal in the metformin group, and 450 ± 26 kcal in the lifestyle-intervention group ($P<0.001$)

Average fat intake, which was 34.1 percent of total calories at base line, decreased by 0.8 ± 0.2 percent in the placebo and metformin groups, and by 6.6 ± 0.2 percent in the lifestyle-intervention group ($P<0.001$). The proportion of participants who took at least 80 percent of the prescribed dose of the study medication was slightly higher in the placebo group than in the metformin group (77 percent vs. 72 percent, $P<0.001$).

Participants assigned to the lifestyle intervention had much greater weight loss and a greater increase in leisure physical activity than did participants assigned to receive metformin or placebo. Reductions in body weight were maximal in the intensive lifestyle intervention and Glucophage groups at 0.5–1 year and tended to reverse thereafter.

At 1 year, metformin reduced weight by an average of around 3% vs. the placebo group in both men and women. The average weight loss at 4 years was 0.1, 2.1, and 5.6 kg in the placebo, metformin, and lifestyle-intervention groups, respectively ($P<0.001$).

Effects following treatment withdrawal:

All participants assigned to either Glucophage or placebo medication who had not developed diabetes at the end of the DPP were asked to have a repeat OGTT after discontinuing the study medication for 1–2 weeks. The predesignated outcome was the odds of diabetes in metformin versus placebo, during the trial and washout combined. It was hypothesized that if the effects of metformin were transient, washout of the drug intervention would result in a high diabetes conversion rate among metformin participants, such that the reported difference in the overall conversion rate to diabetes compared with placebo would be significantly narrowed. Occurrence of DM was defined according to the main DPP study, including the need for a confirmatory OGTT within 6 weeks.

The washout OGTT was performed under different conditions than the other OGTTs in DPP, i.e. with study drug withheld. Furthermore, its timing relative to randomisation differed among participants (ranging from approximately 2–5 years after randomisation). Thus, it was not possible to analyse the washout as simply one additional data point in the same time-to-event (survival) analysis to be used for the main study. Instead, the washout OGTT (combined with a repeat test to confirm a new diagnosis) was used in an analysis of prevalence of diabetes from randomisation to the time of washout. The prevalence of diabetes was thus determined by counting as cases all those diagnosed under the usual DPP follow-up procedure plus those diagnosed by the washout OGTT. The prevalence was expressed as a simple percentage of all subjects enrolled and compared between metformin and placebo treatment groups. The analysis was stratified by DPP study year of randomisation, and the significance and homogeneity of the treatment effect over these strata was assessed by standard statistical methods for stratified proportions data, such as the Mantel-Haenszel summary statistic and the Breslow-Day test for homogeneity over strata.

A total of 1,274 subjects participated. Before the washout, the odds of diabetes in the metformin group were lower than that in the placebo group (odds ratio 0.66, 95% CI 0.54–0.82, $P<0.001$). After the washout (average of 11 days) diabetes was more frequently diagnosed in the metformin participants (OR 1.49, 0.93–2.38, $P=0.098$). Combining diabetes conversions during the DPP and during the washout, diabetes was still diagnosed less frequently in the metformin than the placebo group (0.75, 0.62–0.92, $P=0.005$). Neither age nor BMI at baseline influenced these findings. It was calculated that 26% of the effect of Glucophage was a short-lived effect that reversed quickly after withdrawal of study therapy.

Table 2: Number and percent with diabetes prior to and including washout, plus Mantel-Haenszel randomization date-adjusted odds ratio

Treatment	Diabetes prior to washout		Diabetes including washout	
	No diabetes	Diabetes	No diabetes	Diabetes
Metformin	668 (74.8)	225 (25.2)	620 (69.4)	273 (30.6)
Placebo	606 (66.6)	304 (33.4)	576 (63.3)	334 (36.7)

Data are n (%).

Diabetes diagnosis	Odds ratio	95% CI	P
Prior to washout	0.66	0.54–0.82	<0.001
At washout	1.49	0.93–2.38	0.098
Overall	0.75	0.62–0.92	0.005

Efficacy in Subgroups:

Treatment effects did not differ significantly according either to sex, race or ethnic group. The lifestyle intervention was highly effective in all subgroups. Its effect was significantly greater among subjects with lower baseline glucose concentrations two hours after a glucose load than among those with higher baseline glucose values.

The effect of metformin was less with a lower body-mass index or a lower fasting glucose concentration than with higher values for those variables. Metformin was particularly effective in women with a previous history of gestational DM, providing around a 50% reduction in diabetes risk vs. placebo group, as good as the results in the intensive lifestyle therapy group.

Secondary endpoints:

FPG and HbA1c

In the first year, there was a similar reduction in the mean FPG values in the metformin and lifestyle-intervention groups, whereas the values rose in the placebo group. The values rose in parallel in all three groups in subsequent years. There was a similar temporal pattern in the values for glycosylated haemoglobin, except that the values in the metformin group were in between those in the lifestyle-intervention and placebo groups.

Metformin and the lifestyle intervention were similarly effective in terms of the % patients restored to normoglycaemia on the basis of FPG. However, the lifestyle intervention was more effective in restoring normal glucose values after OGTT.

Renal Function

The time course of changes in urinary albumin: creatinine ratio was similar between treatments.

Hypertension

This was present in 30% of participants at baseline) – it increased similarly on placebo and Glucophage, and decreased with intensive lifestyle intervention.

Lipids

Investigators aggressively followed the ATP III guidelines in all cases. Improvements in triglycerides occurred in all groups, but were larger with intensive lifestyle intervention. HDL-cholesterol level was increased significantly and the incidence of the atherogenic LDL phenotype B was reduced in the intensive lifestyle intervention group. Total cholesterol and LDL-cholesterol were similar between groups. Fewer subjects on intensive lifestyle intervention required pharmacologic treatment for cardiovascular risk factors vs. placebo or Glucophage at 3 years.

B-cell function+ insulin sensitivity

The largest and smallest changes in insulin sensitivity and insulin secretion occurred in the intensive lifestyle intervention group and the placebo group, respectively (there were no significant changes in these variables on placebo), with intermediate effects in the Glucophage group. Results suggested that development of diabetes in the placebo group resulted from continued decreases in insulin sensitivity and β -cell function (i.e., insulin secretion relative to sensitivity), whereas reduction in the incidence of diabetes observed in the two active interventions was due to their ability to increase insulin sensitivity and improve β -cell function.

Cardiovascular risk profile

Cardiovascular risk factors tended to worsen as glycaemic status declined, or to improve as glycaemic status improved in the DPP (i.e. alterations in cardiovascular risk factors paralleled changes in glycaemic status). There was little difference between treatment groups in cardiovascular risk factor status for subjects who progressed to T2DM. However, cardiovascular risk factor status was generally more favourable for the intensive lifestyle intervention arm than for the other arms of the study, consistent with the larger reduction in the risk of developing diabetes in this group.

3.2.2 DDPOS Study

Study Protocol:

DDPOS is the long term open label follow-up study of the DPP participants, which is still on-going. 88 % (n=2,766) of eligible subjects were enrolled in the DDPOS following the washout study at the end of the randomised phase of the DPP.

After participants were informed of the main results from DPP, those in the metformin and placebo groups entered into a 1–2 week drug washout study to identify whether treatment of fasting glucose accounted for the diabetes risk reduction with metformin. They were then unmasked to their treatment assignments.

Glucophage treatment was continued in the original metformin group with participants unmasked to assignment, and the original lifestyle intervention group offered additional lifestyle support. Treatment with placebo was discontinued while treatment with Glucophage 850 mg bid was continued unless changes to medication were required for the management of diabetes or for other reasons. The study continued to provide metformin as long as HbA1C<7%.

