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Positive results from Novartis five-year VERIFY study in type 2 diabetes demonstrate long-term clinical benefits of early combination treatment with vildagliptin and metformin

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- *Early combination treatment strategy with vildagliptin and metformin was superior to standard of care in newly diagnosed type 2 diabetes patients* [1,2]
- *The landmark VERIFY study is the first to investigate the long-term clinical benefits of this early combination strategy in type 2 diabetes (T2DM)*[1]
- *Novartis is committed to optimizing patient management of T2DM to achieve better glycemic control and favorable long-term clinical outcomes*

Basel, September 18, 2019 — Novartis today announced the key results from the Phase IV clinical study VERIFY evaluating the long-term efficacy and safety of early combination treatment strategy with metformin plus vildagliptin (dipeptidyl peptidase-4 [DPP-4] inhibitor) compared to the traditional stepwise approach with metformin as initial therapy followed by vildagliptin, added at the time of metformin failure[1,2]. The key study findings were presented today at the European Association for the Study of Diabetes (EASD) Annual Meeting and published simultaneously in *The Lancet*.

VERIFY is a unique study designed to determine durability, over a pre-specified five-year follow-up of early use of combination therapy strategy with vildagliptin-metformin. The study was conducted across 254 centers in 34 countries and involved 2001 treatment-naïve diverse individuals recently diagnosed with T2DM (HbA1c between 6.5–7.5% [48–58 mmol/mol])[1,2].

In the randomized, double-blind Phase IV study (ClinicalTrials.gov Identifier: NCT01528254), early combination therapy of vildagliptin (50 mg, twice daily) and metformin (individually, 1000–2000 mg, daily) met the primary endpoint with a statistically significant 49% reduction in the relative risk for time to initial treatment failure (HbA1c ≥ 7.0% twice, consecutively, 13 weeks apart), versus metformin alone (HR: 0.51, 95% CI [0.45, 0.58]; P<0·0001)[1,2].

The combination treatment strategy also showed a lower frequency of secondary failure when all patients were receiving combination therapy (HR: 0.74, 95% CI [0.63, 0.86]; P<0.0001). Furthermore, patients treated with early combination had consecutively lower HbA1c levels (below 6.0%, 6.5% or 7.0%) for 5 years versus those receiving combination therapy only after metformin monotherapy failure[1].

“The initial findings from the VERIFY study uniquely demonstrate that early intervention with a combination therapy strategy provides greater and durable long-term benefits for patients. The currently recommended initial monotherapy approach with later treatment intensification in type 2 diabetes management is now shown to be an inferior strategy,” said Professor David Matthews, EASD President and Emeritus Professor of Diabetic Medicine, University of Oxford, UK.

The overall safety and tolerability profile was similar between the treatment approaches, with no unexpected or

new safety findings reported[1].

“Despite type 2 diabetes having become an epidemic with growing mortality and morbidity rates, there is a distinct lack of optimized management strategies at diagnosis that can induce durability and slow down disease progression,” said Marcia Kayath, Global Head Medical Affairs and Chief Medical Officer, Novartis Pharmaceuticals. “These promising results from the VERIFY study have the potential to improve patient outcomes and the way in which we treat type 2 diabetes in the future”.

Additional pre-defined secondary analyses of the VERIFY study results are ongoing and data will be disclosed over the coming months at international and local medical congresses and in scientific journals.

About vildagliptin/metformin combination

The combination of these two anti-diabetic agents with complementary mechanisms of action provides superior efficacy and allows patients to reach glycemic targets without increasing the risk of hypoglycemia, weight gain and other CV risk factors[3]. Vildagliptin-metformin combination was the first single-pill dual therapy of a DPP-4 inhibitor with metformin approved in Japan and Europe [4]. The vildagliptin and metformin dual therapy is used when the patient’s T2DM is insufficiently controlled by metformin monotherapy [5].

About vildagliptin

Vildagliptin is approved as an oral treatment for adults with T2DM in more than 120 countries, including the EU, Japan, Latin America and Asia-Pacific. Vildagliptin is approved for use as monotherapy, dual therapy in combination with metformin, sulfonylurea (SU) or a thiazolidinedione, as a triple oral therapy in combination with a SU and metformin or as an add-on to insulin (with or without metformin)[4,5,6].

