Exploring Early Combination Strategy in Latin American Patients With Newly Diagnosed Type 2 Diabetes: A Sub-analysis of the VERIFY Study

Sergio Vencio (svencio@gmail.com)
ICF - Institute od Pharmaceutical Science https://orcid.org/0000-0001-9283-486X
Juan P Manosalva
Novartis
Chantal Mathieu
University College Leuven-Limburg: UC Leuven-Limburg
Pieter Proot
Novartis Pharma AG
Hernan Yupanqui Lozno
World Obesity Federation
Päivi M Paldánius
University of Helsinki Children's Hospital: Helsingin yliopisto Lastenklinikka

Research Article

Keywords: Early combination, Latin America, Type 2 diabetes mellitus, Vildagliptin

Posted Date: February 16th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-231231/v1

Abstract

Background: Patients with type 2 diabetes mellitus (T2DM) from Latin American countries face challenges in access to healthcare, leading to under-diagnosis, under-achievement of glycemic target, and long-term complications. Early diagnosis and treatment initiation are of paramount importance in this population due to the high prevalence of risk factors such as obesity and metabolic syndrome. The VERIFY study in patients with newly diagnosed T2DM (across 34 countries), assessed the normoglycemic durability (5 years), with early combination (EC) therapy approach versus the traditional stepwise approach of initiating treatment with metformin monotherapy (MET). Here we present the results from the VERIFY study for participants from eight countries in Latin America.

Methods: Newly diagnosed adult patients with T2DM, HbA1c 6.5%–7.5% and body-mass index (BMI) of 22–40 kg/m² were enrolled. The primary endpoint was time to initial treatment failure (TF; HbA1c ≥7.0% at two consecutive scheduled visits 13 weeks apart). Time to second TF was evaluated when patients in both groups were receiving and failing on the vildagliptin combination. Safety and tolerability were also assessed for both treatment approaches during the study.

Results: A total of 537 eligible patients (female, 58.8%) were randomly assigned to receive either EC (n=266) or MET (n=271). EC significantly reduced the relative risk of time to initial TF by 47% versus MET (HR [95% CI] 0.53 [0.4, 0.7]; p<0.0001). Overall, 46.4% versus 66.3% of patients achieved the primary endpoint in the EC and MET groups, with a median (interquartile range [IQR]) time to TF of 59.8 (27.5, not evaluable) and 33.4 (12.2, 60.1) months, respectively. The risk for time to second TF was 31% lower with EC (p<0.0092). A higher proportion of patients receiving EC maintained durable HbA1c <7.0%, <6.5%, and <6.0%. Both treatment approaches were well tolerated, and only 3.2% of participants discontinued the study due to adverse events. All hypoglycemic events (EC: n=7 and MET: n=3) were single, mild episodes and did not lead to study discontinuation.

Conclusion: Similar to the global population, long-term clinical benefits were achieved more frequently and without tolerability issues with EC versus standard-of-care MET in this Latin American sub-population.

This study is registered with ClinicalTrials.gov, NCT01528254.

Background

Diabetes presents a major health crisis in Latin American countries, being one of the leading causes of death from a chronic non-communicable disease [1]. In 2019 an estimated 32 million adults from the Latin American region had diabetes, with a regional prevalence of 9.4%. This prevalence is projected to increase by 55% in the next 25 years in this region [2]. The disproportionate increase in diabetes in Latin America compared with other Western countries can be attributed to the genetic predisposition of this regional population for various risk factors of type 2 diabetes mellitus (T2DM), such as obesity, metabolism disorder, and insulin resistance [3]. These risk factors are predominant in the Latin American

population, with 50% of adults being obese and one-third of the population having metabolic syndrome [4].

In the past decade, the trend toward an increasing incidence of T2DM has been prominent in this region among adults aged 40–60 years [4, 5]. The onset of T2DM at a younger age can result in a greater lifetime exposure to the risk of developing complications, thereby plausibly contributing to the 43.5% of diabetes-related deaths in patients under the age of 60 years [2, 4]. The high incidence of T2DM at a young age, especially among women of child-bearing potential, poses challenges related to fertility and gestational diabetes, which creates a risk cycle with childhood obesity and a long-term risk of adult obesity in the next generation [6].

Diabetes imposes a high economic burden in Latin American countries, incurring a total cost of USD 70 billion annually and constituting up to 6–24% of the annual total expenditure of the national health budgets [2]. The heterogeneity in the economic vulnerabilities towards diabetes across the region [6] might be due to inequalities in the socioeconomic aspects among countries in the Latin American region [7]. Socioeconomic conditions in Latin America present several public health challenges for diabetes care, such as low disease awareness, inadequate diagnosis, treatment and preventive measures, and limited access to healthcare facilities [6, 8, 9]. Diagnosis is often delayed as the prevalence of undiagnosed patients ranges from 10.3–50% in this region [10]. Access to treatment is also a major challenge [11], and less than 50% of patients receiving treatment achieve their glycemic targets [12]. In addition, diabetes-related complications predominate in more than 80% of patients with T2DM in this region [12].

Achieving glycemic targets early in the disease continuum leads to a legacy effect of sustained reduction in the risk of complications such as myocardial infarction, death due to any cause, and microvascular disease [13]. A meta-analysis of studies comparing early intensification using combination therapy versus monotherapy showed better glycemic control with early combination therapy [14]. The most compelling evidence to date signifying the long-term benefits of early intervention with a combination treatment over a 5-year period is available from the VERIFY study [15]. The VERIFY study aimed to determine if an early intervention approach using a combination of vildagliptin plus metformin could provide more durable glycemic and clinical benefits compared with sequentially intensified initial metformin monotherapy in treatment-naïve patients with newly diagnosed T2DM and a glycated hemoglobin (HbA1c) level of 6.5–7.5%. Here, we present a sub-analysis of the VERIFY study in patients with T2DM from eight Latin American countries.

Subjects And Methods

Study Design

VERIFY was a Phase IV, randomized, double-blind, multi-ethnic, two-arm parallel-group study including treatment-naïve patients with T2DM. Details regarding the study design have been previously published [16].

Briefly, after screening, the eligible patients entered a 3-week “run-in period” during which metformin was individually initiated and/or up-titrated. Patients who were able to tolerate a metformin dose of 1000 mg or higher were randomized 1:1 to receive either early combination (vildagliptin 50 mg plus metformin up to 1000 mg twice-daily) therapy or metformin monotherapy (up to 1000 mg with placebo twice daily) in period 1. Patients with initial loss of glycemic control (determined by two consecutive measurements of HbA1c ≥ 7.0% after randomization, 13 weeks apart), while receiving metformin monotherapy, received vildagliptin as add-on treatment during period 2. Those randomized to the early combination therapy continued to receive the same treatment. Further therapy intensification with open-label insulin in addition to the combination therapy was allowed after treatment failure in period 2, following local diabetes treatment guidelines and at the physician’s discretion (period 3). Patients receiving therapy intensification with blood glucose-lowering drugs, other than insulin in period 3, were discontinued from the study.

