Research: Treatment

Study to determine the durability of glycaemic control with early treatment with a vildagliptin–metformin combination regimen vs. standard-of-care metformin monotherapy—the VERIFY trial: a randomized double-blind trial

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Abstract

Aims Durability of good glycaemic control (HbA_{1c}) is of importance as it can be the foundation for delaying diabetic complications. It has been hypothesized that early initiation of treatment with the combination of oral anti-diabetes agents with complementary mechanisms of action can increase the durability of glycaemic control compared with metformin monotherapy followed by a stepwise addition of oral agents. Dipeptidyl peptidase-4 inhibitors are good candidates for early use as they are efficacious in combination with metformin, show weight neutrality and a low risk of hypoglycaemia. We aimed to test the hypothesis that early combined treatment of metformin and vildagliptin slows β-cell deterioration as measured by HbA_{1c}.

Methods Approximately 2000 people with Type 2 diabetes mellitus who were drug-naive or who were treated with metformin for less than 1 month, and who have HbA_{1c} of 48–58 mmol/mol (6.5–7.5%), will be randomized in a 1:1 ratio in VERIFY, a 5-year multinational, double-blind, parallel-group study designed to compare early initiation of a vildagliptin–metformin combination with standard-of-care initiation of metformin monotherapy, followed by the stepwise addition of vildagliptin when glycaemia deteriorates. Further deterioration will be treated with insulin. The primary analysis for treatment failure will be from a Cox proportional hazard regression model and the durability of glycaemic control will be evaluated by assessing treatment failure rate and the rate of loss in glycaemic control over time as co-primary endpoints.

Summary VERIFY is the first study to investigate the long-term clinical benefits of early combination treatment vs. the standard-of-care metformin monotherapy with a second agent added by threshold criteria.

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Introduction

Both insulin resistance and impaired insulin secretion contribute to development and worsening of hyperglycaemia in Type 2 diabetes mellitus. Dipeptidyl peptidase-4 (DPP-4) inhibitors increase the availability of endogenous glucagon-like peptide 1 (GLP-1) and are good candidates for early use in combination with metformin as they are oral agents increasing glucose-sensitive insulin secretion with a very low risk of hypoglycaemia [1]. The combination of the two treatments has no deleterious impact on weight control [2].

One of the known causes of deteriorating glycaemic control is the gradual failure of β-cell function. This is conventionally addressed by adding additional agents over a

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What's new?

- One of the known causes of deteriorating glycaemic control is the gradual failure of β-cell function.
- Different agents cause different rates of glycaemic failure.
- What is unknown is whether dipeptidyl peptidase-4 agents will demonstrate a preservation of β-cell function when used in combination therapy with metformin.
- This is the first trial directly addressing that question.

period of time—often years—to maintain acceptable glycaemia. Different agents may modify the progression of glycaemic failure differently, as was shown in the Diabetes Outcome Progression Trial (ADOPT), which compared thiazolidinedione monotherapy, sulphonylurea monotherapy and metformin monotherapy [3,4]. What is unknown is whether DPP-4 agents will demonstrate a preservation of β-cell function when used in combination therapy with metformin. This trial addresses that question.

The hypothesis underlying the trial is that a proactive approach of initiating early treatment with a vildagliptin–metformin combination will increase the durability of the glycaemic control compared with a policy of prescribing metformin alone, followed by vildagliptin only when glycaemia deteriorates [5].

Methods

The VERIFY study is a 5-year three-period study (Fig. 1) designed to compare early initiation of a vildagliptin–metformin combination with standard-of-care initiation of metformin monotherapy (period 1), followed by the stepwise addition of a second oral anti-diabetic agent (period 2). Insulin will be added if glycaemic control deteriorates while

participants are on combination treatment ('Rescue therapy', period 3, Fig. 2). The study will assess the durability of glycaemic control (HbA$_{1c}$), changes in β-cell function and insulin sensitivity, time to insulin initiation, the effect on diabetic complications and the effects on some specific surrogates. The participant's health status will be continually monitored.