On the basis of the benefits from the intensive lifestyle intervention in the DPP, all participants in the DDPOS were offered this, during a 1 year bridge period between DPP and DDPOS.

Therefore the DDPOS essentially compared metformin as an add-on to intensive lifestyle intervention. The report mentions that "at least some sessions" were attended by the original placebo (57%), metformin (58%) and lifestyle (40%) participants.

Baseline data:

Some differences were noted in the baseline characteristics for those participating in DDPOS - including significant differences between treatment groups for fasting plasma glucose, HbA1c, weight (overall and in men only) and body-mass index (overall and in each sex). There were also significant differences between treatment groups in those without diabetes for fasting plasma glucose, systolic and diastolic blood pressure, HDL cholesterol, and triglycerides, and in those with diabetes for fasting plasma glucose and HDL cholesterol (Table 3).

Table 3: Patient characteristics at DDPOS baseline examination

	All groups (n=2766)	ILS group (n=910)	Metformin group (n=924)	Placebo group (n=932)
Age (years)	55.2 (10.3)	55.3 (11.0)	55.5 (10.1)	54.8 (10.0)
Fasting plasma glucose (mmol/L)	6.03 (1.10)	5.98 (0.98)	5.94 (1.04)	6.18 (1.24)
HbA _{1c} (%)	5.95 (0.69)	5.89 (0.64)	5.94 (0.63)	6.01 (0.79)
Men (n)	888	291	307	290
Weight (kg)	95.6 (20.2)	93.4 (21.6)	95.7 (19.6)	97.7 (19.2)
Height (cm)	175.0 (7.2)	175.0 (7.4)	175.1 (7.0)	174.8 (7.4)
Body-mass index (kg/m ²)	31.1 (5.9)	30.4 (6.3)	31.1 (5.6)	31.9 (5.9)
Women (n)	1878	619	617	642
Weight (kg)	90.3 (21.0)	89.2 (21.7)	90.2 (20.7)	91.4 (20.5)
Height (cm)	162.3 (6.7)	162.4 (6.9)	162.6 (6.8)	162.0 (6.5)
Body-mass index (kg/m ²)	34.2 (7.2)	33.7 (7.3)	34.1 (7.2)	34.7 (7.1)
Without diabetes (n)	1999	739	652	608
Fasting plasma glucose (mmol/L)	5.72 (0.52)	5.72 (0.51)	5.66 (0.53)	5.79 (0.51)
2-h plasma glucose (mmol/L)	8.11 (1.92)	7.98 (1.92)	8.19 (2.02)	8.20 (1.78)
HbA _{1c} (%)	5.78 (0.46)	5.75 (0.48)	5.79 (0.43)	5.80 (0.46)
Systolic blood pressure (mm Hg)	121.8 (14.7)	120.6 (14.9)	122.7 (14.4)	122.3 (14.7)
Diastolic blood pressure (mm Hg)	75.1 (9.0)	74.4 (9.0)	75.9 (8.8)	75.2 (9.2)
Cholesterol (mmol/L)	5.08 (0.90)	5.08 (0.91)	5.07 (0.86)	5.08 (0.93)
HDL cholesterol (mmol/L)	1.23 (0.33)	1.25 (0.34)	1.23 (0.34)	1.19 (0.31)
LDL cholesterol (mmol/L)	3.11 (0.80)	3.12 (0.80)	3.08 (0.75)	3.12 (0.85)
Triglycerides (mmol/L)	1.38 (0.98-1.98)	1.31 (0.93-1.89)	1.41 (1.02-2.00)	1.43 (1.03-2.01)
With diabetes (n)	767	171	272	324
Fasting plasma glucose (mmol/L)	6.83 (1.65)	7.10 (1.56)	6.61 (1.54)	6.88 (1.76)
HbA _{1c} (%)	6.38 (0.96)	6.47 (0.88)	6.30 (0.85)	6.40 (1.07)
Systolic blood pressure (mm Hg)	123.8 (14.2)	123.7 (14.0)	124.5 (13.8)	123.3 (14.6)
Diastolic blood pressure (mm Hg)	76.3 (9.3)	76.8 (9.9)	75.7 (9.5)	76.5 (8.9)
Cholesterol (mmol/L)	5.00 (0.88)	5.05 (0.88)	4.99 (0.89)	4.98 (0.88)
HDL cholesterol (mmol/L)	1.14 (0.29)	1.12 (0.29)	1.20 (0.30)	1.11 (0.28)
LDL cholesterol (mmol/L)	3.02 (0.78)	3.07 (0.76)	2.98 (0.78)	3.02 (0.80)
Triglycerides (mmol/L)	1.60 (1.11-2.16)	1.57 (1.16-2.20)	1.51 (1.12-2.14)	1.65 (1.08-2.21)

Data are mean (SD) apart from triglycerides for which data are median (IQR), or number of participants (n). Data from the study baseline examination were stratified by presence of diabetes as of Sept 1, 2002. At enrolment to the Diabetes Prevention Program Outcomes Study (DPPPOS), we identified significant differences between treatment groups for fasting plasma glucose, HbA_{1c}, weight (overall and in men only) and body-mass index (BMI; overall and in each sex). We also noted significant differences between treatment groups in those without diabetes for fasting plasma glucose, systolic and diastolic blood pressure, HDL cholesterol, and triglycerides, and in those with diabetes for fasting plasma glucose and HDL cholesterol. Data were missing for 22 enrolled people who had no DPPPOS baseline examination. Data were missing for additional people, in varying numbers, for some of the variables. ILS=intensive lifestyle intervention. HbA_{1c}=glycosylated haemoglobin.

Table 2: Characteristics at DPPPOS baseline examination

Main efficacy results:

The average loss to follow-up was 2% per year in each group. In the latest analysis at year 15, crude diabetes incidence rates were 7, 5.7 and 5.2 cases per 100 person years respectively among original placebo, metformin and lifestyle groups, so the positive effects of the metformin and lifestyle interventions seen in the DPP study continue despite an improvement in the placebo group following unblinding of the trial.

The incidence of overt diabetes was reduced by 27% (HR 0.73, 95% CI 0.65-0.83, p<0.0001) in the intensive lifestyle group and by 18% (HR 0.82, 95% CI 0.72-0.93, p<0.001) in the metformin group, compared to placebo.

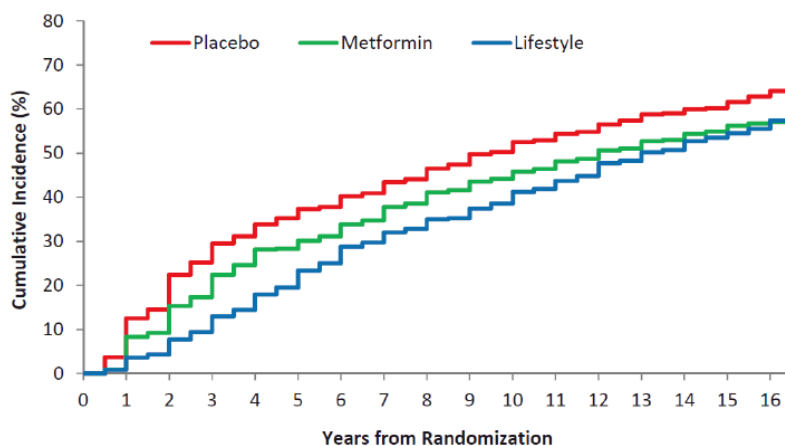
The median delay to onset of diabetes (estimated from the differences between treatment groups in the time to 50% cumulative incidence of diabetes) was 2.5 years in the original metformin group, and 3.5 years in the original intensive lifestyle group - compared to the original placebo group.

