Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial

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Summary

Background Early treatment intensification leading to sustained good glycaemic control is essential to delay diabetic complications. Although initial combination therapy has been suggested to offer more opportunities than a traditional stepwise approach, its validity remains to be determined.

Methods Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of type 2 diabetes (VERIFY) was a randomised, double-blind, parallel-group study of newly diagnosed patients with type 2 diabetes conducted in 254 centres across 34 countries. The study consisted of a 2-week screening visit, a 3-week metformin-alone run-in period, and a 5-year treatment period, which was further split into study periods 1, 2, and 3. Patients aged 18–70 years were included if they had type 2 diabetes diagnosed within 2 years prior to enrolment, and centrally confirmed glycated haemoglobin A1c (HbA_{1c}) of 48–58 mmol/mol (6·5–7·5%) and a body-mass index of 22–40 kg/m². Patients were randomly assigned in a 1:1 ratio either to the early combination treatment group or to the initial metformin monotherapy group, with the help of an interactive response technology system and simple randomisation without stratification. Patients, investigators, clinical staff performing the assessments, and data analysts were masked to treatment allocation. In study period 1, patients received either the early combination treatment with metformin (stable daily dose of 1000 mg, 1500 mg, or 2000 mg) and vildagliptin 50 mg twice daily, or standard-of-care initial metformin monotherapy (stable daily dose of 1000 mg, 1500 mg, or 2000 mg) and placebo twice daily. If the initial treatment did not maintain HbA_{1c} below 53 mmol/mol (7·0%), confirmed at two consecutive scheduled visits which were 13 weeks apart, patients in the metformin monotherapy group received vildagliptin 50 mg twice daily in place of the placebo and entered study period 2, during which all patients received the combination therapy. The primary efficacy endpoint was the time from randomisation to initial treatment failure, defined as HbA_{1c} measurement of at least 53 mmol/mol (7·0%) at two consecutive scheduled visits, 13 weeks apart from randomisation through period 1. The full analysis set included patients who received at least one randomised study medication and had at least one post-randomisation efficacy parameter assessed. The safety analysis set included all patients who received at least one dose of randomised study medication. This study is registered with ClinicalTrials.gov, NCT01528254.

Findings Trial enrolment began on March 30, 2012, and was completed on April 10, 2014. Of the 4524 participants screened, 2001 eligible participants were randomly assigned to either the early combination treatment group (n=998) or the initial metformin monotherapy group (n=1003). A total of 1598 (79·9%) patients completed the 5-year study: 811 (81·3%) in the early combination therapy group and 787 (78·5%) in the monotherapy group. The incidence of initial treatment failure during period 1 was 429 (43·6%) patients in the combination treatment group and 614 (62·1%) patients in the monotherapy group. The median observed time to treatment failure in the monotherapy group was 36·1 (IQR 15·3–not reached [NR]) months, while the median time to treatment failure time for those receiving early combination therapy could only be estimated to be beyond the study duration at 61·9 (29·9–NR) months. A significant reduction in the relative risk for time to initial treatment failure was observed in the early combination treatment group compared with the monotherapy group over the 5-year study duration (hazard ratio 0·51 [95% CI 0·45–0·58]; p<0·0001). Both treatment approaches were safe and well tolerated, with no unexpected or new safety findings, and no deaths related to study treatment.

Interpretation Early intervention with a combination therapy of vildagliptin plus metformin provides greater and durable long-term benefits compared with the current standard-of-care initial metformin monotherapy for patients with newly diagnosed type 2 diabetes.

Funding Novartis.

Published **Online** September 18, 2019 https://doi.org/10.1016/S0140-6736(19)32131-2

See **Online/Comment** https://doi.org/10.1016/S0140-6736(19)32165-8

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Research in context

Evidence before this study

Previous studies have established that use of early glucose-lowering treatments with metformin for the management of type 2 diabetes is associated with a reduction in morbidity and mortality, and a legacy of continued benefit after 10 years. Recent short-term studies on metformin combinations with different anti-hyperglycaemic medications have suggested improvements in glycaemic outcomes but also highlighted the importance of achieving early glycaemic control within the first 12 months of diagnosis. An array of evidence confirms the progressive nature of early type 2 diabetes but also a clinical reality of inertia in therapy intensification, and thus a combination therapy approach with two classes of synergistic drugs early in the disease continuum is intuitively assumed to be more beneficial than later intensification of therapy. However, long-term glycaemic durability and clinical benefits beyond glycaemia of early combination strategies have not been investigated yet, and so cannot be recommended yet.

Added value of this study

Early intervention with a combination therapy of vildagliptin plus metformin provides greater and durable long-term benefits compared with the current standard-of-care initial metformin monotherapy for patients with newly diagnosed type 2 diabetes. The study was designed to reflect the real-world clinical practice of managing treatment-naive patients with an initial standard-of-care monotherapy, and intensifying to late combination when initial treatment fails. The early combination strategy greatly and consistently reduced the relative risk of time to initial treatment failure, but also the relative risk of time to second treatment failure when all patients were already receiving the combination therapy. Additionally, a higher proportion of patients in the early combination treatment group maintained glycated haemoglobin A_{1c} and other lower glycaemic cut-off values for the entire study duration. Both treatment approaches were equally well tolerated.

Implications of all the available evidence

VERIFY is the first study to show the long-term benefits and glycaemic durability of an early combination treatment strategy with metformin and vildagliptin compared with the current standard-of-care, late combination strategy in patients with newly diagnosed type 2 diabetes. The results reflect an enhanced understanding of the pathophysiological mechanisms underlying the progressive nature of newly diagnosed type 2 diabetes, and the expanded therapeutic armamentarium and strategy in optimisation of early diabetes management.

Introduction

Guidelines for the management of hyperglycaemia in type 2 diabetes recommend metformin as first-line pharmacological therapy,[1,2] with sequential intensification and second-line therapy only when glycaemic control (glycated haemoglobin A_{1c} [HbA_{1c}] ≤53 mmol/mol or ≤7·0%) is not achieved. However, with clinical inertia, treatment intensification is often delayed, resulting in loss of glycaemic control[3] and exposure to avoidable hyperglycaemia. The UK Prospective Diabetes Study[4] established that early treatment to lower glycaemia using metformin was associated with reduction in myocardial infarction, diabetes-related deaths, and all-cause mortality, and a legacy of continued benefit after 10 years. Recent studies[5] have highlighted the importance of achieving early glycaemic control within the first 12 months of diagnosis, as this improves long-term glycaemic durability and reduces the risk of associated complications.