Study objectives

The primary aim of the study is to determine whether early combination of vildagliptin 50 mg twice daily with metformin will result in better durability of glycaemic control than metformin monotherapy in treatment-naive people with Type 2 diabetes. Durability of glycaemic control will be assessed by time to failure and rate of loss in glycaemic control over time, which are co-primary objectives. The
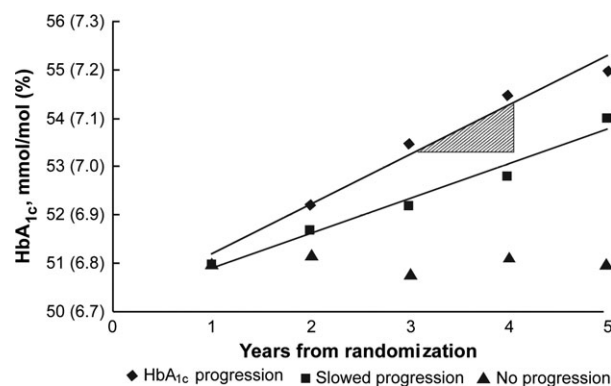
FIGURE 2 Schematic diagram to show coefficient of failure. Putative examples of fictional individual participants' data showing regression of HbA$_{1c}$ with time. The three line examples illustrate the usual progression of β-cell failure (♦), slowed progression (■) and no progression (▲), respectively. Shaded triangle shows calculation of coefficient of failure as annualized slope of HbA$_{1c}$ deterioration.
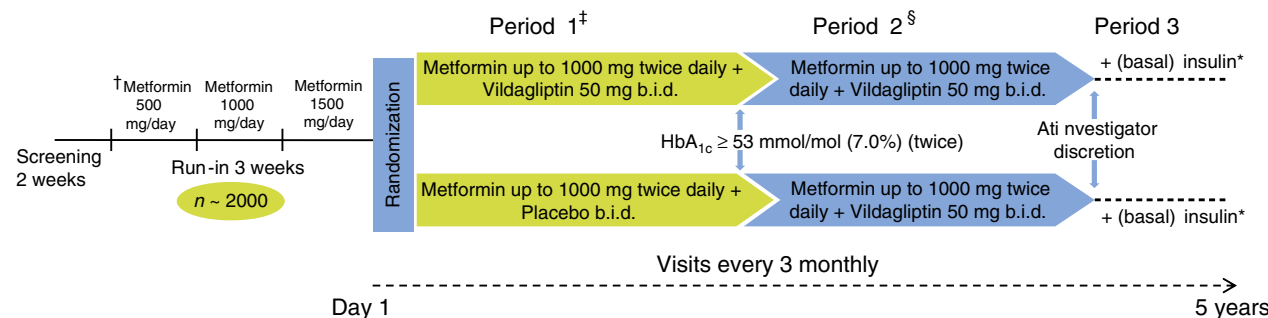
FIGURE 1 Diagram of VERIFY study design. *Insulin initiation according to local guidelines. †Metformin dose can be adjusted in the first 4 weeks of randomization up to 2000 mg, or the maximal tolerated dose. No adjustment is allowed afterwards. ‡Period duration can differ between the two treatments. The end of period 1 is defined by the day when the patient will receive a new vildagliptin medication pack§ because of HbA$_{1c}$ ≥ 53 mmol/mol (7.0%) measured at two consecutive scheduled visits. §Participants in both arms will receive vildagliptin in a medication pack designed differently from the vildagliptin/placebo packs used in period 1.