Participants

Adult patients with centrally confirmed HbA1c of 6.5–7.5% and body-mass index (BMI) of 22–40 kg/m² were enrolled by 53 centers in eight Latin American countries (Argentina, Brazil, Colombia, Dominican Republic, Guatemala, Mexico, Panama, and Peru).

Patients receiving glucose-lowering treatment (except metformin ≤ 2000 mg daily within one month prior to screening) or using weight-loss medications within three months prior to screening were excluded. Additionally, individuals with contraindications for use of either of the study medications, such as those with chronic liver disease or ongoing congestive heart failure (New York Heart Association Functional Classification III – IV) and those with pregnancy or lactation in progress, were excluded.

Outcomes

The primary efficacy endpoint was the time to confirmed initial treatment failure, defined as HbA1c ≥ 7.0% at two consecutive planned visits, 13 weeks apart from randomization (the earliest possible failure time is 6 months’ post-randomization) [15]. Initial treatment failure was compared between the patients receiving early combination (vildagliptin plus metformin) and metformin monotherapy.

The initial treatment failure was also compared between the two treatment groups across the various baseline subgroups including age, gender, race, HbA1c level, BMI and smoking status.

The secondary endpoints included time to second treatment failure, defined as two consecutive values of HbA1c ≥ 7.0% when all patients were receiving combination therapy; change in HbA1c over time, safety and tolerability.

Glycemic control with the two treatment approaches was evaluated over the study duration comparing proportion of patients with HbA1c below 7.0%, 6.5% and 6.0%. Changes in body weight throughout the study period was also compared between the two treatment groups.

Treatment-emergent adverse events (AEs) and serious adverse events (SAEs), including pregnancies and medically significant changes in biochemical and other laboratory parameters, were recorded per initial treatment approach throughout the study along with their severity and relationship to blinded study drug. Hypoglycemic events were separately reported. All patients were provided with a home blood glucose monitor. At the first visit, patients were trained to monitor their blood glucose as well as detect and report hypoglycemia. Apart from typical symptoms of hypoglycemia, a capillary whole blood glucose level of < 50 mg/dL (< 2.8 mM), corresponding to a plasma glucose level of < 56 mg/dL (< 3.1 mM), was considered as a hypoglycemic event. Confirmed hypoglycemic events were also classified based on their severity (G1/G2); i.e., those necessitating assistance were considered to be of Grade 2 severity.

Statistical analysis

Detailed pre-defined statistical analysis plan was published prior to the primary analysis and unblinding [17]. The time to initial and second treatment failures were measured with Cox proportional hazards regression model which included treatment approach and geographical region as factors and baseline HbA1c as a covariate. Subgroup analyses of the initial treatment failure were done using a Cox regression analyses. Cumulative probabilities of initial and second treatment failures over time were assessed using Kaplan-Meier estimates. Patients receiving at least one randomized dose of either study drug or with at least one post-randomization visit for glycemic efficacy contributed to the Kaplan-Meier comparator in each group. Safety outcomes were analyzed for all patients who received at least one dose of randomized study medication (vildagliptin or placebo). AEs were summarized as number and proportions of patients having any AE by treatment group and classified by each primary system organ class. A p value of 0.05 (2-sided) was considered significant. The statistical program used was SAS (versions 9.2 and 9.4; Cary, NC, USA).

Results

Baseline characteristics

The VERIFY global population included 2001 randomized patients [15], 537 of whom were from the Latin American region. A total of 1258 patients were screened from this region; 55.8% (n = 703) failed the screening due to HbA1c value outside of the indicated glycemic range (HbA1c < 6.5% or > 7.5%); 18 (1.4%) patients failed the run-in period (intolerant to at least 1000 mg daily metformin or not compliant). Of the patients who failed screening due to screening HbA1c value outside of the indicated glycemic range, 176 (13.9%) had HbA1c > 7.5% with an average HbA1c of 8.9%, ranging from 7.7–15.0%.

A total of 266 patients received early combination (vildagliptin plus metformin), and 271 patients received initial monotherapy. Overall, 80.8% (n = 215) of patients in the early combination and 78.6% (n = 213) of patients in initial monotherapy group completed the study. Approximately 20.3% (n = 109) of the study population discontinued the study prematurely, mostly for administrative reasons (n = 54) such as

moving to a new city/country for work or studies or general work-related burden/ unable to attend further visits.

The mean (SD) age of the Latin American study population was 52.7 (9.9) years, with a mean (SD) BMI of 31.0 (4.7) kg/m^2. The absolute weight of the patients ranged between 44.8 kg and 142.4 kg. Of the 537 study participants, 316 (58.8%) were females. One in 10 patients (10.2%, n = 55) was diagnosed with T2DM before the age of 40 years. The majority (80.8%, n = 434) of patients included were aged between 40 and 65 years at study enrollment. Among the 537 patients randomized, Native American (39%) or Caucasian (35%) participants were predominant. A total of 27.9% (n = 150) of the population had HbA1c ≥ 7.0% at baseline, and patients had a median (interquartile range [IQR]) duration of diabetes of 4.3 (1.3, 11.5) months (Table 1).

Table 1
Patient characteristics and disposition

Baseline characteristics	**Latin American region**			**Global**
	Early combination (n = 266)	**Initial monotherapy (n = 271)**	**Total (N = 537)**	**Total (N = 2001)**
Age (years), mean (SD)	52.0 (10.0)	53.4 (9.7)	52.7 (9.9)	54.3 (9.4)
Age group, n (%)				
< 40	31 (11.7)	24 (8.9)	55 (10.2)	159 (8.0)
40–<65	214 (80.5)	220 (81.2)	434 (80.8)	223 (11.1)
≥ 65	21 (7.9)	27 (10.0)	48 (8.9)	1619 (80.9)
Women, n (%)	153 (57.5)	163 (60.1)	316 (58.8)	1060 (53.0)
Predominant race, n (%)				
Native American	102 (38.3)	107 (39.5)	209 (38.9)	210 (10.5)
Caucasian	96 (36.1)	91 (33.6)	187 (34.8)	1217 (60.8)
Median (IQR) duration of T2DM (months)	4.2 (1.6, 11.1)	4.4 (1.1, 11.9)	4.3 (1.3, 11.5)	3.3 (0.9, 10.0)
HbA1c (%)[a]				
Mean (SD)	6.7 (0.5)	6.7 (0.5)	6.7 (0.5)	6.7 (0.5)
Median (IQR)	6.7 (6.4, 7.0)	6.6 (6.4, 7.0)	6.7 (6.4, 7.0)	6.7 (6.4, 7.0)
7.0%, n (%)	191 (71.8)	196 (72.3)	387 (72.1)	1427 (71.3)
≥ 7.0%, n (%)	75 (28.2)	75 (27.7)	150 (27.9)	572 (28.6)
Median (IQR) FPG (mmol/L)[a]	6.6 (5.8, 7.4)	6.6 (5.8, 7.5)	6.6 (5.8, 7.5)	6.9 (6.1, 7.8)
BMI (kg/m^2)				
Mean (SD)	31.0 (4.6)	31.0 (4.7)	31.0 (4.7)	31.1 (4.7)
Median (IQR)	30.4 (27.6, 34.3)	30.3 (27.8, 34.2)	30.4 (27.7, 34.2)	30.8 (27.4, 34.6)