One potential strategy to improve the achievement and maintenance of glycaemic control is to introduce combination therapy with two or more agents as early as possible. The rationale for this approach is based on the multiple pathophysiologic mechanisms underlying chronic hyperglycaemia,[6] and the complementary mechanisms of action of available glucose-lowering agents.[7,8] In a recent meta-analysis of 15 randomised clinical trials evaluating initial combination therapy with metformin versus metformin monotherapy in patients with untreated type 2 diabetes, Phung and colleagues[9] reported that combination therapy with metformin significantly reduced HbA_{1c}, increased attainment of HbA_{1c} below 53 mmol/mol (7·0%), and reduced fasting plasma glucose compared with metformin alone.

Despite these encouraging results, the most recent American Diabetes Association and European Association for the Study of Diabetes consensus statement[1] for the treatment of hyperglycaemia in type 2 diabetes noted that although there is some support for early combination therapy because of the greater initial reduction of HbA_{1c} compared with metformin alone, evidence for the superiority of the strategy of early combination therapy over later combination therapy for maintaining glycaemic control is scarce.

The Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of type 2 diabetes (VERIFY) study was therefore designed as a 5-year efficacy and safety study, comparing an early combination therapy of metformin plus dipeptidyl peptidase-4 inhibitor vildagliptin with standard-of-care metformin monotherapy, defined as a traditional stepwise approach with metformin as initial therapy and vildagliptin added at the time of metformin failure. The choice of exploring the combination of a dipeptidyl peptidase-4 inhibitor with metformin is supported by glucose-dependent β-cell stimulation by vildagliptin[7] and concomitant insulin sensitisation by metformin,[10] as well as the established favourable safety profile of both drugs.[7,11]

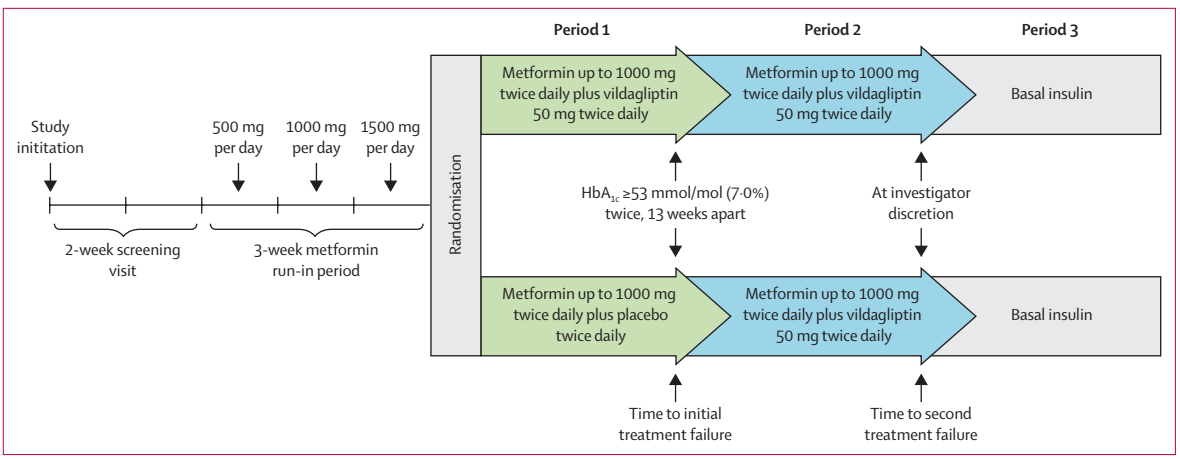


Figure 1: **Study design**
Adapted from Del Prato and colleagues.[12] The duration of period 1 can differ between the two treatments. HbA_{1c}=glycated haemoglobin A_{1c}.

Methods

Study design and participants

The VERIFY study design has been previously reported.[12] Briefly, VERIFY was a randomised, double-blind, parallel-group study of newly diagnosed patients with type 2 diabetes conducted in 254 centres across 34 countries. The study consisted of a 2-week screening visit, a 3-week metformin-alone run-in period, and a 5-year treatment period, which was further split into study periods 1, 2, and 3. During the 5-year treatment period, treatment was initially intensified when loss of glycaemia occurred and thereafter when clinically indicated, at the discretion of study investigators (figure 1).

The study protocol was approved by the local ethics committees of all study sites and all patients provided written informed consent for participation in the trial. The study was designed and carried out in accordance with International Conference on Harmonisation Tripartite Guidelines for Good Clinical Practice[13] and according to the ethical principles of the Declaration of Helsinki, and was overseen by an independent data monitoring committee.

The trial enrolled individuals aged 18–70 years with type 2 diabetes, diagnosed within 2 years as per local diagnostic criteria, with centrally confirmed HbA_{1c} of 48–58 mmol/mol (6·5–7·5%) and body-mass index (BMI) of 22–40 kg/m². Only patients who received appropriate lifestyle modification advice before enrolment, including diet counselling and exercise training, were included in the study. Individuals were excluded if they were receiving glucose-lowering treatment (except metformin ≤2000 mg daily within 1 month prior to the first screening visit) within 3 months prior to screening, or for more than 3 consecutive months or a combined total of more than 3 months in the past 2 years. Individuals were also excluded if they were using any weight-loss medications within 3 months prior to screening, had chronic liver disease or ongoing congestive heart failure (New York Heart Association Functional Classification III–IV), or were pregnant or nursing.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio either to the early combination treatment group or to the initial metformin monotherapy group, with the help of an interactive response technology system (Cenduit Interactive Response Technology, version 1.48.1; Durham, NC, USA) and simple randomisation without stratification. Patients, investigators, clinical staff performing the assessments, and data analysts were masked to treatment allocation. For the study period 1, patients in the monotherapy group received a placebo in addition to the existing stable dose of metformin. Patients in study periods 2 and 3 were masked for the use of combination therapy. The use of insulin in study period 3 was open label (figure 1).

Procedures

After the 2-week screening visit, all eligible participants entered a run-in period of metformin up-titration (targeting 1500 mg per day or maximum tolerated dose). At the end of the run-in period, participants who were able to tolerate at least 1000 mg per day of metformin entered study period 1 and were randomly assigned to receive either the early combination treatment with metformin (stable daily dose of 1000 mg, 1500 mg, or 2000 mg) and vildagliptin 50 mg twice daily, or standard-of-care initial metformin monotherapy (stable daily dose of 1000 mg, 1500 mg, or 2000 mg) and placebo twice daily (figure 1). All doses of metformin (500 mg tablet form) and vildagliptin (50 mg tablet form) were administered orally twice daily, as single pills. Dose adjustment of metformin in both treatment groups was permitted during the first 4 weeks in the trial, to allow adjustment to a dose of 2000 mg per day or the maximum tolerable dose of at least 1000 mg per day post randomisation. No adjustment was allowed afterwards.