Table 1 Secondary and exploratory endpoints

Secondary endpoints	Exploratory endpoints
Rate of loss in glycaemic control, determined by HbA$_{1c}$, from 26 weeks after the start of period 2 to the end of period 2	Change in body weight
Rate of loss in glycaemic control, determined by fasting plasma glucose, during study periods 1 and 2	Time to insulin initiation
Change in HbA$_{1c}$ from baseline to end of study	β-cell function assessed by HOMA-%B
In a subgroup of participants performing meal test to determine area under the curve of insulin secretion rate relative to glucose:	Insulin resistance assessed by HOMA-%S
• Change in β-cell function from baseline to the end of periods 1 and 2 and to the end of the study	
• Rate of loss in β-cell function from baseline to the end of periods 1 and 2 and to the end of the study	
In a subgroup of participants performing meal test to determine oral glucose insulin sensitivity:	Change in health status assessed by EuroQoL (EQ-5D) questionnaire
• Change in insulin sensitivity from baseline to the end of periods 1 and 2 and to the end of the study	
• Rate of change in insulin sensitivity from baseline to the end of periods 1 and 2 and to the end of the study	
	In a subgroup of participants, change in retinal micro-aneurism count

HOMA-B, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance.

study will be declared positive if one of them is met after period 1 of the study (Fig. 1).

The full list of secondary and exploratory study endpoints is presented in Table 1.

Study design

VERIFY is a randomized 1:1, double-blind, parallel-group study consisting of a screening visit, a 3-week run-in period and a 5-year treatment period (Fig. 1). After the screening visit, approximately 2000 eligible participants will enter a run-in period, during which metformin will be up titrated to a target dose of 1500 mg or maximum tolerated dose. At the end of the run-in period, participants who are able to tolerate a dose of 1000 mg or higher will be randomized 1:1 to the addition of vildagliptin 50 mg twice daily or placebo and will enter period 1. Dose adjustment of metformin in both treatment arms will continue during the first 4 weeks of period 1, with the aim of reaching a dose of 2000 mg, or the maximum tolerated dose. HbA$_{1c}$ will be determined approximately every 3 months. While in period 1, when measurements of HbA$_{1c}$ from two consecutive scheduled study visits are ≥ 53 mmol/mol (7.0%), participants in the metformin group will add vildagliptin 50 mg twice daily (period 2). Participants in the early initiation vildagliptin–metformin group will continue the same treatment, so that participants in both treatment groups will receive vildagliptin and metformin during period 2. The blinding to the study group allocation at randomization will be maintained. If during period 2 local diabetes guidelines require treatment

intensification with insulin, participants will start insulin treatment in addition to the vildagliptin–metformin combination treatment (period 3). Open-label insulin treatment will be initiated with an insulin type and regimen at the investigator's discretion, although the protocol expresses a preference for once-daily basal insulin. If an alternative anti-diabetes medication is considered necessary for intensification during period 2, the participant will be discontinued from the study.

Study population

Key inclusion and exclusion criteria are presented in Table 2. The rationale for choosing treatment-naive people with Type 2 diabetes (also including participants who have been on metformin treatment for less than 1 month) with HbA$_{1c}$ between 48 and 58 mmol/mol (6.5% and 7.5%) is to ensure that participants in the early stage of diabetes with relatively preserved β-cell function will be included in the study. The upper limit of HbA$_{1c}$ is set to 58 mmol/mol (7.5%) to allow for inclusion of participants with good glycaemic control and to minimize the effect of glucotoxicity on the β-cells.

Data collection

All participants will visit the study sites every 13 weeks to perform study procedures (Table 3). Laboratory samples will be collected at each visit and all the samples will be analysed at a central laboratory. A subgroup of approx-