In the follow up phase alone (in which all patients were offered intensive lifestyle intervention) the cumulative incidence of diabetes at year 15 was 62% in the placebo group, 56% in the metformin group

and 55% in the intensive lifestyle group.

This is further described in the figure and table below.

Figure 2: Cumulative incidence of diabetes over DPP and DPPOS



Years	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Placebo	935	818	726	658	611	573	532	498	459	421	397	373	348	322	306	164
Metformin	926	849	784	716	653	627	585	544	506	474	451	427	399	377	354	176
Lifestyle	915	882	845	796	748	690	631	594	558	524	484	456	413	378	351	183

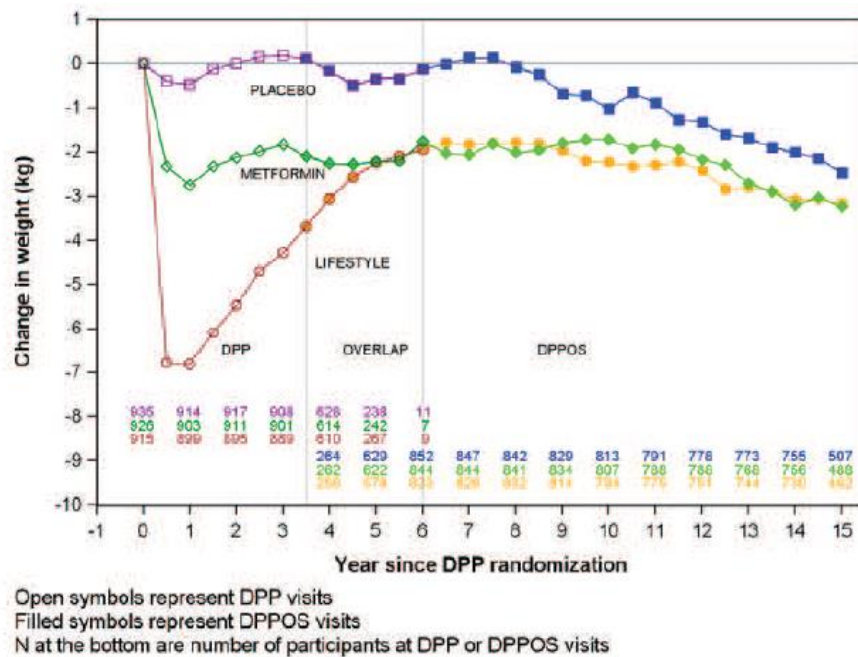
Table 4: Diabetes incidence summary (DPPOS, 2016)

	Placebo	Metformin	Lifestyle
Number of subjects	935	926	915
Total Number of Events	560	499	480
Year 15 cumulative Incidence (SE)	62%	56%	55%
Total Person Yrs (PYR)	7988	8709	9296
Crude Rate per 100 PYR	7.01	5.73	5.16
Median time to diabetes	9.5 years	12 years	13 years

	Log Rank Test			Proportional Hazards Analysis
	df	Chi-square	p-value	% Risk Reduction (95% CI)
Metformin vs. Placebo	1	10.22	0.0014	18.2 (7, 28)
Lifestyle vs. Placebo	1	24.02	<.0001	26.6 (17, 35)
Lifestyle vs. Metformin	1	2.77	0.0958	10.3 (-2, 21)
Placebo vs. Metformin vs. Lifestyle	2	25.16	<.0001	

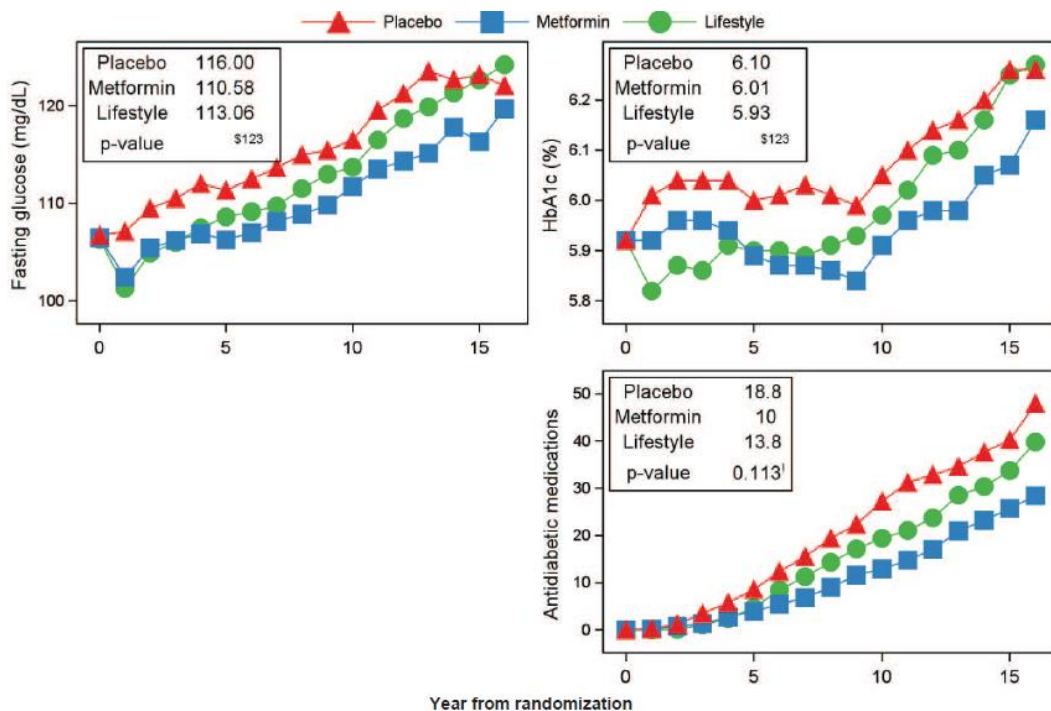
The next figure shows mean body weight over time:

Figure 3: Changes in weight over time by treatment group



Fasting glucose initially declined in both the metformin and lifestyle groups during DPP, and has steadily increased over time in all groups, with metformin participants having the lowest fasting glucose throughout follow-up (figure 4).

Figure 4: Changes in FPG, HbA1c and use of antidiabetic medications over time, by treatment group



The text within each figure denotes the mean level or percent over follow-up from mixed and GEE models, respectively. The 3 way p-value is presented with significant pairwise p-values noted in the superscript (1=placebo versus metformin, 2=placebo versus lifestyle, and 3=metformin versus lifestyle). The dollar sign (\$) indicates significant time*treatment interaction. Time 0 represents DPP randomization.

The BP and lipid benefits of intensive lifestyle intervention in the DPP study disappeared over time in the DDPOS.

Microvascular endpoints

An aggregate endpoint comprised of nephropathy, retinopathy and neuropathy was studied and recently reported.

Nephropathy was defined as albuminuria of 30 mg/g creatinine or more in a spot urine collection on two consecutive tests, an estimated glomerular filtration rate (GFR) of less than 45 mL/min per 1.73 m² on two consecutive tests, or renal failure (end-stage renal disease, dialysis, or transplantation). Participants taking antihypertensive drugs at the final assessment that did not meet albuminuria or estimated GFR criteria at that time were regarded as having reached the nephropathy outcome if the nephropathy criteria were met previously at two consecutive visits.

Retinopathy was diagnosed if the Early Treatment Diabetic Retinopathy Study grade was 20 or greater in either eye, or if treatment of retinopathy with laser or intravitreal injections was required.

Neuropathy was based on loss of light touch sensation measured with a 10 g monofilament.