Baseline characteristics	Latin American region			Global
	Early combination (n = 266)	Initial monotherapy (n = 271)	Total (N = 537)	Total (N = 2001)
30 kg/m^2, n (%)	122 (45.9)	123 (45.4)	245 (45.6)	875 (43.7)
≥ 30 kg/m^2, n (%)	144 (54.1)	148 (54.6)	292 (54.4)	1126 (56.3)
GFR (mL/min/1.73 m^2)[b]				
Normal (80)	202 (75.9)	217 (80.1)	419 (78.0)	1321 (66.1)
Mild (≥ 50–≤80)	64 (24.1)	54 (19.9)	118 (22.0)	670 (33.5)
Median (IQR) weight (kg)	77.8 (69.0, 92.5)	78.4 (68.0, 90.0)	78.0 (68.5, 91.5)	84.3 (72.3, 97.0)
Current smokers, n (%)	32 (12.0)	29 (10.7)	61 (11.4)	290 (14.5)
Discontinued study participation prematurely, n (%)	51 (19.2)	58 (21.4)	109 (20.3)	403 (20.1)

Baseline refers to randomization visit.

HbA1c, glycated hemoglobin; BMI, body mass index; FPG, fasting plasma glucose, GFR, glomerular filtration rate; IQR, interquartile range; SD, standard deviation; T2DM, type 2 diabetes mellitus.

[a]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 early combination therapy group did not have baseline HbA1c and fasting plasma glucose measurements on or prior to randomization.

[b]Baseline GFR was calculated using the Modification of Diet in Renal Disease Study equation. Serum creatinine and body weight measurements were obtained on Day 1 or at a later visit (scheduled or unscheduled) if the Day 1 measurements were missing.

Outcomes

At the end of 5 years, 46.4% (n = 121) of patients in the early combination group had met the criteria for initial treatment failure compared with 66.3% (n = 177) in the monotherapy group. Similar to the global results, the median (IQR) time to initial treatment failure was 59.8 (27.5, not evaluable) months in the early combination group compared with 33.4 (12.2, 60.1) months in the monotherapy group. A significant reduction in the risk for time to initial treatment failure was observed in the early combination group compared with monotherapy group over the 5-year study duration (hazard ratio [HR] 0.53 [95% confidence interval (CI): 0.42–0.67]; p < 0.0001) (Fig. 1).

The subgroup analysis for time to initial treatment failure for all pre-defined baseline variables, such as age, HbA1c at screening or race, with both treatment approaches is presented in Fig. 2. Across all pre-

defined subgroups, the risk for initial treatment failure was lower with early combination therapy.

During period 2, 33.7% (n = 88) of patients in the early combination group experienced a secondary treatment failure, versus 43.4% (n = 116) of patients in the monotherapy group. A significant reduction in risk of secondary treatment failure was observed with the early combination group compared with the monotherapy group (HR [95% CI] 0.69 [0.52, 0.91]; p = 0.0092) (Fig. 3). Additionally, a higher proportion of patients in the early combination group compared with the initial monotherapy group had HbA1c values < 7.0%, < 6.5% and < 6.0% over five years (Fig. 4).

Across the study period, body weight remained stable in both treatment groups. The median (IQR) body weight at baseline was 77.6 (68.3–91.0) kg and at the end of study was 77.0 (67.9–89.9) kg (Fig. 5**).**

The overall safety and tolerability profiles were similar between treatment approaches, with no unexpected safety findings reported. The incidence of AEs and SAEs over five years among Latin American participants between the two treatment approaches were 240 (89.8%) and 37 (13.8%), respectively, in the combination treatment group and 230 (85.2%) and 41 (15.2%), respectively, in the initial monotherapy group. Most of the AEs were of mild nature and a small fraction of AEs was reported to be related to the study treatment (< 4%). Only 2.6% (n = 7) of patients in early combination and 3.7% (n = 10) of patients in initial monotherapy group discontinued the treatment due to AEs. Majority of the drug-related AEs were gastrointestinal disorders likely to be related to metformin. Four patients in each group died during the study, but no deaths were considered to be related to any of the study drugs (Table 2).

Table 2
Adverse events by preferred terms in the Latin American study population

Patients with AEs, n (%)	Early combination n = 267 n (%)	Initial monotherapy n = 270 n (%)
Patients with at least one AE	240 (89.8)	230 (85.2)
Diarrhea	47 (17.6)	36 (13.3)
Back pain	41 (15.4)	32 (11.9)
Influenza	41 (15.4)	24 (8.9)
Arthralgia	40 (15.0)	43 (15.9)
Urinary tract infection	34 (12.7)	29 (10.7)
Hypertension	34 (12.7)	39 (14.4)
Nasopharyngitis	33 (12.4)	38 (14.1)
Headache	31 (11.6)	28 (10.4)
Pain in extremity	31 (11.6)	42 (15.6)
Anxiety	18 (6.7)	31 (11.5)
Dyslipidemia	23 (8.6)	27 (10.0)
Pharyngitis	21 (7.9)	22 (8.1)
Hypertriglyceridemia	20 (7.5)	10 (3.7)
Bronchitis	16 (6.0)	13 (4.8)
Gastroenteritis	14 (5.2)	16 (5.9)
Abdominal pain	13 (4.9)	14 (5.2)
Hepatic steatosis	13 (4.9)	9 (3.3)

AE, adverse events.

Patients with multiple adverse events under one treatment approach were counted only once in the adverse event category for that treatment approach

Hypoglycemic events were reported in seven patients in the early combination group and three in the initial monotherapy group, all of which were single events of grade 1 severity and did not lead to study discontinuation. One of the hypoglycemic events in each treatment group occurred during insulin treatment after 33 and 51 months in individuals whose diabetes rapidly progressed. One participant from

this Latin American region reported a pregnancy, and consequently, the study treatment (vildagliptin plus metformin) was permanently discontinued; the participant delivered a healthy baby at term.

Discussion

This regional analysis of the VERIFY study in Latin American participants demonstrated that early combination therapy with vildagliptin plus metformin improved glycemic durability in patients with newly diagnosed T2DM compared with standard-of-care initial metformin monotherapy followed by sequential combination with vildagliptin. The early combination therapy approach among Latin American participants with a low diagnostic HbA1c (6.5–7.5%) significantly reduced the risk of initial treatment failure by 47% compared with metformin monotherapy throughout the 5-year study duration. Early combination approach also reduced the risk of secondary treatment failure by 31% compared with timely and immediate intensification of metformin monotherapy based on the mandate as per the study protocol. In addition, the outcomes of this sub-analysis showed the applicability of the benefits of early combination therapy approach across the sub-groups of patients in the Latin American region. Overall, the findings of this regional analysis are consistent with those of the VERIFY global study.