Table 2 Key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
Diagnosis of Type 2 diabetes mellitus ≤ 24 months (as per local diagnostic criteria for Type 2 diabetes)	Any anti-diabetes treatment within 3 months prior to visit 1 (except for metformin, which is allowed within 1 month prior to visit 1) and any anti-diabetes treatment for more than three consecutive months or adding up to a total of more than 3 months in the last 2 years
HbA_{1c} ≥ 48 mmol/mol (6.5%) and ≤ 58 mmol/mol (7.5%)	Use of weight control products, including weight-loss medications in the previous 3 months
Treatment-naive participants	Chronic oral (> 7 consecutive days), parenteral or intra-articular corticosteroid treatment within 8 weeks prior to study
Participants who initiated metformin within 1 month prior to visit 1 and take a total daily dose up to 2000 mg metformin	Ketoacidosis, lactic acidosis or hyperosmolar state (including coma), myocardial infarction, coronary artery bypass surgery or percutaneous coronary intervention, stroke or transient ischaemic attack within the past 6 months, unstable angina within the past 3 months
Age ≥ 18 and ≤ 70 years	Current diagnosis of congestive heart failure [New York Heart Association (NYHA) III or IV], sustained and clinically relevant ventricular arrhythmia, second- or third-degree atrio-ventricular block without a pacemaker, long QT syndrome or corrected QT > 500 ms
BMI ≥ 22 and ≤ 40 kg/m^2	Acute or chronic liver disease, evidence of hepatitis, cirrhosis or portal hypertension, history of imaging abnormalities that suggest liver disease (except hepatic steatosis), such as portal hypertension, capsule scalloping, cirrhosis
	Malignancy of an organ system (other than localized basal cell carcinoma of the skin) within the past 5 years
	Pregnant or nursing (lactating) women
	Significant laboratory abnormalities

Table 3 Assessments performed after randomization

Assessment	Every 13 weeks	Every year	Years 4 and 5
HbA$_{1c}$, fasting plasma glucose	X		
Hypoglycaemia, weight	X		
Vital signs, adverse event and serious adverse event	X		
Haematology and biochemistry, urine analysis		X	
Insulin, C-peptide		X	
Liver function tests	X*		
Microalbuminuria		X	
Electrocardiogram		X	
Euro-QoL (EQ-5D) questionnaire	X		
Standard meal test (subgroup)		X†	
Retinal photography (subgroup)			X

*After year 1, liver function tests will be taken every 6 months.
†A meal test will also be performed at week 13.

imately 400 participants (200 per group) will perform a standard meal test at baseline, at 3 months and every year. Except for the baseline visit when study drugs will not be taken prior to the standard meal, at all other visits the study drugs will be taken 15 min before the start of the meal. A standard breakfast containing 500 kcal (60% carbohydrates, 30% fat and 10% proteins) will be served. Blood samples will be collected at –15, 0, 15, 30, 60, 90 and 120 min. Plasma glucose, insulin and C-peptide will be determined and indices of β-cell function [insulin secretion rate relative to glucose and homeostasis model assessment of β-cell function (HOMA%B)] and insulin sensitivity (oral glucose sensitivity index and HOMA%S)

will be calculated [6,7]. Safety assessment will be performed at every visit.

A subset of approximately 200 participants will have retinal photographs for assessment of microaneurysm counts at baseline and at years 4 and 5. The assessment will be performed at a central facility experienced in screening and grading of diabetic retinopathy. Generic multidimensional health-related quality of life will be assessed with the EuroQoL (EQ-5D) questionnaire.

Statistical methods

The primary analysis will be performed based on the intention-to-treat principle and will cover period 1, during which the vildagliptin-metformin combination is compared with the metformin monotherapy.

The time to failure will be derived as the time from randomization to the first of two consecutive visits at which HbA$_{1c}$ ≥ 58 mmol/mol (7.0%) is measured, starting from visit 4 (13 weeks after randomization). The Cox proportional hazards regression model will be used to assess the probability of initial treatment failure, with treatment as classification variable and baseline HbA$_{1c}$ as a covariate. The hazard ratio and associated 95% confidence interval and the null hypothesis *P*-value estimated from the above model will be presented by treatment. The initial treatment failure rate over time by treatment will be summarized and plotted with associated 95% confidence intervals, using estimates from a Kaplan–Meier analysis.

The rate of loss in glycaemic control over time will be estimated as the coefficient of failure [8] by the slope of HbA$_{1c}$ over time (in years) as a random coefficient in a linear

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Vildagliptin plus metformin durability study • S. Del Prato et al.

mixed effect model: the model will be fitted to HbA$_{1c}$ data collected from week 24 and onwards up to and including the second of the two consecutive values above or equal to 53 mmol/mol (7.0%). The mean slopes within each treatment and the difference in mean slopes between two treatments, as well as the *P*-value obtained from the test using the above model, will be presented. For duration assessment the intercept of the regression line with a 58 mmol/mol (7.5%) arbitrary threshold will be used to quantify duration.