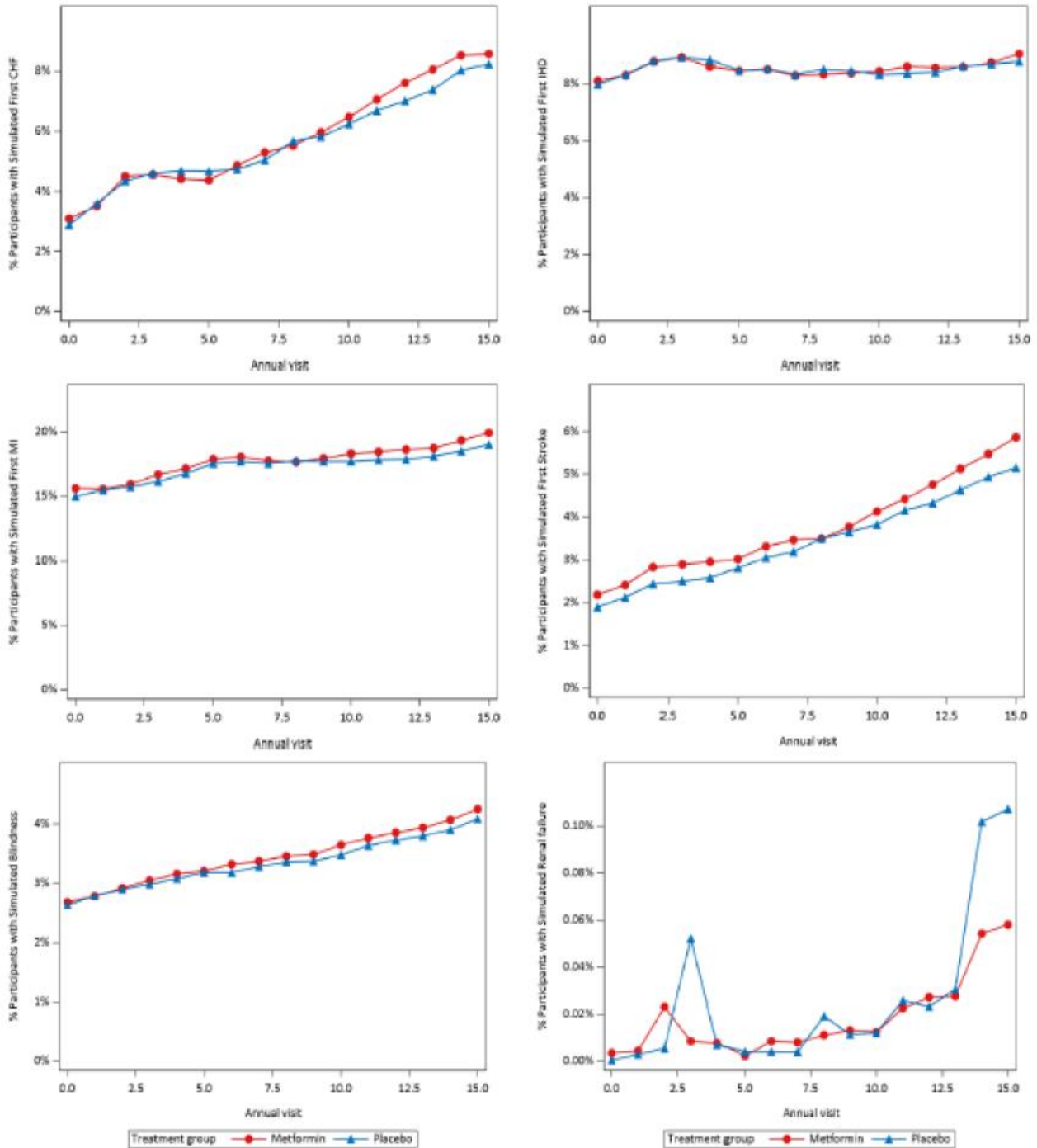
With this aggregate microvascular endpoint, outcome was not significantly different between treatment groups in the total cohort after 15 years follow-up (placebo 12.4%, 95% >CI 11.1-13.8; metformin 13.0%, 95% CI 11.7-14.5, intensive lifestyle intervention 11.3%, 95% CI 10.1-12.7). Neither was there any benefit of metformin vs. placebo group in any of the components. However, patients who had not developed overt diabetes, had a 28% lower prevalence of microvascular complications (RR 0.72, 95% CI 0.63-0.83, p<0.001) than those who had not. The DPP/DPPOS investigators acknowledge the changes over time in the standards of care for management of vascular risk factors for patients with diabetes. Further data was submitted that showed that after 10 years, 41% of the participants in the lifestyle group without diabetes had hypertension compared with 50% and 45% in the metformin and placebo groups, respectively. This data suggests that 10 years after randomisation, all groups have similarly good lipid and blood pressure control and thus any future difference in cardiovascular disease events by treatment group would likely reflect a legacy effect of the DPP intervention period.

As there was no difference between the original metformin and placebo groups in the 15 year assessment of microvascular outcomes, the Marketing Authorisation Holder submitted additional modelling data to simulate long-term outcomes based on the results of the DPP study. In a set of simulations, the DPP/DPPOS investigators estimated the lifetime risk of important diabetes related complications in DPP/DPPOS using the UKPDS-OM2 prediction (Hayes et al., 2013). To provide another perspective on the risk for cardiovascular disease (CVD) events, the Framingham equations for the prediction of future CVD events were used (Temprosa, 2016).

UKPDS-OM2 prediction

The figure below shows increasing estimated risk for all diabetes complications except ischaemic heart disease over 15 years of follow up for both metformin (red circle) and placebo (blue triangle) groups. By 15 years of follow-up, the estimated percentages of subjects with complications over the subsequent 15 years (i.e., 30 years of average follow-up) in both groups are 8-9% for the first occurrence of congestive heart failure and ischaemic heart disease, 19-20% for first myocardial infarction, 5-6% for stroke, 4% for blindness, and <0.10% for renal failure. From the figure below, metformin seems to have an advantage over placebo in preventing renal disease.

Figure 5. Estimated risk for all diabetes complications except ischaemic heart disease over 15 years in DPP/DPPOS