The diverseness of baseline characteristics confirms that the VERIFY study protocol genuinely allowed enrollment of a globally heterogeneous population reflective of currently diagnosed individuals with diabetes. In Latin America as in other global regions outside Northern Europe [18], a deeper analysis of the glycemic data from the screening phase reverberates the challenges in accurate, early and timely diagnosis of T2DM based on glycemia as reported for Latin America [6, 8]. Therefore, in this region where there is less-structured public healthcare infrastructure, socioeconomic inequality, and limited access to care, it is sensible that recommendations and procedures facilitate early diagnosis and intervention.

The majority of the Latin American sub-population from the VERIFY study were relatively young at the time of T2DM diagnosis, between the age of 40 and 65 years, which corresponds to the age range that has been reported to have the sharpest rise in diabetes prevalence in many Latin American countries (Argentina, Chile, Uruguay, and Peru) [5]. The overall inclusion of approximately 10% of young-onset diabetes (YOD) patients (diagnosed before the age of 40 years) in Latin America was similar to the overall VERIFY global study population, while the highest proportion of YOD were enrolled from Asia [19]. While the VERIFY study protocol had limited, if any gender-specific exclusion criteria beyond those related to current pregnancy and breast-feeding, the even more pronounced predominance of female participants in this regional sub-population (Latin American: 59% vs Global: 53%) suggests increased disease awareness and health-seeking behavior among women compared to men, supporting similar observations from previous real-world studies from the Latin American region [12]. Therefore, the study population from Latin America included in our sub-analysis represented the overall current demographics of those with newly-diagnosed T2DM within the region.

Obesity in Latin American countries is highly prevalent and is influenced by heterogeneous socioeconomic factors such as lifestyle and diet [20], which may have been the underlying reason for the

wide range of body weight (with identical mean BMI value) versus the global, observed in this Latin American sub-population of VERIFY. An earlier real-world study reported that the majority of patients with T2DM from Latin America were obese (BMI ≥ 30 kg/m^2), and only 46.2% of these obese patients achieved glycemic control with sequential treatment intensification [12]. However, in our regional as well as global study populations, the early combination approach showed glycemic benefits in both sub-groups of patients with BMI ≥ 30 kg/m^2 and BMI < 30 kg/m^2. In addition, the overall body weight of the study participants remained stable over 5 years, with both the treatment approaches.

Earlier studies with the traditional sequential treatment intensification approach in clinical practice among patients from Latin America have shown that only 25–30% of patients achieved their glycemic target [11, 12]. A recent review of Latin American studies showed that non-attainment of glycemic control is primarily associated with longer duration of disease, a complex regimen, and inadequate access to healthcare and insurance coverage [10]. In this sub-analysis, 53.6% of patients using early combination therapy achieved and sustained glycemic control over a long term.

The current diabetes management guidelines from the Latin American Diabetes Association (ALAD, Asociación Latinoamericana de Diabetes) recommend early combination therapy only in patients with diagnostic HbA1c value > 8.0% [21]. However, in clinical practice in Latin America, failing monotherapy treatment is intensified using combination therapies only at an average HbA1c of 8.5% [22]. In addition, less than 40% of patients receive combination oral antidiabetics within the first 2 years of T2DM diagnosis [11]. In a cross-sectional study from Colombia, of 363 patients with T2DM with a median HbA1c of 6.8%, only 43.8% received combination therapy at their first consultation, and therapeutic inertia was reported in more than 50% of the consultations. Interestingly, the risk of therapeutic inertia at follow-up consultations was low with better HbA1c control [23]. A surveybased study from Brazil in 2017 showed that 75% of physicians do not consider combination therapy at treatment initiation and prefer to use it as second-line therapy [9]. These observations indicate presence of therapeutic inertia as one of the major barriers to optimized management of glycemia [24].

Based on the clinical benefits of early combination therapy demonstrated by the VERIFY global study, the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) have updated their consensus statement suggesting that healthcare providers should engage in shared decision making around initial combination therapy in new-onset cases of T2DM [25]. Similarly, the latest update of the Brazilian guidelines recommends early combination therapy in treatment-naïve patients with HbA1c 6.5–7.5% to delay treatment failure and improve glycemic control based on the clinical benefits [26].

This Latin American sub-analysis of the VERIFY study has shown that with early combination therapy, patients achieved a durable glycemic control, with a higher proportion maintaining HbA1c levels below 7.0%, 6.5%, and 6.0% over 5 years compared with those who received initial metformin monotherapy across various sub-groups. These findings suggest that regardless of the disparities in the social

situation in Latin America, an early combination strategy can help achieve glycemic control in patients newly diagnosed with T2DM in this region.

Strengths And Limitations

The observed glycemic durability and improved safety parameters confirm the clinical applicability (and generalizability) of the previously presented global results of the benefits of early combination therapy in the Latin American population with newly diagnosed T2DM. The findings strengthen the global clinical applicability of the VERIFY study results. The long-term study duration of 5 years is one of the main strengths of the VERIFY study and its sub-analysis. The pragmatic design of the study made it feasible to include a study population reflective of the current and characteristically diverse T2DM population in the Latin American region, including patients with YOD, obese individuals, and a predominance of female patients who otherwise so often are excluded from clinical studies with no valid reasons.

Conclusion

In this Latin American regional analysis of the VERIFY study, an early combination approach with vildagliptin plus metformin significantly and consistently improved long-term glycemic durability compared with initial metformin monotherapy in patients with newly diagnosed T2DM.

Abbreviations

ADA
American Diabetes Association
AE
Adverse event
ALAD
Asociación Latinoamericana de Diabetes
BMI
Body mass index
CI
Confidence interval
EASD
European Association for the study of Diabetes
EC
Early combination
HbA1c
Glycated hemoglobin
HR
Hazard ratio
IQR

Interquartile range
MET
Metformin
SAE
Serious adverse event
SD
standard deviation
TF
Treatment failure
T2DM
Type 2 diabetes mellitus
VERIFY
Vildagliptin Efficacy in combination with. metfoRmIn For earlY treatment of Type 2 diabetes