To adjust for multiplicity, Hochberg and Benjamini's multiple testing step-up procedure [9] will be used to maintain an overall one-sided significance level of 0.025. The study will be declared positive if a significant between-treatment difference is found for at least one of the two variables (time to failure or rate of loss in glycaemic control).

The time to insulin will use the same Cox proportional hazards regression model as for the primary endpoint. The slopes of progression of HbA$_{1c}$, indexes of β-cell function and insulin sensitivity will be analysed using a similar random coefficient model as used for the rate of loss of glycaemic control over time. An analysis of covariance (ANCOVA) model with treatment, pooled centre as classification variables and baseline HbA$_{1c}$ as a covariate will be used to assess the change in HbA$_{1c}$ from baseline to endpoint.

Sample size

The sample size calculation assumes that all randomized participants are to be followed up for 5 years unless participants dropped out from the study for various reasons (lack of efficacy, adverse events, abnormal laboratory results, lost to follow-up, etc.). The simulations showed that, assuming an annual initial treatment failure rate of 3% per annum over 3 years in the metformin monotherapy arm [10], incorporating a 10% initial failure rate after 6 months in each treatment arm [attributable to some participants with baseline HbA$_{1c}$ ≥ 58 mmol/mol (7.0%)], 1000 participants per treatment arm would be sufficient to detect a hazard-ratio of 0.75 between vildagliptin + metformin and metformin alone (corresponding to a risk reduction rate of 25% in the vildagliptin + metformin group vs. metformin alone) with approximately 66% power and a one-sided significance level of 0.0125 (corresponding to a two-sided test at 0.025). The sample size of 1000 participants per arm will provide approximately 66% power to detect a difference of 0.08 in the rate of loss in glycaemic control (i.e. mean slopes of HbA$_{1c}$ over time estimated from the random coefficient mixed model) at a one-sided alpha level of 0.0125, assuming the common standard deviation of the mean slopes on both arms is 0.6.

Power to reject the intersection null hypothesis for both primary endpoints is calculated assuming a multiple testing procedure by Hochberg and Benjamini [9]. Given that the study is considered as a success if either of the two

hypotheses on the two primary efficacy variables is rejected, and that the marginal power is approximately 77% and 84% for the time to failure and the rate of glycaemic control over time endpoints at a one-sided alpha of 0.025, respectively, the overall power of the study is approximately 82% at a one-sided alpha level of 0.025. This calculation used a bivariate *t*-statistic with a correlation of 0.5 for the test statistics corresponding to the two primary efficacy variables.

Discussion

Addressing the defects in insulin secretion and the increased insulin resistance with appropriate treatments early in the course of Type 2 diabetes could be more beneficial than the existing paradigm of stepwise introduction of treatments only when glycaemia deteriorates [11,12]. VERIFY's main objective is to test that hypothesis

Time-to-failure determination has often been based on a patient's glycaemia exceeding a single threshold value, with analysis by the use of survival (Kaplan–Meier) analysis [10]. Coefficient of failure analysis examines, by means of least-squares regression, the trend in deterioration with the time to failure estimated by intersection of this line through a predetermined threshold [8]. This has the advantage that HbA$_{1c}$ data can be utilized from all participants to assess rate of failure, as both the slope and the intercept can be used. A specific HbA$_{1c}$ cut-off value for insulin initiation is not specified in VERIFY because of the multinational character of the study and the existing differences in national and local recommendations about insulin treatment in Type 2 diabetes. The threshold will be nationally determined and reported. The coefficient of failure is independent of threshold levels. We aim to use both conventional Kaplan–Meier and regression analysis as co-primary analyses for durability.