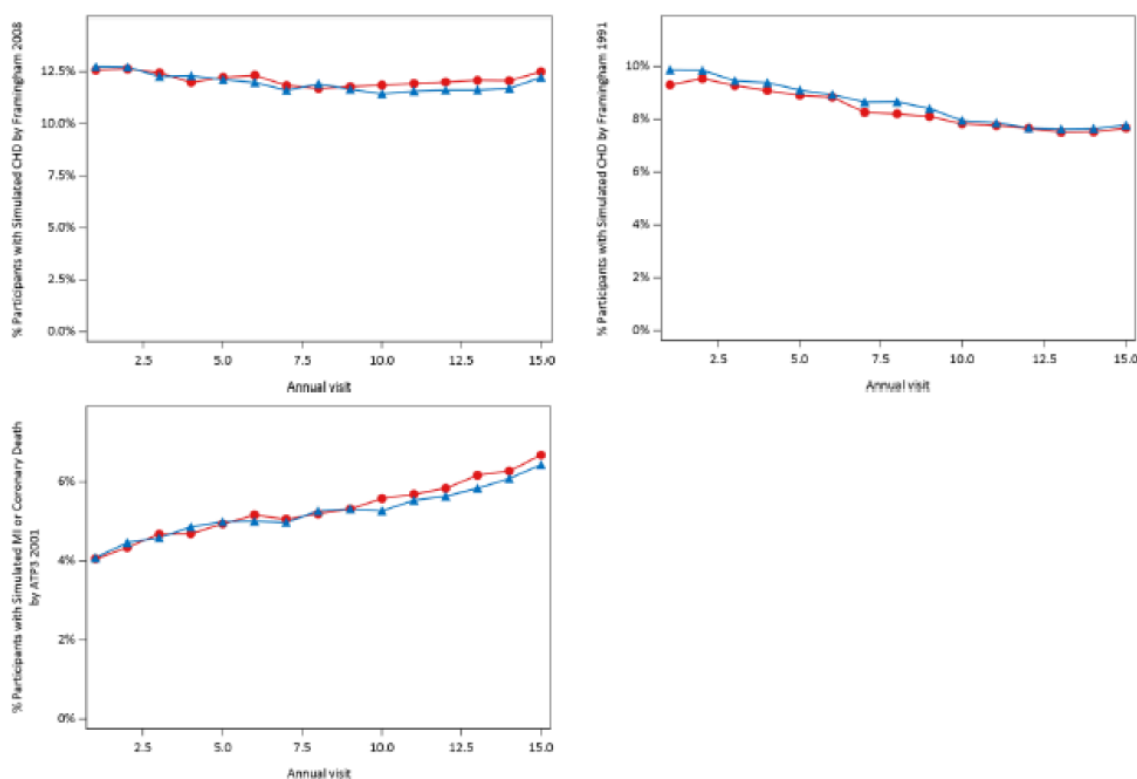


Framingham Risk Equations

The figure below depicts the simulated annual percentage of participants with CVD for the 3 versions of the Framingham equations. The 1991 equation predicts a decrease in CVD events over time which seems unlikely due to the aging cohort since age is a strong predictor for future events.

Framingham 2008 shows a relatively stable percentage of CVD events over time, similar to the pattern from UKPDS-OM2 for first ischaemic heart disease. Percentage with hard events (myocardial infarction or coronary death) shows an increase over time for both placebo and metformin which is consistent with an aging cohort. There are a few limitations for these equations, namely, unaccounted effects for medication use in 2008, and diabetes diagnoses in 1991.

Figure 6. Annual percentage of participants with CVD in DPP/DPPOS using 3 versions of Framingham equations



These simulations have shown varying patterns for the annual rates of diabetes complications which may be attributable to the limitations of applying the UKPDS-OM2 and Framingham equations to the DPP cohort.

The true benefit of diabetes prevention with regards to microvascular and macrovascular events can only be addressed with continued longer term follow-up. The DPPOS will be able to provide additional data on the long term benefit of metformin for microvascular disease by 2021 and macrovascular complications by 2025. The study is continuing to follow-up participants to address these important questions with sufficient power based on extensive power analyses.

3.2.3 Supportive studies

Additional studies with Metformin:

Additional studies also demonstrated an effect of metformin on diabetes risk reduction. Of these, one was not however randomised, and another looked at the combination of metformin and rosiglitazone. These will not be discussed further.

The largest remaining study included a total of 531 Asian Indian patients, for 2.5 years. Both intensive lifestyle modification and metformin significantly reduced the incidence of diabetes in Asian Indians with IGT compared to a control group of standard lifestyle modification, although there was no added benefit from combining them.

Smaller randomised studies demonstrated a significant effect of metformin on diabetes risk reduction in Chinese subjects with IGT during one year of treatment, and in Pakistani subjects with IGT during 18 months of treatment. In the latter study, combining an intensive lifestyle intervention with metformin was not more effective for preventing diabetes compared with the intensive lifestyle intervention alone, as shown in the Indian study.

Supportive studies on cardiovascular endpoints:

Specifically in European populations:

A 12-year follow up of men with IGT who participated in a Swedish study revealed that all-cause mortality among men in the lifestyle intervention group was lower (and similar to that in men with normal glucose tolerance) than that among men who had received 'routine care' (6.5 vs. 6.4 per 1000 person-years at risk; P = 0.009)

In a follow-up of healthy non-diabetic Norwegian men, it was found that men in the highest glucose quartile [fasting blood glucose of 4.7 mmol/l; still in the upper normal range] had a significantly higher mortality rate from cardiovascular diseases compared with those in the three lowest quartiles. Even after adjusting for age, smoking habits, serum lipids, blood pressure, FEV1 and physical fitness, the relative risk of cardiovascular death for men with fasting blood glucose >4.7 mmol/l remained 1.4 (95% CI 1.04–1.8). Non cardiovascular deaths were unrelated to fasting blood glucose level.

In the 10-year follow-up of the Finnish Diabetes Prevention Study, total mortality and cardiovascular disease incidence were no different between the intervention and control groups, but the study participants, who had IGT at baseline, had lower all-cause mortality and cardiovascular disease incidence compared with a Finnish population-based cohort of people with IGT.

Another group studied the 20-year mortality of non-diabetic, working men, age 44-55 years, in three European cohorts, study 1 (n = 10,025), study 2 (n = 6,629) and study 3 (n = 631). Subjects were identified by their 2h glucose levels following OGTT and by no diagnosis of diabetes. Men in the upper 20% of the 2h glucose distributions and those in the upper 2.5% for fasting glucose had a significantly higher risk of all-cause mortality in comparison with men in the lower 80% of these distributions, with age-adjusted hazard ratios of 1.6 (95% CI 1.4-1.9) and 2.0 (1.6-2.6) for the upper 2.5%. For death from cardiovascular and coronary heart disease, men in the upper 2.5% of the 2-h and fasting glucose distributions were at higher risk, with age-adjusted hazard ratios for coronary heart disease of 1.8 (1.4-2.4) and 2.7 (1.7-4.4), respectively.

These findings are generally supported by other studies in the US, Asia and Australia.

3.3 Clinical safety

The most common side-effects associated with metformin in diabetic patients are mild to moderate gastrointestinal events including diarrhoea, nausea, and vomiting, abdominal pain and decreased appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases.

Serious side-effects with metformin are very rare. The main concern is lactic acidosis, which has a high mortality rate in the absence of prompt treatment. This occurs primarily in patients with impaired renal failure or acute worsening of renal function. For this reason, metformin is contra-indicated when creatinine clearance is less than 45ml/min, and in patients with less severe renal impairment there are additional warnings. The maximum labelled dose in patients with moderate renal impairment is 1000 mg per day, and this also would apply to use in pre-diabetes. Metformin is also contra-indicated in other conditions that may impair renal function or cause tissue hypoxia.

Following review of all available data, CHMP recommended in October 2016 that the use of metformin

could be extended to include use in patients with GFR down to 30ml/min, with some changes to dose and additional guidance.

A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities; however gestational diabetes is not managed with metformin.

3.3.1 DDP and DDPOS studies

In the DPP study, 3819 study participants were randomly assigned to one of the four interventions (1082 to placebo, 1073 to metformin, 1079 to intensive lifestyle intervention, and 585 to troglitazone). The troglitazone treatment arm was discontinued in June 1998 due to concerns of liver toxicity.

Of 3819 randomised participants, 3755 had one or more adverse event (AE) in any primary body system during 11,002 participant years of follow-up. These 3755 participants had a total of 46,645 AEs. Out of 1073 participants assigned to the metformin treatment, 1066 participants experienced AEs occurring in all primary body system groups compared to 1,051 participants in the lifestyle intervention group and 1066 participants in the placebo group experiencing AEs. The rate of AEs in the metformin group compared to the placebo group was similar except for the digestive system (869 participants in metformin group and 676 participants in placebo group), and haematological/lymphatic system (178 participants in metformin group and 150 participants in placebo group). Slightly fewer patients in the metformin group (208) experienced cardiovascular events compared to placebo (213). Rates of serious adverse events (SAEs) were similar across the treatment groups, with no significant differences between groups in SAEs for any specific body system.