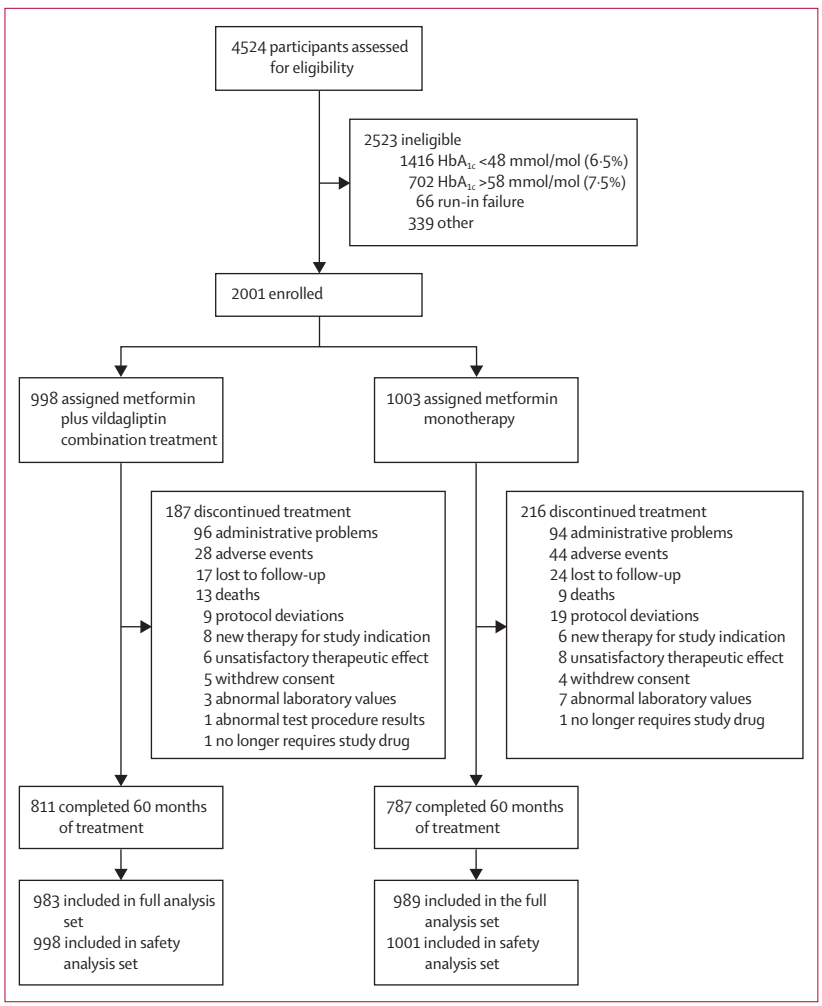


Figure 2: **Trial profile**
HbA_{1c}=glycated haemoglobin A_{1c}.

HbA_{1c} was measured every 3 months. If the initial treatment did not maintain HbA_{1c} below 53 mmol/mol (7·0%), confirmed at two consecutive scheduled visits which were 13 weeks apart, patients in the metformin monotherapy group received vildagliptin 50 mg twice daily in place of the placebo and entered study period 2, during which all patients received the combination therapy. Patients in both groups received vildagliptin in a medication pack designed differently from the vildagliptin or placebo packs used in period 1. At study period 3, rescue therapy with insulin was added to the metformin and vildagliptin combination therapy, to maintain glycaemic control in patients as per local diabetes treatment guidelines and as per investigator discretion. Patients discontinued study treatment if an alternative glucose-lowering medication was considered by the treating physician. Study procedures were completed every 13 weeks when participants visited the study site.[12] Safety assessments were completed at every study visit and included collection of all adverse events and serious adverse events. A cardiovascular adjudication committee was established to adjudicate the incidence of macrovascular events.

Outcomes

The primary efficacy endpoint was the time from randomisation to initial treatment failure, defined as HbA_{1c} measurement of at least 53 mmol/mol (7·0%) at two consecutive scheduled visits, 13 weeks apart from randomisation through period 1 (the earliest possible failure time is 6 months).[14] The four secondary endpoints were: progression of HbA_{1c} after the start of period 2 to the end of period 2 assessed by rate of loss in glycaemic control over time, both by threshold (second treatment failure) and slope of glycaemia; progression of fasting plasma glucose over time assessed by estimated annualised slope; change in HbA_{1c} based on baseline characteristics; and safety and tolerability. Exploratory endpoints included analysis of cardiovascular outcomes as assessed by time to first adjudicated macrovascular event, including cardiovascular death, non-fatal myocardial infarction or stroke, or hospital admission for heart failure. The findings from period 1 and period 2 of the study are presented here. Findings from period 3 (figure 1) are part of the secondary analysis, which will be presented elsewhere.

Statistical analysis

The statistical analysis plan with one primary efficacy endpoint was finalised and published prior to unlocking treatment codes for analysis.[14] A specific order of analysis was redefined for the analysis approach in the updated statistical analysis plan in order to avoid methodological duplication and potential dilution of alpha spending. The planned sample size of 1000 patients per treatment approach was expected to provide an approximate 75% power to detect a risk reduction of 25% in time to initial treatment failure with the combination treatment approach, compared with monotherapy. The full analysis set included patients who received at least one randomised study medication and had at least one post-randomisation efficacy parameter assessed. The safety analysis set included all patients who received at least one dose of randomised study medication.

Comparability of the two treatment approaches was assessed by demographic and baseline characteristics. The primary efficacy endpoint of time to initial treatment failure was measured in the full analysis set with a Cox proportional hazards regression model that included treatment approach and geographical region as factors and baseline HbA_{1c} as a covariate. The time to second treatment failure during period 2 was measured in the full analysis set using the same Cox regression model. Kaplan-Meier estimates for cumulative probability of initial and second treatment failure over time were assessed. In simple terms, for each treatment strategy, the first treatment failure is defined as two consecutive