Declarations

Competing interest

The authors declare that they have no competing interests

Acknowledgements

The authors thank all the VERIFY study investigators from all sites of the Latin American countries, site personnel and patients who participated in this study. The investigators were Silvia Gorban de Lapertosa, Diego Aizenberg, Ines Palmira Bertolacci, Silvia Inés Orio, Federico Perez Manghi, Laura Maffei, Jorge Roberto Aiub, Maria Teresa Zanella, Carolina Jungers de Siqueira Chrisman, Freddy Goldberg Eliaschewitz, João Soares Felicio, Luis Henrique Santos Canani, Joao Lindolfo Cunha Borges, Maria Jose José Araújo Gomes Cerqueira, Miguel Nasser Hissa, Emerson Cestari Marino, João Eduardo Nunes Salles, Rosa Ferreira dos Santos, Jaime Orlando Ibbara Gomez, Arturo Orduz Lopez, Fernando Manzur Jattin, Casimiro Velazco Espaillat, Dolores Mejía, Juan Carlos Vargas, Sergio Bran, Clara Elizabeth Chang, Lorena Isabel Gracia Batres, Luis Ramirez, Guerrero Guerrero, Juan Pablo Moreira Diaz, Flor de Maria Ranchos Monterroso, Leobardo Sauque Reyna, Sergio Cesar Hernandez Jimenez, Guadalupe Morales Franco, Enrique Cuitlahuac Morales Villegas, Jorge Aldrete Velasco, Guillermo Fanghanel Salmon, Manuel Enrique Aguilera Real, Jose Villagordoa Mesa, Marilyn Donato, Pablo E. Fletcher Vasquez, Giselle Rodriguez, Angelica M. Valdivia Portugai, Cesar Manuel Delgado Butron, Jose Enrique Solis Villanueva, Miguel Eduardo Pinto Valdivia, Luis Alberto More, Luis Alberto Camacho Cosavalente, Luis Humberto Zapata Rincon. The authors also thank Shaswati Khan for medical writing support from Novartis Healthcare Pvt. Ltd., Hyderabad, India. The study was presented as ePoster during the 80th American Diabetes Association congress 2020 held on June 12–16, 2020 in Chicago, USA

Funding

Study was funded by Novartis Pharma AG, Basel, Switzerland

Availability of data and materials

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 based on scientific merit. All data provided are anonymized to respect the privacy of patients who had participated in the trial in line with applicable laws and regulations. The criteria and process for trial data availability are described online at https://www.clinicalstudydatarequest.com/

Author information

Contributions

- Concept and study design: PMP, PP
- Data acquisition: PMP, PP, JMP, HYL, SV, CM
- Analysis OR interpretation of data: PMP, CM, PP, SV
- Drafting or substantively revision of manuscript: PMP, PP, CM, SV, JMP, HYL

Ethical Declarations

The study protocol was approved by local ethics committees of all study sites and written informed consent was provided by all participants before the start of the trial. The study was designed and carried out in accordance with International Conference on Harmonization Tripartite Guidelines for Good Clinical Practice (ICH Expert Working Group) and according to the ethical principles of the Declaration of Helsinki, and was overseen by an independent, unmasked data monitoring committee for all safety events.

References

[1] Calazans JA, Queiroz BL. The adult mortality profile by cause of death in 10 Latin American countries (2000-2016). Rev Panam Salud Publica. 2020; 44: e1

[2] International Diabetes Federation. IDF Diabetes Atlas Ninth Edition; 2019. https://www.diabetesatlas.org/en/. Accessed on Dec 1, 2020

[3] Caballero AE. Diabetes in the Hispanic or Latino population: genes, environment, culture, and more. Curr Diab Rep. 2005; 5: 217–25

[4] Aschner P, Aguilar-Salinas C, Aguirre L, et al. Diabetes in South and Central America: an update. Diabetes Res Clin Pract. 2014; 103: 238–43

[5] Shen J, Kondal D, Rubinstein A, et al. A Multiethnic Study of Pre-Diabetes and Diabetes in LMIC. Glob Heart. 2016; 11: 61–70

[6] Gallardo-Rincon H, Cantoral A, Arrieta A, et al. Review: Type 2 diabetes in Latin America and the Caribbean: Regional and country comparison on prevalence, trends, costs and expanded prevention. Prim Care Diabetes. 2020; S1751-9918(20): 30286–2

[7] Hofman AA. The Economic Development of Latin America in the Twentieth Century. UK and USA. Edward Elgar Publishing Limited, 2000

[8] Blasco-Blasco M, Puig-Garcia M, Piay N, Lumbreras B, Hernandez-Aguado I, Parker LA. Barriers and facilitators to successful management of type 2 diabetes mellitus in Latin America and the Caribbean: A systematic review. PLoS One. 2020; 15: e0237542

[9] Vencio S, Paldanius PM, Bluher M, Giannella-Neto D, Caiado-Vencio R, Strain WD. Understanding the barriers and improving care in type 2 diabetes: Brazilian perspective in time to do more in diabetes. Diabetol Metab Syndr. 2017; 9: 46

[10] Aviles-Santa ML, Monroig-Rivera A, Soto-Soto A, Lindberg NM. Current State of Diabetes Mellitus Prevalence, Awareness, Treatment, and Control in Latin America: Challenges and Innovative Solutions to Improve Health Outcomes Across the Continent. Curr Diab Rep. 2020; 20: 62

[11] Lopez Stewart G, Tambascia M, Rosas Guzman J, Etchegoyen F, Ortega Carrion J, Artemenko S. Control of type 2 diabetes mellitus among general practitioners in private practice in nine countries of Latin America. Rev Panam Salud Publica. 2007; 22: 12-20

[12] Irazola V, Rubinstein A, Bazzano L, et al. Prevalence, awareness, treatment and control of diabetes and impaired fasting glucose in the Southern Cone of Latin America. PLoS One. 2017; 12: e0183953

[13] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008; 359: 1577–89

[14] Cai X, Gao X, Yang W, Han X, Ji L. Efficacy and Safety of Initial Combination Therapy in Treatment-Naive Type 2 Diabetes Patients: A Systematic Review and Meta-analysis. Diabetes Ther. 2018; 9: 1995–2014

[15] Matthews DR, Paldanius PM, Proot P, et al. 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. Lancet. 2019; 394: 1519–29

[16] Del Prato S, Foley JE, Kothny W, et al. 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. Diabet Med. 2014; 31: 1178–84

[17] Matthews DR, Paldanius PM, Stumvoll M, et al. A pre-specified statistical analysis plan for the VERIFY study: Vildagliptin efficacy in combination with metformin for early treatment of T2DM. Diabetes Obes Metab. 2019; 21: 2240–7

[18] Chan JC, Vencio S, Proot P et al. Screening values of glycated haemoglobin suggest regional barriers in detecting T2DM early: Analysis of the VERIFY study. Poster presented at Internalthional Diabetes Federation Congress 2019. OP-0279. https://doi.org/10.26226/morressier.5d9b622bea541d6ca8493b20

[19] Chan JC, Paldánius PM, Mathieu C et al. Early combination therapy delayed treatment escalation in newly diagnosed young-onset type 2 diabetes: A subanalysis of the VERIFY study. Diabetes Obes Metab. 2021; 23(1):245–51

[20] Filozof C, Gonzalez C, Sereday M, Mazza C, Braguinsky J. Obesity prevalence and trends in Latin-American countries. Obes Rev. 2001; 2: 99–106

[21] Association of Latin America Diabetes. ALAD guidelines on the diagnosis, control and treatment of type 2 diabetes mellitus with medicine based on evidence. Edition. 2019; https://www.revistaalad.com/guias/5600AX191_guias_alad_2019.pdf. Accessed on Dec 1, 2020