As of 15 March 2013, an interim analysis of DPPOS (DPPOS annual report, 2013) reported that a total of 456 metformin participants had 997 serious adverse events. No serious unexpected suspected adverse reaction has been reported up to the most recent DPPOS report in March 2013, and no dropouts due to adverse experiences have been noted. No death has been reported as due to metformin treatment. A total of 103 participants of the metformin group experienced 154 serious adverse events belonging to the cardiovascular system during 12 years follow-up in the DPPOS corresponding to an incidence rate of 1.23 events per 100 patient-years. No case of lactic acidosis has been reported.

3.3.2 Other studies

In the other smaller randomised diabetes prevention trials, no new safety issue was highlighted. Again, no case of lactic acidosis was reported and the majority of adverse events were gastrointestinal effects which resolved on long-term treatment.

3.3.3. Post marketing experience/risk management

No post-marketing data specific to the indication are submitted, and no changes to the risk management plan are required as a result of this variation. In the EU, metformin has only been licenced for a pre-diabetes indication in Hungary and Poland. It is not possible to separate out AEs arising from use or off-label in this setting, and spontaneous report data is unlikely to be helpful for such a well-established product with multiple generic formulations available.

4. Evaluation

4.1 Efficacy

The DDP study recruited patients aged over 25 who were overweight, with FPG of 5.3-6.9 mmol/l and IGT (BG 7.8-11.0 two hours after a 75-g oral glucose load). Ignoring a troglitazone group which was terminated early for safety reasons, 3234 eligible participants were randomly assigned to standard lifestyle recommendations plus Glucophage IR or blinded placebo, or an intensive program of lifestyle modification.

The standard and intensive lifestyle measures in each group were well documented, and in the intensive lifestyle group the compliance criteria pre-defined.

Pre-diabetes and BMI inclusion criteria were in line with the guidelines at the time. Whilst there was a liberal definition based on lower limit of fasting glucose (5.3, compared to 6.1 currently preferred by WHO and CHMP) - the standard IGT criteria were required in addition, on which prediabetes can be diagnosed alone.

The exclusion criteria were acceptable and included the contraindications for metformin, conditions precluding physical activity, and the use of thiazides or beta-blockers (which may both cause IGT). Treatment groups were well balanced at baseline for risk factors and demographic variables - the patients enrolled were at high risk of developing T2DM, and included about 45% of participants from ethnic groups with higher risk of developing T2DM compared with Caucasians.

The choice and definition of the primary diabetes endpoint was acceptable. The headline results showed a lower cumulative incidence of diabetes in the metformin and lifestyle-intervention groups than in the placebo group throughout the follow-up period. The crude incidence was 11.0, 7.8, and 4.8 cases per 100 person-years for the placebo, metformin, and lifestyle-intervention groups, respectively. The incidence of diabetes was 31% lower (95 % CI 17-43) in the metformin group than in the placebo group. The estimated cumulative incidence of diabetes at three years was 28.9 %, 21.7 %, and 14.4 % in the placebo, metformin, and lifestyle-intervention groups respectively. The median onset of overt diabetes based on plasma glucose levels was delayed by about 4 years by intensive lifestyle and 2 years by metformin, compared with placebo.

Treatment effects did not differ significantly according either to sex, race or ethnic group. As might be expected, the effect of metformin was reduced with a lower body-mass index or a lower fasting glucose concentration. Metformin was particularly effective in women with a previous history of gestational DM, providing around a 50% reduction in diabetes risk vs. placebo group, equal to the results in the intensive lifestyle therapy group.

Metformin does not have any adverse effects on lipids or blood pressure. It has a modest effect on weight, but this does not by itself account for the entirety of beneficial effects. Proportional hazards regression analysis showed that 64% of the beneficial effect of Glucophage vs. placebo on diabetes risk was accounted for by weight loss, 81% was accounted for by effects on weight, fasting insulin, pro-insulin, and other metabolic factors (although the association between Glucophage and reduced risk of diabetes was still independently significant), and 99% of the effect of Glucophage was explained by effects of metformin on these parameters plus fasting glucose.

Whilst there is only 1 large study, with no other product being licenced in the UK for the proposed indication, the study was adequately sized with clinically meaningful results, with some supporting studies, as well as a literature background of similar studies for other oral antidiabetics (including thiazolidinediones, which are also insulin sensitizers). Use of metformin in selected patients with prediabetes is noted in US, EU and UK treatment guidelines.

The DPP study is statistically valid. The methods for controlling the type I error in are appropriate and all three pairwise comparisons give p-values that are highly statistically significant compared to the critical value of 0.0159. It is assumed that, with Bonferroni correction, the appropriate critical value for each test is 0.0053 and, again, all pairwise comparisons are statistically significant.

The literature shows that microvascular disease associated with overt DM may already be present in the prediabetic patient, and as in established diabetes, patients with prediabetes are at increased risk of developing cardiovascular disease. This has been shown in multiple single studies and in meta-analyses. At a population level, the environment is changing, with increasing prevalence of obesity and T2DM, and these results also depend on the population studied, the definition of IGT, IFG or OGTT, methods for measuring blood glucose, as well as the definition of the cardiovascular endpoints and the length of follow-up. However, overall there is good evidence to link prediabetes to cardiovascular disease.

There is also a reasonable mechanistic basis for the effects observed. IGT is characterised by both insulin resistance and impaired beta-cell function. The main pharmacological effect of metformin is to reduce insulin resistance. Hyperglycemia itself may impair insulin secretion, because high glucose levels desensitize β cells or cause β -cell dysfunction. Reducing the amount of insulin required to maintain glucose levels should reduce the demand on pancreatic beta cells. In the DPP study, results suggested that development of diabetes in the placebo group resulted from continued decreases in insulin sensitivity and β -cell function (i.e., insulin secretion relative to sensitivity), whereas reduction in the incidence of diabetes observed in the two active interventions was due to their ability to increase insulin sensitivity and improve β -cell function, with each variable having an independent effect on the risk of developing diabetes. Mechanistic studies have shown differences between subjects characterised mainly by IGT vs. subjects characterised mainly by IFG populations. IFG is often characterised by reduced hepatic insulin sensitivity, stationary beta cell dysfunction and/or chronic low beta cell mass, whereas IGT is characterised by reduced peripheral insulin sensitivity, near-normal hepatic insulin sensitivity, progressive loss of beta cell function and reduced secretion of glucose-dependent insulinotropic polypeptide. The study was done in patients with both IFG and IGT in order to enrol patients with a higher risk of developing DM, so that a treatment effect could be assessed within a reasonable timescale

The proposed indications define prediabetic hyperglycaemia (IGT and/or IFG, and/or increased HbA1C) - so this includes patients with IGT alone, without IFG. However, as the indications are restricted to patients at high risk for developing overt T2DM, this is acceptable.

Some longer-term information is provided by the DDPOS trial - this was a long term open label follow-up study of the DPP participants, which is still on-going. 88 % (n=2,766) of eligible subjects were enrolled in the DDPOS following the washout study at the end of the randomized phase of the DPP. At 15 years follow-up, the positive effects of the metformin and lifestyle interventions for diabetes incidence seen in the DPP study continued, despite an improvement in the placebo group following unblinding of the trial. The effect of increasing the lifestyle intervention in the placebo group can also be seen, and a gradual progressive weight gain in the previous intensive lifestyle intervention group indicates practical difficulties in sustaining this over 15 years. Over time, metformin was at least as effective as intensive lifestyle intervention in prevention of DM. Another explanation for the fall in diabetes incidence rates in the former metformin and placebo groups might be because participants who were susceptible to diabetes developed the disease during the DPP, leaving a reduced number at risk during the present study. However, this hypothesis is not supported, given stability over time of diabetes incidence in the lifestyle group.