	Combination therapy group (n=998)	Monotherapy group (n=1003)
Sex		
Female	545 (54·6%)	515 (51·3%)
Male	453 (45·4%)	488 (48·7%)
Age (years)		
Mean	54·1 (9·5)	54·6 (9·2)
Median	55 (48–62)	56 (49–62)
<51	372 (37·3%)	335 (33·4%)
51–59	297 (29·8%)	330 (32·9%)
>59	329 (33·0%)	338 (33·7%)
Race		
Caucasian	605 (60·6%)	612 (61·0%)
Black	26 (2·6%)	23 (2·3%)
Asian	186 (18·6%)	187 (18·6%)
Native American	103 (10·3%)	107 (10·7%)
Other	78 (7·8%)	74 (7·4%)
Ethnicity		
Hispanic or Latino	268 (26·9%)	277 (27·6%)
Chinese	28 (2·8%)	25 (2·5%)
Indian (subcontinent)	94 (9·4%)	91 (9·1%)
Mixed ethnicity	0	2 (0·2%)
Other	608 (60·9%)	608 (60·6%)
Median duration of type 2 diabetes (months)	3·3 (1·0–9·8)	3·4 (0·9–10·4)
HbA_{1c} (mmol/L; %)*		
N	996	1003
Mean	50·0 (4·4); 6·7 (0·4)	50·0 (5·5); 6·7 (0·5)
Median	50·0 (46·0–53·0); 6·7 (6·4–7·0)	50·0 (46·0–53·0); 6·7 (6·4–7·0)
<53 mmol/mol (7·0%)	772 (72·3%)	705 (70·3%)
≥53 mmol/mol (7·0%)	274 (27·5%)	298 (29·7%)
Fasting plasma glucose (mmol/L)*		
N	996	1003
Median	6·9 (6·1–7·8)	6·9 (6·2–7·9)
BMI (kg/m^2)		
Mean	31·2 (4·8)	31·0 (4·7)
Median	30·9 (27·5–34·8)	30·6 (27·4–34·5)
<30	428 (42·9%)	447 (44·6%)
≥30	570 (57·1%)	556 (55·4%)
Baseline eGFR (mL/min per 1·73 m^2)†		
Normal (≥90)	432 (43·3%)	444 (44·3%)
Mild (60–<90)	529 (53·0%)	521 (51·9%)
Moderate (30–<60)	35 (3·5%)	37 (3·7%)
Severe (<30)	0	1 (0·1%)
Median weight (kg)	85·0 (72·8–97·3)	84·0 (72·0–97·0)
Current smoker		
Yes	154 (15·4%)	136 (13·6%)
No	844 (84·6%)	867 (86·4%)

Data are n (%), mean (SD), or median (IQR). Baseline refers to randomisation visit. HbA_{1c}=glycated haemoglobin A_{1c}. BMI=body-mass index. eGFR=estimated glomerular filtration rate. *Baseline values were obtained on screening (day 1) or at a later visit (scheduled or unscheduled) if the day 1 measurements were missing. Two patients in the combination therapy group did not have baseline HbA_{1c} and fasting plasma glucose measurements on or prior to randomisation. †Baseline eGFR was calculated using the Modification of Diet in Renal Disease Study equation. Serum creatinine and bodyweight measurements were obtained on day 1 or at a later visit (scheduled or unscheduled) if the day 1 measurements were missing.

Table 1: **Baseline characteristics of the study population**

values of HbA_{1c} of at least 53 mmol/mol (7·0%) and the second treatment failure as two further consecutive values of HbA_{1c} of at least 53 mmol/mol (7·0%). All patients contributed to the Kaplan-Meier comparator in each group. The monotherapy comparator group comprised patients with one treatment failure (in period 1) who were receiving the vildagliptin combination in period 2, as well as those on metformin monotherapy without treatment failure in period 1. Subgroup analyses for time to initial treatment failure were done using similar Cox regression analyses and treatment-by-subgroup interaction was assessed.

Mean HbA_{1c} values and change from baseline by treatment approach and visit were evaluated. The proportion of patients with HbA_{1c} below 53 mmol/mol (7·0%), 48 mmol/mol (6·5%), and 42 mmol/mol (6·0%) were assessed over time during the study. Loss of glycaemic control, assessed by the annualised slope of HbA_{1c} over time from week 26 to the end of period 1, was measured with a linear mixed effect model that included treatment approach and region as factors, baseline HbA_{1c} and time of HbA_{1c} measurement (in years) as covariates, and interaction of treatment approach by time. An unstructured covariance method was used. CIs and p values for secondary endpoints and subgroup effects have not been adjusted for multiplicity. Handling of missing data has been previously described in detail.[14] Briefly, for the primary efficacy variable, patients who prematurely discontinued during period 1 were included as no event at the time of discontinuation (ie, censored for time values at the time of discontinuation). Equally, patients remaining under glycaemic threshold or with no confirmed value above it at the next scheduled visit were included as no event and only censored for time during the last study visit. When assessing the primary endpoint, available HbA_{1c} values were used without imputation for missing values. For the analysis of second treatment failure, patients remaining in period 1 contributed to the percentage of patients without treatment failure, and for those with treatment failure in period 1 but not in period 2, time from randomisation to the end of period 2 was calculated as no event (censored for time).

Significance in the analyses was established on the basis of a two-sided 0·05 significance level (equivalent to a one-sided 0·025 significance level). Analysis details of demographic and background data as well as safety data

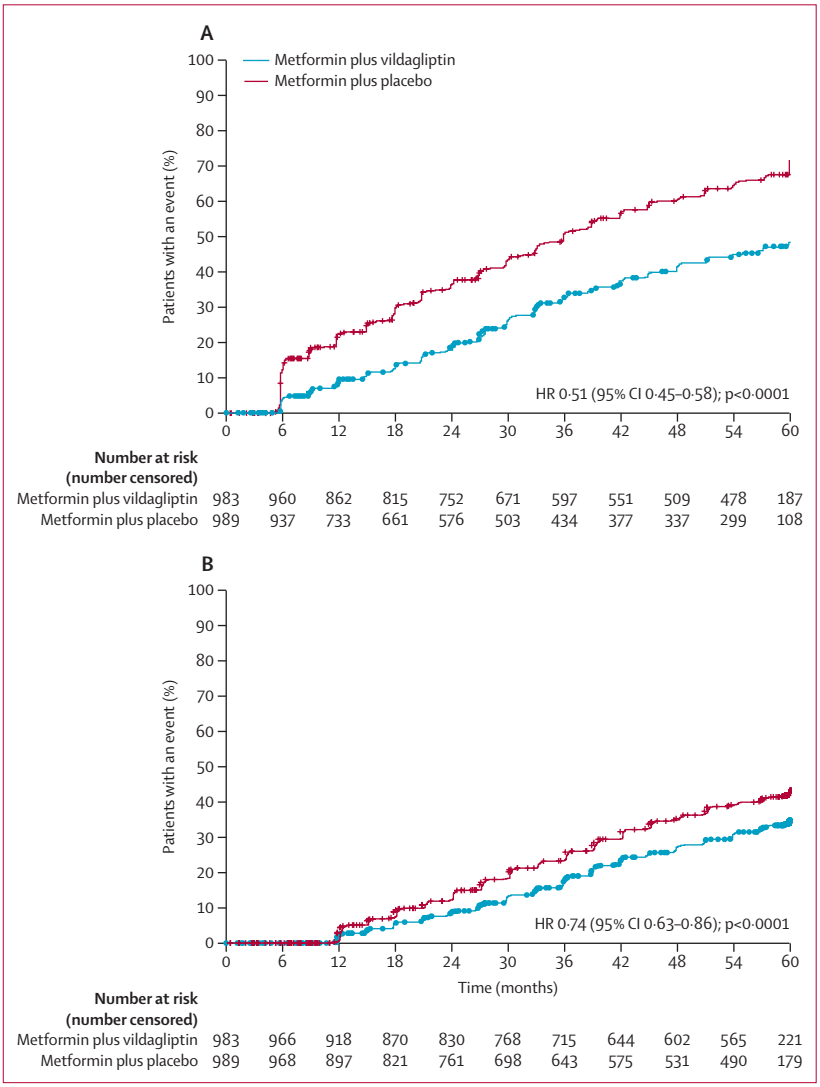


Figure 3: **Time to treatment failure**
(A) Cumulative probability of initial treatment failure. (B) Cumulative probability of second treatment failure. HRs are based on Cox regression analysis. HR=hazard ratio.