[22] Mendivil CO, Marquez-Rodriguez E, Angel ID, et al. Comparative effectiveness of vildagliptin in combination with other oral anti-diabetes agents in usual-care conditions: the EDGE-Latin America study. Curr Med Res Opin. 2014; 30: 1769–76

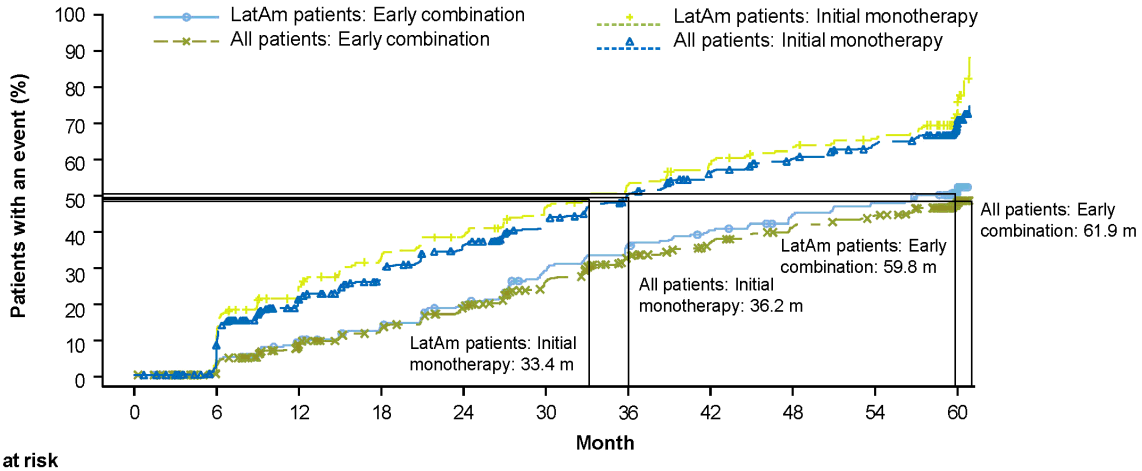
[23] Machado-Duque ME, Ramirez-Riveros AC, Machado-Alba JE. Effectiveness and clinical inertia in patients with antidiabetic therapy. Int J Clin Pract. 2017; 71

[24] Guzman JR, Lyra R, Aguilar-Salinas CA, et al. Treatment of type 2 diabetes in Latin America: a consensus statement by the medical associations of 17 Latin American countries. Latin American Diabetes Association. Rev Panam Salud Publica. 2010; 28: 463–71

[25] Buse JB, Wexler DJ, Tsapas A, et al. 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2020; 43: 487–93

[26] Bertoluci MC, Salles JEN, Silva-Nunes J, et al. Portuguese-Brazilian evidence-based guideline on the management of hyperglycemia in type 2 diabetes mellitus. Diabetol Metab Syndr. 2020; 12: 45

Figures



No. of patients still at risk

LatAm patients: Early combination	261	256	226	211	193	166	150	139	127	118	50
LatAm patients: Initial monotherapy	267	249	190	167	149	127	112	96	84	76	25
All patients: Early combination	983	960	862	815	752	671	597	551	509	478	187
All patients: Initial monotherapy	989	937	733	661	576	503	434	377	337	299	108

No. of events until this time point

LatAm patients: Early combination	0	1	23	33	48	71	87	96	105	114	120
LatAm patients: Initial monotherapy	0	12	63	82	98	117	131	145	155	161	171
All patients: Early combination	0	6	81	119	175	240	302	335	373	402	425
All patients: Initial monotherapy	0	32	201	259	336	397	460	509	544	576	605

For All patients:

- Hazard ratio (95% CI): 0.54 (0.48, 0.61), p value: <0.0001
- Median (IQR) in months (Early combination): 61.9 (29.9, -)
- Median (IQR) in months (Initial monotherapy): 36.1 (15.3, -)

For Latin American patients:

- Hazard ratio (95% CI): 0.53 (0.42, 0.67), p value: <0.0001
- Median (IQR) in months (Early combination): 59.8 (27.5, -)
- Median (IQR) in months (Initial monotherapy): 33.4 (12.2, 60.1)

Figure 1

Primary treatment failure* among Latin American patients randomized to early combination versus initial monotherapy CI, confidence interval; HR, hazard ratio; LatAm, Latin America. *Primary treatment failure is defined as HbA1c ≥7.0% at two consecutive scheduled visits, starting from 13 weeks after randomization. The time to initial treatment failure is the time from randomization to the second consecutive scheduled visits with HbA1c ≥7.0%. Patients who discontinued the study for any reason during period 1 were censored at the date of discontinuation. Patients with HbA1c <7.0% (or whose measurement ≥7.0% was not confirmed at next scheduled visit) were censored at the date of last study visit. The Kaplan-Meier estimates were performed for patients who had received at least one randomized medication and one post-randomization efficacy parameter assessed.

Subgroup	Early combination	Initial monotherapy	Hazard ratio (95% CI)	P value
Overall	121/261 (46.36)	177/267 (66.29)	0.53 (0.42, 0.67)	<0.0001
HbA1c				0.78
<7%	69/189 (36.51)	113/194 (58.25)	0.48 (0.35, 0.65)	
≥7%	52/72 (72.22)	64/73 (87.67)	0.53 (0.37, 0.77)	
BMI (kg/m^2)				0.64
<30	57/121 (47.11)	85/121 (70.25)	0.50 (0.36, 0.70)	
≥30	64/140 (45.71)	92/146 (63.01)	0.56 (0.41, 0.77)	
Age (years)				0.50
≤51	69/125 (55.20)	85/102 (83.33)	0.42 (0.31, 0.58)	
51 - ≤59	32/70 (45.71)	53/86 (61.63)	0.58 (0.37, 0.90)	
>59	20/66 (30.30)	39/79 (49.37)	0.50 (0.29, 0.85)	
Gender				0.85
Male	51/110 (46.36)	72/106 (67.92)	0.54 (0.37, 0.77)	
Female	70/151 (46.36)	105/161 (65.22)	0.53 (0.39, 0.72)	
Current smoker				0.28
No	110/231 (47.62)	157/239 (65.69)	0.55 (0.43, 0.71)	
Yes	11/30 (36.67)	20/28 (71.43)	0.38 (0.18, 0.79)	
Race				0.90
Caucasian	44/93 (47.31)	59/91 (64.84)	0.55 (0.37, 0.81)	
Black	3/6 (50.00)	7/10 (70.00)	0.50 (0.13, 1.97)	
Native American	44/102 (43.14)	69/105 (65.71)	0.49 (0.33, 0.71)	
Other	30/60 (50.00)	42/61 (68.85)	0.58 (0.36, 0.93)	
eGFR (mL/min/1.73m^2)				0.44
<90	44/113 (38.94)	69/112 (61.61)	0.48 (0.33, 0.70)	
≥90	77/148 (52.03)	108/155 (69.68)	0.57 (0.43, 0.76)	
eGFR (mL/min/1.73m^2)				0.32
<60	1/4 (25.00)	2/3 (66.67)	0.22 (0.02, 2.57)	
≥60	120/257 (46.69)	175/264 (66.29)	0.54 (0.43, 0.68)	
eGFR (mL/min/1.73m^2)				0.50
30-<60	1/4 (25.00)	2/3 (66.67)	0.22 (0.02, 2.57)	
60-<90	43/109 (39.45)	67/109 (61.47)	0.50 (0.34, 0.73)	