Delaying the onset of diabetes may be important but the primary endpoint needs to be supported by additional data showing a resulting benefit on microvascular and/or macrovascular endpoints. A publication arising from the DPP assessed fundus photography around 3.1 years after the development of diabetes in 594 of 878 participants who had developed diabetes during the study, and in a random sample of 302 participants who remained non-diabetic. Diabetic retinopathy was detected in 12.6 and 7.9% of the diabetic and non-diabetic participants, respectively (p=0.03), demonstrating that retinopathy characteristic of diabetes is already present in patients with prediabetic hyperglycaemia. This has been seen in other several studies independent of the DPP data.

In the DDPOS trial, an aggregate microvascular endpoint composed of nephropathy, retinopathy, and neuropathy was not significantly different between treatment groups in the total cohort, although there was a 14% reduction in the original intensive lifestyle group vs. metformin. Patients who had not developed overt diabetes had a significantly lower prevalence of microvascular complications, reflecting the clinical importance of delaying diabetes. However, given the time when studies were initiated, these results should be discussed in light of changes in the other standard of care to manage vascular risk factors.

Although 88% of eligible subjects were enrolled in the DDPOS following the washout study at the end of the randomised phase of the DPP, there is some potential for bias in enrolment. Enrolment into this

follow-up study from the DPP cohort did not differ significantly by sex or ethnic origin, but was lower in women with a history of gestational diabetes than in those without, and higher in participants who had developed diabetes. Enrolment was also related to greater age, HbA1c, cholesterol concentrations, and in women, by lower weight and body-mass index. Differences in compliance with the lifestyle interventions between groups and the treatment modification at the end of the DPP study also mean that the conclusions of DDPOS should be treated with caution.

Because there were no differences between the original metformin and placebo groups in the 15 year assessment of microvascular outcomes, and given the confounding issues in the DDPOS noted above, additional supportive modelling data regarding microvascular and/or macrovascular complications were submitted by the Marketing Authorisation Holder. The modelling data are helpful to frame the debate on the level of uncertainty.

The question is whether treatment in a "prediabetic" stage prevents more long-term consequences than waiting until diagnosis of T2DM. The combined microvascular endpoint composed of nephropathy, retinopathy, and neuropathy was not significantly different between treatment groups in the total cohort, although there was a 14% reduction in the original intensive lifestyle group vs. metformin. Overall, in participants who had not developed diabetes, the prevalence of microvascular outcomes was 28% lower compared with those who had. In the intensive lifestyle intervention and metformin groups, there was a reduction in CV disease risk factors and metabolic syndrome compared to the placebo group. However the duration of these benefits and whether they result in reduced event rates over the longer-term has not yet been established.

The follow-up phase is still on-going; DDPOS is expected to provide additional data on the long term benefit of metformin for microvascular disease by 2021, and on macrovascular complications by 2025. It is not clear how definitive these will be, as all long-term participants were offered increased lifestyle interventions, with some biases in enrolment and differences in lifestyle interventions compliance between groups. It is also doubtful that a new fully randomised trial of metformin is going to happen.

As the applicant is not making any claim on CV outcome data, it needs to be shown that there is at minimum no adverse effect of metformin on these in the prediabetes context. On balance, especially considering the relevant subgroup in the UK prospective diabetes study, a beneficial clinical effect is thought likely, but unproven, so the consideration is whether the potential benefits outweigh this uncertainty.

There is a likely role for the use of metformin in selected individuals, and particular benefit in patients who are unable to manage lifestyle measures, in whom progression to actual diabetes is really undesirable because of other risk factors - patients on antipsychotic drugs being an example. The patients for whom benefit is most likely have been discussed by the applicant and this is sufficiently captured in the SmPC and PIL.

The SmPC in section 5.1 has further information on eligibility of patients, which is advised to be based on national guidelines, and as now added to the SmPC - patients at high risk should be identified by a validated risk-assessment tool.

Macrovascular outcomes are the focus of the current stage of DDPOS, but the same limitations as for microvascular outcomes will apply. However, a randomised trial to show differences in macrovascular endpoints would be impractically large and lengthy in the prediabetes setting. For the treatment of established diabetes, a positive effect of metformin on the risk of cardiovascular disease and all-cause mortality complications was demonstrated in the UKPDS 34 study.

The relevant CHMP guidance in trials for prediabetes notes that a wash-out phase of appropriate duration (e.g. at least 3 months) is needed to show that the product is truly delaying progression to diabetes, rather than masking the diagnosis. In the DPP, after 1 to 2 weeks, a significant reduction in the

incidence of T2DM remained in the metformin treatment group (25% reduction relative to placebo), as compared to the 31% reduction seen while on-treatment. Certainly 3 months would be needed to diagnose DM by HbA1c (because of the red blood cell half-life, HbA1c levels take around 12 weeks to reach equilibrium) and HbA1c is less affected by short-term lifestyle changes. The authors considered that the pharmacological effects of metformin would be gone within 1-2 weeks (in fact, the initial plan was to complete all assessments by 1 week) and that if metformin was having substantial sustained effects in delaying diabetes, a more prolonged withdrawal period might have been adverse to the well-being of the participants. The authors acknowledged in the protocol that a 1-2 week washout would only look at the effects of acute withdrawal, with some evidence of a withdrawal effect at least in a subgroup, and that more information would then be needed on the durability and possible mechanisms of a chronic effect of metformin.

It is not fully agreed that washing out for a few months would have had a substantial adverse impact on participants. It is thought that the predominant effect of metformin is inhibition of hepatic gluconeogenesis, via inhibition of the mitochondrial respiratory-chain, with subsequent activation of the enzyme adenosine monophosphate activated protein kinase (AMPK). In skeletal muscle, activation of AMPK increases glucose uptake and lipid oxidation, whilst in adipose tissue, activation of AMPK reduces both lipolysis and lipogenesis. However, despite being introduced in the 1950s, the underlying mechanisms are still not fully elucidated, making it difficult to definitively comment on the adequacy of the washout period.

Further washout data from another study in subjects with IGT are available, involving 20 subjects on metformin (500 mg twice daily) and 20 on placebo. In this study, metformin resulted in an improvement in glucose tolerance that lasted for up to 6 months after cessation of metformin - however this is a small study, the improvement in IGT at 6 months was small and 1 subject from each groups converted to T2DM during the 6 month period.

Another consideration is whether the results can be extrapolated to the UK population, the study having been done exclusively in the US. Treatment effects did not differ significantly according either race or ethnic group, and the UK standard of care is reasonably similar in the management of diabetes and other cardiovascular risk factors. Likewise, food culture and levels of physical activity are similar, with risk factors and prevalence of prediabetic hyperglycaemia converging between the US and UK over recent years.

4.2 Posology

Whilst the MAH proposes to later extend the indication to their immediate release metformin product, this variation is for the prolonged release product, Glucophage SR. The pivotal study was conducted with immediate release metformin, as at the start of the DPP, Glucophage SR was not available in the US. However, on the basis of bioequivalence between this formulation and Glucophage SR in comparative PK trials, in patients already treated with metformin tablets [up to 2000mg per day], the starting dose of Glucophage SR is equivalent to the daily dose of metformin immediate release tablets. This has already been established and noted in the current SmPC.

There is no dose-finding study available for metformin in the prediabetes indication. Doses used in the clinical trials varied, however in practice the dose will be titrated according to effect and tolerability. The proposed dose is consistent with the range of doses used in the DPP and other studies that demonstrated a beneficial effect of metformin in reducing the risk of progression to type 2 diabetes. The dose aligns with the current NICE guidelines, and fits within the current posology for metformin in type 2 diabetes.