See Online for appendix

were summarised and provided in the appendix (pp 30–32). Adverse events were summarised as number and percentage of patients having any adverse event by treatment group and in each primary system organ class. Hypoglycaemic events, microvascular and macrovascular complications were assessed separately. Time to first adjudicated macrovascular events was assessed using the Cox regression model and all suspected macrovascular events were subject to adjudication. The incidence of neoplasms was compared using the χ^2 test. The statistics program used for analyses was SAS (versions 9.2 and 9.4; Cary, NC, USA). This study is registered with ClinicalTrials.gov, NCT01528254.

Role of the funding source

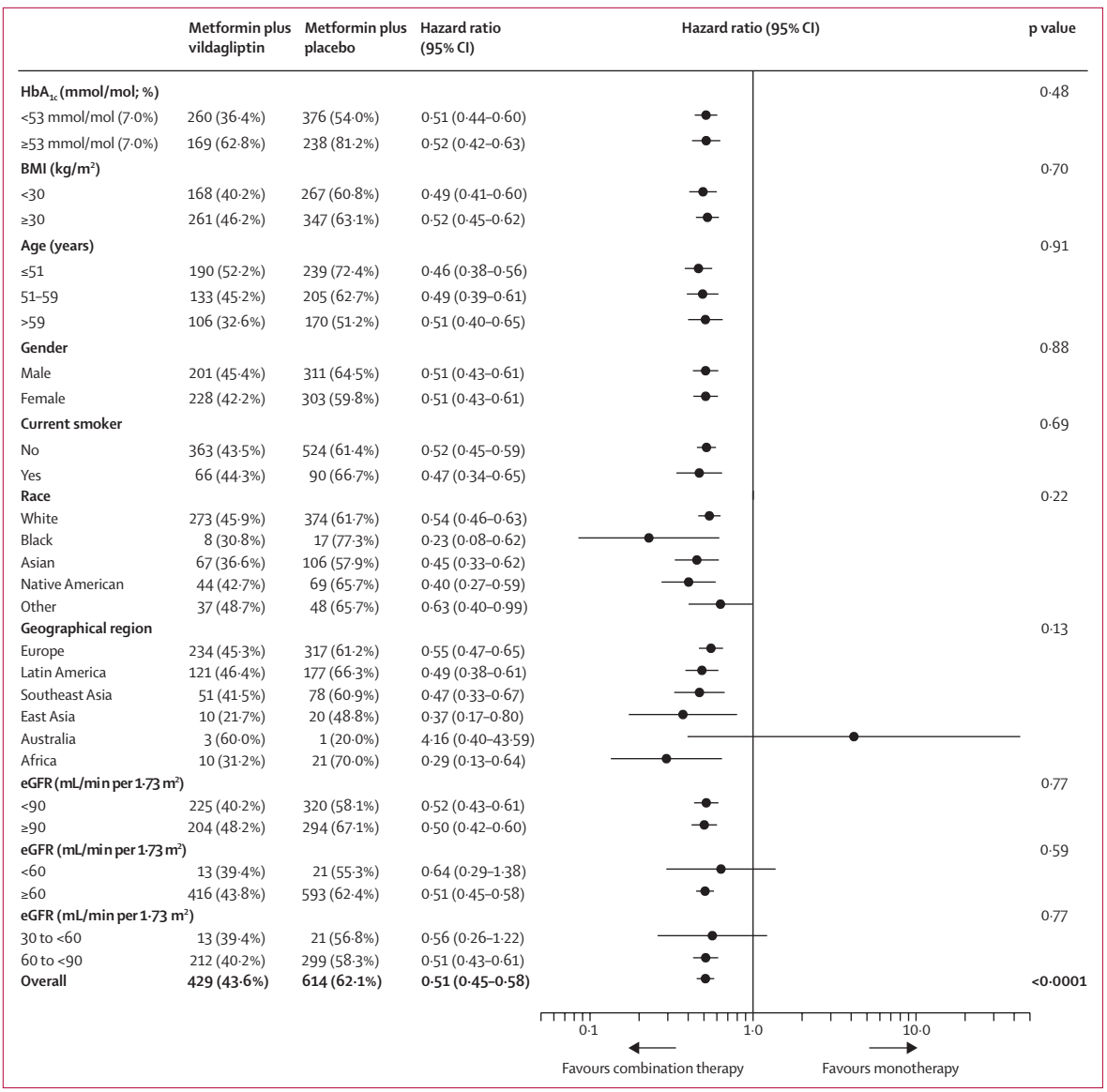
Novartis funded the study, which was led by an international steering committee who designed the study in collaboration with the sponsor. The sponsor was responsible for the trial monitoring, data collection, reporting, and analysis plan defined in the protocol and refined in the prespecified statistical analysis plan.[14] Scientists employed by the funder were on the steering committee and contributed to trial design, trial implementation, and data interpretation. All authors and the sponsor jointly made the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the integrity of the data and the decision to submit for publication.

Results

Trial enrolment began on March 30, 2012, and was completed on April 10, 2014. The last trial visit was on April, 2019. Of the 4524 participants screened, 2001 eligible participants[15] were randomly assigned to either the early combination treatment group (n=998) or the initial metformin monotherapy group (n=1003; figure 2). The most common reasons for study exclusion were HbA_{1c} outside the protocol-defined range and metformin intolerance prior to up-titration. A total of 1598 (79·9%) patients completed the 5-year study: 811 (81·3%) in the early combination therapy group and 787 (78·5%) in the monotherapy group (figure 2). The median follow-up time was 59·8 months (IQR 59·4–60·0] for patients in the early combination treatment group and 59·8 months (IQR 59·3–60·0) for patients in the monotherapy group. 17 patients in the combination treatment group and 24 in the monotherapy groups were lost to follow-up.