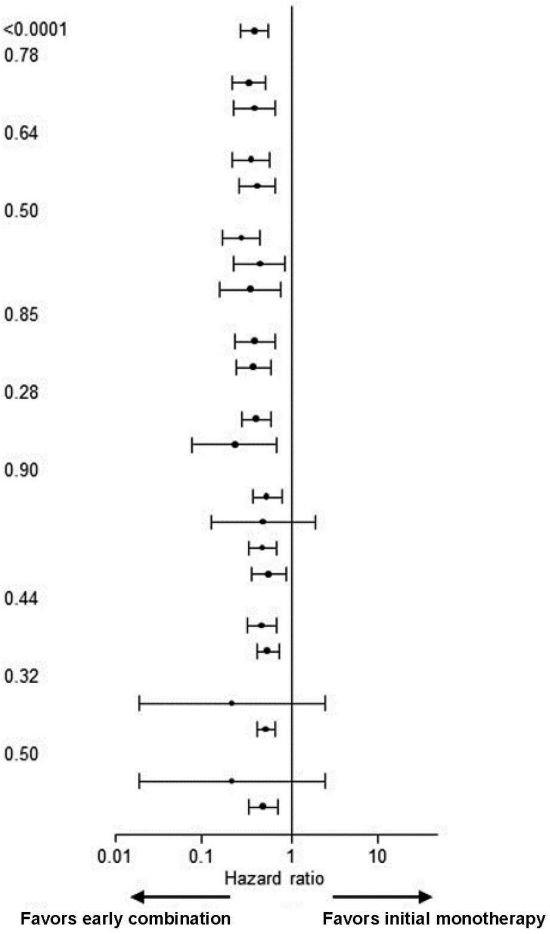


Figure 2

Subgroup analysis of time to initial treatment failure BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio. HRs and the associated CIs and p values were obtained from a Cox proportional hazards model containing terms for treatment approach, geographical region, and baseline HbA1c. 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. BMI, body mass index; CI, confidence interval; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; HR, hazard ratio; N, total number of patients considered for each subgroup analysis; n, number of patients with relevant results within each subgroup.

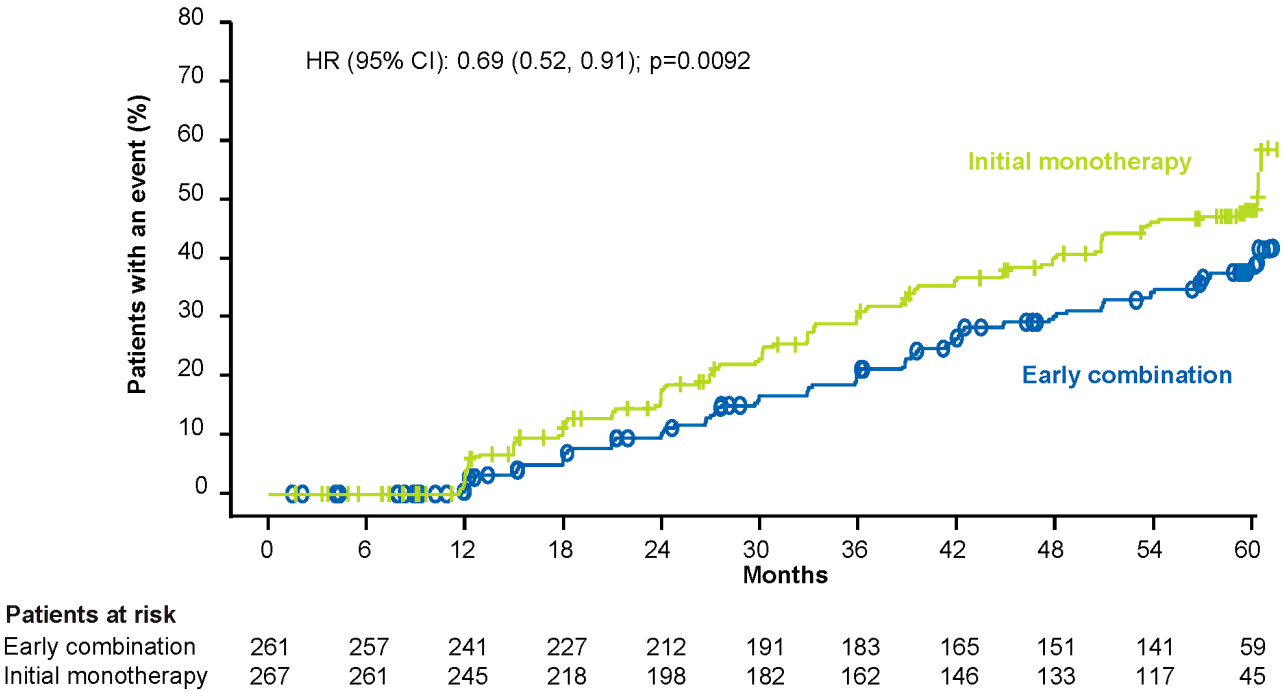
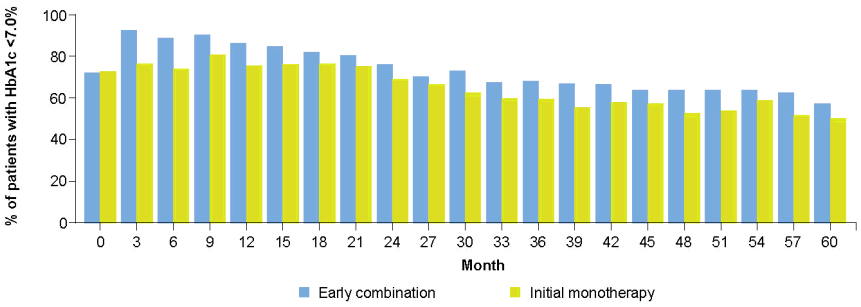


Figure 3

Secondary treatment failure* among patients with early combination versus initial monotherapy followed by vildagliptin addition CI, confidence interval; HbA1c, glycated hemoglobin; HR, hazard ratio. *Secondary treatment failure is defined as two consecutive scheduled visits with HbA1c ≥7.0% during period 2 (i.e., after period 1 comparing metformin monotherapy versus early combination therapy with metformin and vildagliptin and up to end of period 2 when both groups are on combination therapy after primary treatment failure. The time to secondary treatment failure is the number of days from randomization to the second confirmed HbA1c ≥7.0% during consecutive scheduled visits, three months apart, in period 2. The Kaplan Meier estimates were performed for patients who had received at least one randomized medication and one post-randomization efficacy parameter assessed. Patients who had no event and discontinued the study for any reason during period 1 or period 2 were censored at the date of discontinuation. Patients who entered period 3 from period 1 were censored to last study visit prior to start of period 3. Two-sided p value was obtained from a Cox proportional hazards model containing terms for treatment approach. Baseline HbA1c was the value obtained on Day 1, or the value obtained at an earlier visit (scheduled or unscheduled) which was closest to Day 1, if Day 1 measurement was missing.