The time-to-failure approach was used in the ADOPT study, which compared the durability of glycaemic control between rosiglitazone, metformin and glibenclamide [10]. In that study, the criterion for treatment failure was based on fasting plasma glucose > 10.0 mmol/l [corresponding to an HbA$_{1c}$ of approximately 64 mmol/mol (8.0%)] and, based on that criterion, the risk reduction in the cumulative incidence of treatment failure with rosiglitazone vs. metformin was approximately 30%. In VERIFY, the time to treatment failure with the vildagliptin–metformin combination vs. metformin monotherapy will be determined based on the HbA$_{1c}$ target of 53 mmol/mol (7.0%), reflecting changes in treatment guidelines [13,14].

VERIFY will also assess time to insulin with the early vildagliptin–metformin combination vs. the stepwise introduction of the two therapies. Time to insulin initiation is an important clinical endpoint. Insulin therapy is complex, expensive, has significant educational requirements, and can cause hypoglycaemia. Any systematic delay in glycaemic deterioration will have cost and healthcare provision benefits.

Pooled data from clinical trials conducted in drug-naive participants with Type 2 diabetes who received 24-week treatment with vildagliptin monotherapy have shown consistent improvements in both fasting and meal test-derived measures of β-cell function [1,2,5,6,15]. The synergistic effect of vildagliptin and metformin in increasing active GLP-1 levels may result in long-term improvement and preservation of β-cell function in people with Type 2 diabetes initiated with vildagliptin–metformin combination therapy early in the course of the disease. In VERIFY, HOMA-B will be determined in all participants and dynamic measures of β-cell function will be assessed during a standard meal test in a subgroup of participants at yearly intervals. These tests will demonstrate whether the enhancement of GLP-1 levels by the vildagliptin–metformin combination started early in the course of Type 2 diabetes would result in preservation of β-cell function. Studies with vildagliptin have suggested the possibility of extra-pancreatic effects on insulin resistance and triglyceride metabolism that have not been reported with other DPP-4 inhibitors. Vildagliptin has been shown to directly reduce overnight hepatic glucose production, leading to an additional effect on fasting plasma glucose, and to reduced lipotoxicity-induced insulin resistance [16]. VERIFY will evaluate if these extra-pancreatic effects will be maintained with long-term treatment with the vildagliptin–metformin combination.

The VERIFY study population is early in the diabetes progression and therefore at relatively low risk of micro- or macrovascular complications. VERIFY is not powered to detect differences in diabetic complications. Other trials of DPP-4 inhibitors have demonstrated, in high-risk groups, no cardiovascular differences in outcome with a study period of approximately 2 years [17,18]. However, with 2000 participants exposed for up to 5 years to the vildagliptin–metformin combination vs. metformin monotherapy, followed by the addition of vildagliptin and, eventually, insulin, it is of interest to explore for trends in the development of micro- and macrovascular complications. Therefore prognostic markers for diabetic complications such as microalbuminuria, as well as trends in cardiovascular, events will be assessed. In addition, development of microaneurysms will be assessed in a subset of participants. Results from the Diabetic Retinopathy Candesartan Trials (DIRECT) suggest that microaneurysm counts are important prognostic indicators for worsening of retinopathy [19] and that changes already occur relatively early in the disease. Any differences observed could be predictive for future risk for more advanced retinopathy or other micro- or macrovascular complications.

Conclusion

The 5-year VERIFY study will investigate if addressing the different pathophysiological defects in Type 2 diabetes mellitus by early initiation of vildagliptin–metformin combi-

nation treatment will result in lower treatment failure rate or in lower HbA$_{1c}$ progression over time, compared with metformin monotherapy, followed by the addition of a second oral anti-diabetic agent (vildagliptin). The study will also provide long-term data on β-cell function and insulin resistance, diabetic complications and the effect on health status under treatment with a vildagliptin–metformin combination.

Previous presentations

The VERIFY study design abstract has been presented at the 5th International Congress on Prediabetes and Metabolic Syndrome.

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1183

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