Baseline demographic and clinical characteristics were similar between treatment groups. Mean age of the patients at randomisation was 54·1 (SD 9·5) years in the combination treatment group and 54·6 (9·2) years in the monotherapy group, and mean BMI was 31·2 (SD 4·8) kg/m² in the combination treatment group and 31·0 (4·7) kg/m² in the monotherapy group. Mean HbA_{1c} at randomisation was 50·0 (SD 4·4) mmol/mol in the combination treatment group and 50·0 (5·5) mmol/mol in the monotherapy group (table 1). 937 (93·9%) of 998 patients in the combination treatment group and 937 (93·4%) of 1003 patients in the monotherapy group had concomitant medications equally administered during the study for management of prevalent concomitant conditions. A similar proportion of patients in both treatment groups (405 [40·6%] in the combination treatment group and 412 [41·1%] in the monotherapy group) received metformin less than 4 weeks prior to study entry (appendix p 33). A few female patients (one in the combination treatment group and three in the monotherapy group) received short-term insulin because of gestational diabetes prior to having been diagnosed with type 2 diabetes.

The incidence of initial treatment failure during period 1 was 429 (43·6%) patients in the combination



	Metformin plus vildagliptin	Metformin plus placebo	Hazard ratio (95% CI)	p value
HbA_{1c} (mmol/mol; %)				0·48
<53 mmol/mol (7·0%)	260 (36·4%)	376 (54·0%)	0·51 (0·44–0·60)	
≥53 mmol/mol (7·0%)	169 (62·8%)	238 (81·2%)	0·52 (0·42–0·63)	
BMI (kg/m²)				0·70
<30	168 (40·2%)	267 (60·8%)	0·49 (0·41–0·60)	
≥30	261 (46·2%)	347 (63·1%)	0·52 (0·45–0·62)	
Age (years)				0·91
≤51	190 (52·2%)	239 (72·4%)	0·46 (0·38–0·56)	
51–59	133 (45·2%)	205 (62·7%)	0·49 (0·39–0·61)	
>59	106 (32·6%)	170 (51·2%)	0·51 (0·40–0·65)	
Gender				0·88
Male	201 (45·4%)	311 (64·5%)	0·51 (0·43–0·61)	
Female	228 (42·2%)	303 (59·8%)	0·51 (0·43–0·61)	
Current smoker				0·69
No	363 (43·5%)	524 (61·4%)	0·52 (0·45–0·59)	
Yes	66 (44·3%)	90 (66·7%)	0·47 (0·34–0·65)	
Race				0·22
White	273 (45·9%)	374 (61·7%)	0·54 (0·46–0·63)	
Black	8 (30·8%)	17 (77·3%)	0·23 (0·08–0·62)	
Asian	67 (36·6%)	106 (57·9%)	0·45 (0·33–0·62)	
Native American	44 (42·7%)	69 (65·7%)	0·40 (0·27–0·59)	
Other	37 (48·7%)	48 (65·7%)	0·63 (0·40–0·99)	
Geographical region				0·13
Europe	234 (45·3%)	317 (61·2%)	0·55 (0·47–0·65)	
Latin America	121 (46·4%)	177 (66·3%)	0·49 (0·38–0·61)	
Southeast Asia	51 (41·5%)	78 (60·9%)	0·47 (0·33–0·67)	
East Asia	10 (21·7%)	20 (48·8%)	0·37 (0·17–0·80)	
Australia	3 (60·0%)	1 (20·0%)	4·16 (0·40–43·59)	
Africa	10 (31·2%)	21 (70·0%)	0·29 (0·13–0·64)	
eGFR (mL/min per 1·73 m²)				0·77
<90	225 (40·2%)	320 (58·1%)	0·52 (0·43–0·61)	
≥90	204 (48·2%)	294 (67·1%)	0·50 (0·42–0·60)	
eGFR (mL/min per 1·73 m²)				0·59
<60	13 (39·4%)	21 (55·3%)	0·64 (0·29–1·38)	
≥60	416 (43·8%)	593 (62·4%)	0·51 (0·45–0·58)	
eGFR (mL/min per 1·73 m²)				0·77
30 to <60	13 (39·4%)	21 (56·8%)	0·56 (0·26–1·22)	
60 to <90	212 (40·2%)	299 (58·3%)	0·51 (0·43–0·61)	
Overall	**429 (43·6%)**	**614 (62·1%)**	**0·51 (0·45–0·58)**	**<0·0001**

Figure 4: **Subgroup analysis of time to initial treatment failure**
Hazard ratios and the associated CIs and p values were obtained from a Cox proportional hazards model containing terms for treatment approach, geographical region, and baseline HbA_{1c}. Significance was established on the basis of a two-sided 0·05 significance level. The treatment-by-subgroup interaction p values are provided for tests of homogeneity of between-group differences among subgroups, with no adjustment for multiple testing. The p value for treatment comparison in the overall population is also provided. HbA_{1c}=glycated haemoglobin A_{1c}. BMI=body-mass index. eGFR=estimated glomerular filtration rate.

treatment group and 614 (62·1%) patients in the monotherapy group. The median observed time to treatment failure in the monotherapy group was 36·1 (IQR 15·3–not reached [NR]) months, while the median time to treatment failure time for those receiving early combination therapy could only be estimated to be beyond the study duration at 61·9 (29·9–NR) months. A significant reduction in the relative risk (RR) for time to initial treatment failure was observed in the early combination treatment group compared with the monotherapy group over the 5-year study duration (hazard ratio [HR] 0·51 [95% CI 0·45–0·58]; p<0·0001; figure 3A). The RR for time to second treatment failure during period 2 was also significantly reduced in the combination treatment group compared with monotherapy group (HR [95% CI]: 0·74 [0·63, 0·86], p<0·0001) (figure 3B). There was also a consistently lower HbA_{1c} observed over time with the combination treatment group compared with the monotherapy group throughout the study duration, with a greater proportion of patients in the early combination treatment group with HbA_{1c} below 53 mmol/mol (7·0%), 48 mmol/mol (6·5%), and 42 mmol/mol (6·0%; appendix p 39). Subgroup analyses for time to initial treatment failure revealed a consistently

	Combination therapy group (n=998)	Monotherapy group (n=1001)
Arthralgia	100 (10·0%%)	94 (9·4%)
Hypoglycaemic events	13 (1·3%)	9 (0·9%)
Benign, malignant, and unspecified neoplasms (including cysts and polyps)	62 (6·2%)	54 (5·4%)
Pancreatic cancer	3 (0·3%)	2 (0·2%)*
Prostate cancer	6 (0·6%)	0
Breast cancer	3 (0·3%)	1 (0·1%)
Ovarian cyst	1 (0·1%)	4 (0·4%)
Pancreatitis and other related events		
Pancreatic cyst	0	2 (0·2%)
Pancreatic disorder	2 (0·2%)	0
Pancreatic mass	1 (0·1%)	0
Pancreatic pseudocyst	1 (0·1%)	0
Pancreatic steatosis	2 (0·2%)	2 (0·2%)
Pancreatitis	2 (0·2%)	0
Acute pancreatitis	1 (0·1%)	2 (0·2%)
Chronic pancreatitis	1 (0·1%)	1 (0·1%)
Pancreatic infection	0	1 (0·1%)
Pancreatic enzymes increased	0	1 (0·1%)
Urinary tract infection	73 (7·3%)	71 (7·1%)

Data are n (%). Patients with multiple adverse events under one treatment approach were counted only once in the adverse event category for that treatment approach. *Fatal outcome for both events.