In the DPP study, metformin immediate release was initiated at 850 mg once daily and increased as needed to 850 mg twice daily, initiation with 425mg daily was optional. 84 % percent of those taking metformin were given the full dose of 850 mg twice a day, i.e. 1700mg per day; the remainder were given 850 mg once a day. None of the 1073 subjects in the metformin group started with 425 mg daily,

so the proposal in the SmPC to initiated with one tablet Glucophage SR 500 mg once daily is conservative - however this is reasonable for extrapolation of the study to a wider population, noting also that the current NICE guidelines recommend a low starting dose.

The available Glucophage SR tablet strengths are 500, 750 and 1000 mg, these cannot be divided. So in theory there are 3 dose steps available, but 7 steps if 2 tablets can be combined (500, 750, 1000, 1250, 1500, 1750, and 2000)

Overall, it is acceptable for the study data with IR metformin to be extrapolated to Glucophage SR. The MAH notes that Glucophage SR has the advantage of better gastrointestinal tolerability than the immediate release tablets, and that once daily dosing may lead to better patient adherence. These advantages have not been directly compared in prediabetic patient population.

The proposed posology with Glucophage SR, including monitoring requirements, is generally acceptable, and the range of strengths available adequate to implement the proposed posology. The MAH considers that while the ideal outcome of treatment would be a normalisation of glycaemic control, given the tendency of patients with prediabetes to progress to type 2 diabetes, stable glycaemic parameters over time can also indicate treatment success. Moreover, they consider that given the benefits of metformin in the treatment of prediabetes observed in the DPP and other studies, in such patients with stable glycaemic parameters, discontinuation of treatment can be anticipated to increase the risk and hasten the onset of further progression to overt type 2 diabetes. However, this does not take into account that the patient's risk factors may improve over time such that the risk: benefit of metformin treatment is adversely affected. The recommendation in UK practice guidance is also to monitor fasting plasma glucose or HbA1C levels at 3-month intervals, stopping the drug if no effect is seen. A decision to continue therapy is also required if the patient subsequently implements improvements to their diet and/or exercise, or if changes to their medical condition will allow increased lifestyle interventions to be possible. These considerations have been sufficiently addressed in section 4.2 of the SmPC.

4.3 Safety aspects

Due to the high and increasing prevalence of prediabetes, the proposed indication could increase significantly the use of metformin in the UK. Because of the large potential population and the fact that the alternative is a non-pharmacological intervention of lifestyle change, a favourable safety assessment is clearly needed, and this is generally the case.

In the DPP - as expected, the main AE associated with metformin was gastrointestinal symptoms, Hospitalisation and mortality rates were unrelated to treatment and no deaths were attributed to the study intervention. Metformin does not cause hypoglycaemia, or adversely affect BP, lipids, or urinary albumin creatinine ratio. No unexpected safety concern was observed during its use in patients with prediabetic hyperglycaemia. The use of metformin in prediabetes potentially increases the overall duration of use. However, there are no specific issues with metformin and long-latency adverse drug reactions (ADRs).

There are no changes to the current contra-indications and warnings in the SmPC, and the proposed new indication does not extend metformin into subgroups where metformin is previously unstudied, or in whom metformin would have additional risks. Indeed, earlier use in younger patients with less morbidity than patients with established DM might be expected to lower the risk. Clearly, some patients will be ineligible for metformin (e.g., due to renal impairment) and the indications are specifically in high risk patients in who intensive lifestyle intervention has not succeeded.

The proposed starting dose is within the existing posology for metformin, and titrated according to effect and tolerability. Metformin has a well-known ADR profile, which in general did not differ in the prediabetes setting.

5. Conclusion

There is no doubt that the incidence of type 2 diabetes is a concern in the UK and that this has major consequences for the individual and for public health. It is unclear how much interventions at the population and individual level will impact these concerning trends, but there is good evidence that behavioural interventions to support people to maintain a healthy weight and be more active can significantly reduce the risk of developing T2DM. As mentioned in this assessment, in March 2016, a Diabetes Prevention Programme for NHS England was announced, to offer personalised lifestyle and behavioural modification advice to individuals at risk of developing T2DM.

There is always debate about the extent to which medicine is extending the boundaries of illness through "new" disorders, with a consequent risk of treating more people than necessary. However there is a good consensus that a prediabetic state can be defined, and that it is associated both with progression to overt diabetes and pre-existing microvascular complications characteristic of established diabetes.

Progression from "prediabetes" to diabetes is not inevitable - not all subjects at risk for developing type 2 diabetes will eventually develop the disease. In these subjects, pharmacological treatment might be given without a chance of benefit, although lifestyle interventions might have other benefits. Some patients will in fact revert to normoglycaemia - lower fasting glucose, lower 2-h OGGT, prior weight loss and younger age all predicted reversion from IGT to normal glucose tolerance in the DPP study. The proposed indication is however in patients at high risk of progression.

The most important and first-line intervention in pre-diabetic hyperglycaemia is intensive lifestyle intervention, given its safety and the strength of evidence for its effectiveness in improving glycaemia and reducing cardiovascular risk factors. The effectiveness of structured lifestyle interventions was conclusively demonstrated in the DPP study. If it can be achieved, intensive lifestyle modification has additional benefits over metformin, including in blood pressure and lipid reduction.

However, intensive lifestyle intervention is difficult to implement for many patients, and long term adherence is hard to maintain, thus limiting its effectiveness. There must be caution in extrapolating the efficacy of lifestyle interventions in a clinical trial to the real-life situation. Some patients may be unable to fully participate in exercise due to other morbidity or disability, and unfortunately good lifestyle intervention programmes might not always be available. The rising individual and public health burden of diabetes should be taken into account, plus the lack of other licenced pharmacological therapy in the proposed indication. The use of metformin in selected patients is part of current UK, EU and international guidance, and the proposed indications and posology (with some further restrictions, see the list of questions) is in line with this guidance.

The main DPP trial was generally well designed and conducted. It showed that treatment with metformin and intensive modification of lifestyle were both effective means of delaying type 2 diabetes in patients at high risk of this. In patients on standard lifestyle measures, metformin also showed a benefit over blinded placebo. This was supported by follow-up data in the DDPOS trial as well as several supportive trials. Benefits of the intensive lifestyle intervention and metformin group in the DDPOS cohort also included a reduction in CV disease risk factors and the presence of metabolic syndrome.

The key question is whether earlier treatment (in a prediabetic stage) prevents more long-term consequences than starting when T2DM is diagnosed. The background literature shows that microvascular disease associated with overt DM may already be present in the prediabetic patient, and - as in established diabetes - patients with prediabetes are at increased risk of developing cardiovascular disease.

Although more lengthy follow-up is on-going to assess macrovascular outcomes and there are some limitations in interpretation of the DDP follow-up data (DDPOS trial). Among the participants who had not developed diabetes during DPP/DDPOS, the prevalence of microvascular outcomes was 28% lower

compared with those who had developed diabetes (RR 0.72, 95% CI 0.63–0.83; $p < 0.0001$). After 15 years, there was no significant difference between the original metformin-treated and intensive lifestyle groups in the microvascular disease endpoint. However, this is confounded as all participants in the DDPOS, were offered increased lifestyle interventions. The authors concluded that given the strong relationship between duration of DM and HbA1c levels with the prevalence of complications, longer follow-up may show a differential effect of the original DPP interventions on complications.

On balance, the risk benefit is positive in patients with prediabetic hyperglycaemia, who are at high risk for developing overt type 2 diabetes mellitus and in whom intensive lifestyle change has not resulted in adequate glycaemic control.

Metformin might particularly be considered in patients with particularly high BMI, especially with higher or rapidly progressing FPG or IGT values, and when there are additional risk factors including family history, gestational diabetes, dyslipidaemia, hypertension, cardiovascular disease, PCOS and hepatic steatosis.

6. Decision

Approved on 16 May 2017

Satisfactory updated SmPC fragments and PIL were submitted in support of the variation application.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website.