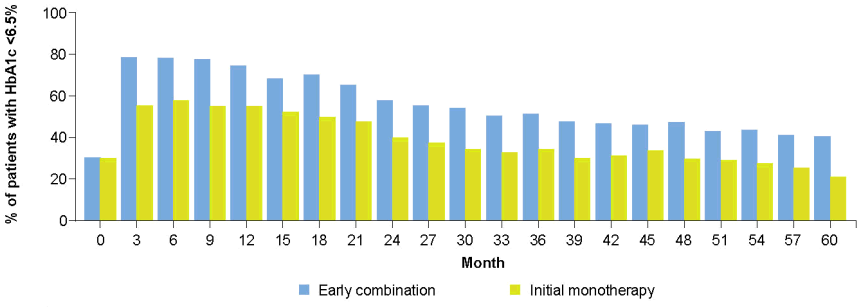


No. of patients with HbA1c <7.0% at each month

Early combination	189	241	222	221	214	203	195	190	179	163	168	155	153	150	150	141	140	138	138	133	124
Initial monotherapy	194	202	190	200	187	187	184	181	165	159	146	140	139	130	134	130	118	117	129	111	108

No. of patients evaluated at each month

Early combination	261	260	249	244	247	239	237	235	234	231	229	229	224	224	225	220	218	215	215	212	215
Initial monotherapy	266	263	256	247	247	245	240	240	238	238	233	233	233	233	231	226	223	217	218	213	214

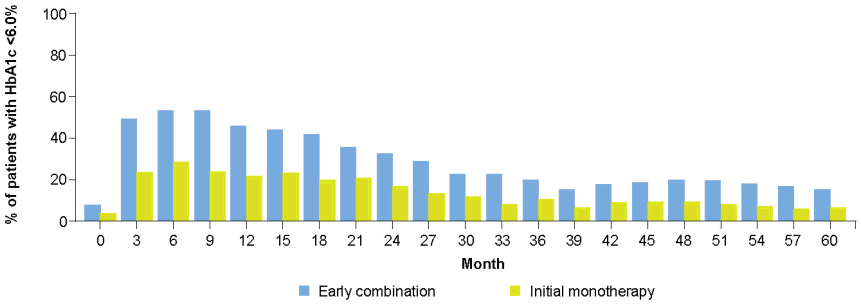


No. of patients with HbA1c <6.5% at each month

Early combination	79	204	195	189	184	163	166	153	135	128	124	115	115	107	105	101	103	92	94	87	87
Initial monotherapy	80	145	148	136	136	128	119	114	95	89	80	76	80	70	72	76	66	63	60	54	45

No. of patients evaluated at each month

Early combination	261	260	249	244	247	239	237	235	234	231	229	229	224	224	225	220	218	215	215	212	215
Initial monotherapy	266	263	256	247	247	245	240	240	238	238	233	233	233	233	231	226	223	217	218	213	214



No. of patients with HbA1c <6.0% at each month

Early combination	21	128	133	130	113	105	99	84	76	67	52	52	45	34	40	41	43	42	39	36	33
Initial monotherapy	10	62	73	59	54	57	48	50	40	32	28	19	25	15	21	21	21	18	16	13	14

No. of patients evaluated at each month

Early combination	261	260	249	244	247	239	237	235	234	231	229	229	224	224	225	220	218	215	215	212	215
Initial monotherapy	266	263	256	247	247	245	240	240	238	238	233	233	233	233	231	226	223	217	218	213	214

Figure 4

Success rate of early combination and initial monotherapy approaches (cut-off HbA1c 7.0%, 6.5% and 6.0%) HbA1c, glycated hemoglobin.

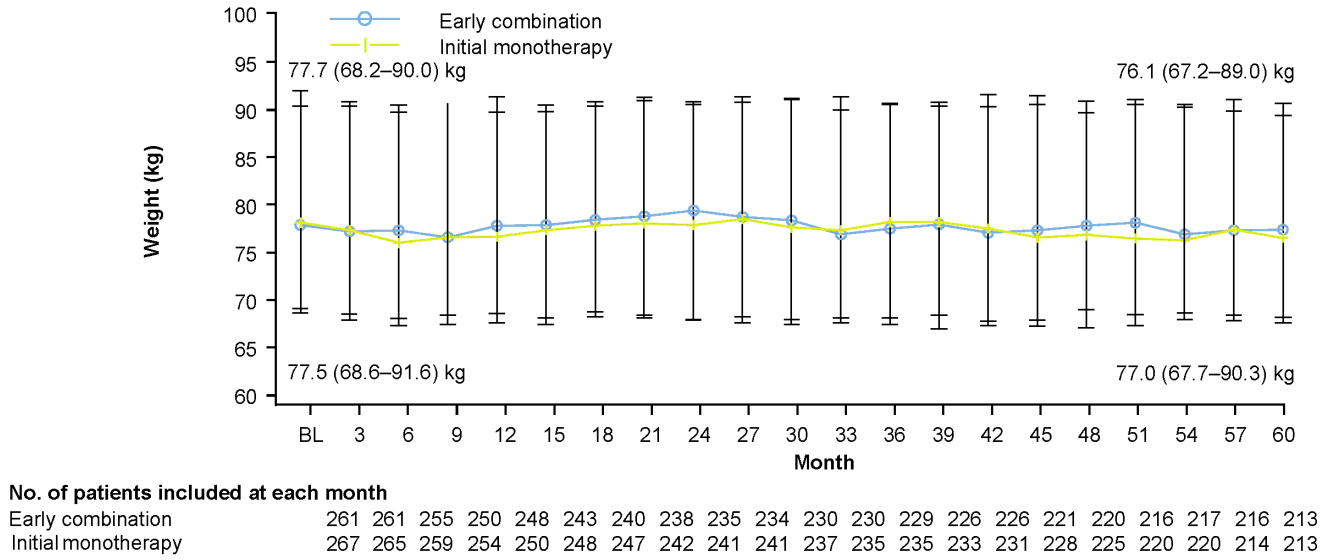


Figure 5

Body weight of patients in early combination and initial monotherapy groups BL, baseline. Body weight measures are given in median and interquartile range (vertical bars) Baseline weight is the measurement obtained on Day 1 or on sample obtained on an earlier visit (scheduled or unscheduled). Day is relative to the first day of treatment (Day 1)