Table 2: **Adverse events in the study population**

significant benefit of early combination treatment over monotherapy for the primary outcome (figure 4). This benefit was shown for predefined subgroups of HbA_{1c}, BMI, age, gender, smoking status, race, geographical regions, and estimated glomerular filtration rate (eGFR) categories, with no evidence of heterogeneity.

Glycaemic control also deteriorated more rapidly in the monotherapy group than in the early combination treatment group. The difference in adjusted mean rate of change in HbA_{1c} per year (coefficient of failure) was –0·02 (SD 0·01; 95% CI –0·05 to 0·00; two-sided p=0·085) at the end of period 1. Over the 5-year study, mild reduction in bodyweight from baseline was reported in patients treated with early combination therapy as well as metformin monotherapy (appendix p 40).

The trial was not powered to assess differences in cardiovascular outcomes, but all potential cardiovascular events were subject to adjudication. Over the 5-year study duration, a numerical reduction in the risk of time to first adjudicated macrovascular event was seen with the early combination treatment approach compared with initial monotherapy (HR 0·71 [95% CI 0·42–1·19]; two-sided p=0·19; appendix p 41). Adjudicated first macrovascular events occurred in 24 (2·4%) patients in the combination treatment group and in 33 (3·3%) patients in the monotherapy group. The absolute cumulative number of recurrent events by treatment approach was low (30 in the combination treatment group *vs* 44 in the monotherapy group).

The overall safety and tolerability profile was similar between treatment approaches, with no unexpected safety findings reported. The incidence of adverse events and serious adverse events, excluding the cardiovascular events described above but including those considered to be related to the study drug, were similar between the treatment groups (833 [83·5%] had adverse events and 166 [16·6%] had serious adverse events in the combination treatment group, 833 [83·2%] had adverse events and 183 [18·3%] had serious adverse events in the monotherapy group; appendix pp 35–38). The incidence of hypoglycaemic events was low, all of them were grade 1 and similar between groups (13 [1·3%] in the combination treatment group, nine [0·9%] in the monotherapy group). The incidence of events related to pancreatitis (four [0·4%] in the combination treatment group, three [0·3%] in the monotherapy group) and pancreatic carcinoma (three [0·3%] in the combination treatment group, two [0·2%] in the monotherapy group) was also low in both groups. The incidence of neoplasms was low and not significantly different between treatment groups (62 [6·2%] in the combination treatment group *vs* 54 [5·4%] in the monotherapy group; p=0·43; table 2). No bullous pemphigoids were reported. Elevated liver function tests were also rare and balanced between groups. Overall, the 4% annualised rate of discontinuation was low compared with the anticipated rate of 11%, and similar between the groups (4·1% in the combination treatment group, 5·3% in the monotherapy group). 22 deaths were reported during this study (13 in the combination treatment group, nine in the monotherapy group), none of which were considered related to the study drugs (figure 2).

Discussion

The VERIFY study has shown that early combination treatment with metformin and vildagliptin improves glycaemic durability in patients with type 2 diabetes compared with standard-of-care initial metformin monotherapy followed by sequential combination with vildagliptin. Early combination treatment significantly reduced the probability of initial treatment failure, the time to second treatment failure, and the time to treatment failure compared with monotherapy throughout the 5-year study duration. Secondary glycaemic parameters (loss of glycaemic control) support the durability of the combination approach. The longer time to second treatment failure in the combination treatment group showed that our observations were not simply the result of comparing a therapy of two drugs with a therapy of one, since all patients entering period 2 received the combination therapy. Finally, the early combination treatment was safe and well tolerated.

VERIFY is the first study to examine long-term clinical benefits of an early combination treatment strategy

and provides a step forward with respect to previous approaches. What was considered as intensive therapy in the UK Prospective Diabetes Study[4] is the comparator treatment strategy in VERIFY,[12] reflecting enhanced understanding of the pathophysiological mechanisms underlying the progressive nature of type 2 diabetes and the expanded therapeutic armamentarium.

The issue of two drugs versus one for glycaemic control requires careful consideration. It is expected that failure onto further therapy would occur more frequently with a monotherapy strategy, so this trial was established to assess further measures of failure. This has been achieved with the analysis of the second treatment failure, essentially the point of equipoise between the strategy of metformin monotherapy with vildagliptin added as necessary, versus an initial combination therapy strategy. In the monotherapy group some patients did not receive the rescue onto combination therapy since their glycaemia did not deteriorate, so they contributed to the percentage of non-failures, and thus introduced no bias. A secondary endpoint was the slope of HbA_{1c} deterioration from week 26, which showed a lower slope of deterioration for those receiving the combination therapy. The clinical efficacy of vildagliptin alone and in combination with metformin is well established from shorter-term studies;[11,16–20] these findings are supported by the significantly increased glycaemic durability seen with combination treatment in VERIFY, an effect that was maintained throughout its preplanned 5-year duration. This could be attributed to the complementary mechanism of action of metformin and the dipeptidyl peptidase-4 inhibitor vildagliptin, in newly diagnosed patients with relatively preserved β-cell function. The glycaemic durability observed in patients receiving the early combination treatment could be the result of both concomitant insulin sensitisation by metformin[10] and glucose-mediated modulation of insulin and glucagon secretion by vildagliptin.[7,8]

Obviously, early treatment initiation with a synergistic combination of vildagliptin and metformin is one of the many possible treatment combinations. Results from the ongoing GRADE study comparing the durability of different agents in combination with metformin will add evidence to the proposed early combination treatment strategy, although the population has a longer duration of diabetes and higher baseline HbA_{1c}.[21]