Vildagliptin is a selective and potent DPP-4 inhibitor that acts by preventing the usually rapid degradation of the incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which in turn, enhances the α- and β-cell sensitivity to glucose and inhibits glucagon secretion, thereby improving glycemic control in T2DM7,8,9,10. Vildagliptin has been widely studied in randomized clinical trials but it also has an extensive pool of evidence in real world settings within diverse patient populations across the disease continuum [11].

About metformin

Metformin hydrochloride is widely-used and is the recommended first-line therapy in patients with newly-diagnosed T2DM either immediately after diagnosis, or in those not able to achieve glycemic targets despite diet and other lifestyle interventions [12].

Despite its discovery already in 1922, the exact mode of action for metformin is not yet known. However, its effect in management of diabetes is through reduction of glucose output in the liver and secondarily, through increase of glucose uptake in the peripheral tissues. However, recent data suggests that some clinical activity may also arise from the synthesis and stimulation of intestinal release of incretin hormones[12,13].

About VERIFY study[1,2]

The VERIFY study is a five-year, multi-center, randomized, double-blind Phase IV trial designed to assess the durability of glycemic control of a combination regimen strategy with vildagliptin and metformin compared with standard-of-care monotherapy approach with metformin initiated in treatment-naïve, diverse patients with recently diagnosed T2DM (HbA1c between 6.5-7.5% [48–58 mmol/mol]).

The study involved 2001 patients prescribed with stable dose of metformin (1000–2000 mg daily) 4 weeks

prior to or during the trial and randomized (1:1) to receive additional vildagliptin 50 mg twice daily or placebo. Dose adjustment of metformin in both treatment arms was permitted during the first 4 weeks in the trial, to allow adjustment to a dose of up to 2000 mg/day or the maximum tolerable dose of at least 1000 mg/day post-randomization. If the initial treatment strategy failed to maintain an HbA1c level <7.0%, participants in the metformin monotherapy group were administered vildagliptin 50 mg twice daily in place of the placebo.

The primary endpoint was time to confirmed initial treatment failure, defined as HbA1c ≥7% at two consecutive scheduled visits, 13 weeks apart. Secondary endpoints included rate of loss of glycemic control, HbA1c development over time, rate of loss in glycemic control in fasting plasma glucose, rate of loss of beta cell function from baseline to end of study, rate of change in insulin sensitivity from baseline to end of study, and rate of adverse events. Exploratory endpoints include adjudication of cardiovascular events and changes in glucose homeostasis (HOMA).

About T2DM

Diabetes mellitus is a condition characterized by increasing hyperglycemia due to defects in both insulin production and insulin sensitivity[14]. The prevalence of diabetes has quadrupled in the past three decades with approximately 1 in 11 adults now having the disease worldwide, of these approximately 90% have T2DM[15]. Additionally, factors such as glucose intolerance (pre-diabetes), underdiagnosed and/or delayed diagnosis of T2DM are causing a rapid increase in disease burden. This is especially seen in developing countries, which contributes to the continuously growing burden of diabetes. The International Diabetes Federation estimates that there is a new diagnosis every 6 seconds somewhere in the world[16].

After diagnosis, the majority of patients are unable to achieve and maintain the recommended glycemic control targets as defined by the guidelines[17]. This universal lack of achievement of glycemic control is partly attributed to the current treatment paradigm involving sequential monotherapy, frequent early treatment failure and delayed therapy intensification leading to prolonged periods of sustained hyperglycemia. Combatting inertia in treatment intensification could also include a strategy of earlier and more comprehensive introduction combination therapy approach[11,18].

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1. https://prod1.novartis.com/ph-en/ph-en/news/media-releases/positive-results-from-novartis-five-year-verify-study-type-2-diabetes-demonstrate-long-term-clinical-benefits-early-combination-treatment-vildagliptin-and-metformin
2. https://clinicaltrials.gov/ct2/show/NCT01528254
3. https://www.novartis.com/news/novartis-corporate-fact-sheet/innovative-medicines-en
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