A potential favourable effect of early combination treatment was supported by the meta-analysis of Phung and colleagues.[9] Our results confirm the clinical benefits of the policy of early combination approach in patients with newly diagnosed type 2 diabetes, indicating that with careful selection of glucose-lowering agents, glycaemic control can be achieved with no added hypoglycaemia risk and no effect on bodyweight. Of note, the slight decrease in bodyweight was apparent in both groups of the study over the 5-year follow-up. Similarly, no increased risk of hypoglycaemia was observed despite persistent good glycaemic control with the combination treatment, as expected with the specific mechanisms of action of metformin and vildagliptin.[11,16] The early combination treatment was well tolerated, with no signal for adverse events of special interest, in line with previous evidence from vildagliptin studies.[22,23] As part of safety surveillance, cardiovascular events were monitored and adjudicated. Although the VERIFY study was not designed or powered to assess the effect of combined treatment on cardiovascular outcomes, an imbalance favouring the early combination treatment was nevertheless observed. Such an observation, obtained in a low-risk population, is at odds with the neutral cardiovascular effect reported in cardiovascular outcomes trials of patients with long-standing type 2 diabetes and much greater cardiovascular risk. Our observation of cardiovascular outcomes must be interpreted with caution, particularly in the context of the current debate regarding the ultimate goals of diabetes management beyond glycaemia[24,25] with cardiovascular benefits reported with modern glucose-lowering therapies.[26,27] Only careful patient follow-up and adequately powered, specific cardiovascular follow-up studies will be able to prospectively assess cardiovascular events in an early primary prevention population with newly diagnosed type 2 diabetes and low HbA_{1c}. The reasons for a potential early cardiovascular benefit beyond glycaemia also remain to be determined. Recent meta-analysis and claims database studies[28–30] have suggested that early use and synergistic effects of dipeptidyl peptidase-4 inhibitors in combination with metformin could have a potential moderating effect on cardiovascular outcomes.

The findings of VERIFY support and emphasise the importance of achieving and maintaining early glycaemic control. In the UK Prospective Diabetes Studies,[4,31] early treatment intensification was associated with a legacy effect, whereby the reduction in vascular complications in the intensive group was maintained or strengthened over 10 years after study completion. In the Diabetes and Aging epidemiology study,[5] HbA_{1c} of at least 6·5% for the first year following diagnosis was associated with worse outcomes (increasing microvascular events and mortality risk) over the subsequent 10 years of follow-up. However, durable HbA_{1c} values below 6·5% are unlikely to be achieved with monotherapy alone. Real-world evidence has shown how delayed treatment intensification after monotherapy failure results in increasing time spent with avoidable hyperglycaemia, raising a crucial barrier to optimised care.[3] The durable effect we observed with an early combination strategy therefore provides initial support for such an approach as an effective way to combat clinical inertia.

The strengths of this study include the diverse, geographically distributed and multiethnic population (with a low HbA_{1c} cutoff) and long-term duration.[15] The adherence rates were high, with no major safety issues reported. Glycaemic durability observed in this

heterogeneous study population ensures applicability of clinical benefits to almost the entire population with newly diagnosed type 2 diabetes. Potential limitations include the HbA_{1c} cutoff selected for study entry and the assessment of only one treatment combination.

In conclusion, the strategy of an early combination treatment approach with vildagliptin plus metformin in patients with newly diagnosed type 2 diabetes significantly and consistently improves long-term glycaemic durability compared with metformin monotherapy. Our results indicate that long-term clinical benefits can be achieved more frequently and without tolerability issues with early combination treatment compared with standard-of-care metformin monotherapy.

For the **Good Publication Practice guidelines** see http://www.ismpp.org/gpp3

Contributors

As academic steering committee members, SDP, MS, and DRM contributed to study design and data collection. As employees of the sponsor, PMP and PP contributed to trial design, and with YTC to data analysis. All authors contributed to the trial conduct, oversight, interpretation of the results, and helped to develop and finalise the statistical analysis plan and manuscript. All authors had full access to all data and had final responsibility for the decision to submit for publication.

Declaration of interests

DRM has served on advisory boards or as a consultant for Novo Nordisk, GlaxoSmithKline, Novartis, Eli Lilly, Sanofi-Aventis, Janssen, and Servier. He is currently the President of the European Association for the Study of Diabetes and has given lectures for Novo Nordisk, Servier, Sanofi-Aventis, Eli Lilly and Company, Novartis, Janssen, and Aché Laboratories. MS has received speaker's honoraria and consulting fees from Novartis, Novo Nordisk, AstraZeneca, Aegerion, Eli Lilly and Company, and Boehringer Ingelheim. PMP and PP and YTC are employed by and own stocks in Novartis. SDP serves or has served on advisory boards for AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, GlaxoSmithKline, Hanmi Pharmaceuticals, Intarcia, Janssen Pharmaceutics, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi, Servier and Takeda; serves or has served on the speakers' bureau for AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Janssen Pharmaceutics, Merck Sharp & Dohme, Novartis, Novo Nordisk, Sanofi and Takeda; and has received research support from Boehringer Ingelheim, Merck Sharp & Dohme, and Novartis.

Data sharing

Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided is anonymised to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. The criteria and process for trial data availability are described online.

For the **trial data availability** see https://www.clinicalstudydatarequest.com/

Acknowledgments

This trial was funded by Novartis Pharma. We gratefully acknowledge design and scientific contributions during early stages of the study by James Foley, Wolfgang Kothny, and Plamen Kozlovski, and statistical support by Giovanni Bader, Jackie Han, and Ranjan Tiwari, at Novartis. The independent data monitoring committee members were Prof Chantal Mathieu as Chairperson (Catholic University Hospital, Leuven, Belgium), Prof Baptist Gallwitz (University of Tübingen, Tübingen, Germany), Prof Martin Cowie (Royal Brompton Hospital, Imperial College London, London, UK), Prof Eduard Montanya (Bellvitge University Hospital, University of Barcelona, Barcelona, Spain), and Prof Richard Stevens (University of Oxford, Oxford, UK). Cardiovascular adjudication committee members were Prof Aldo Maggioni as Chairperson (Associazione Nazionale Medici Cardiologi Ospedalieri, Firenze, Italy), Prof Georg Ertl (University Hospital Würzburg Center for Internal Medicine, Würzburg, Germany), and Apostolos Tsapas (Ippokratio General Hospital, Aristotle University, Thessaloniki, Greece). We thank Steve Aldington (Gloucestershire Hospitals NHS Foundation Trust, Gloucester, UK) for the assessment of the retinal sub-study images. The authors thank Mary-Clare Cathcart of Novartis Ireland and Sashi Kiran Goteti of Novartis Healthcare in Hyderabad, India for providing medical writing support for the manuscript, in accordance with Good Publication Practice guidelines. We are also grateful for the support of all those involved in the execution of this study. This clinical investigation could not have been carried out without the altruistic volunteering spirit of those who participated in the VERIFY study. We are grateful for their time and dedicated contribution.

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