



REVIEW

Use of Tirzepatide in Adults with Type 2 Diabetes Mellitus: Scientific Evidence and Practical Aspects

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ABSTRACT

Tirzepatide is a novel antidiabetic medication a single-molecule, agonist to the glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors. It is approved in the USA and EU for the treatment of type 2 diabetes mellitus (T2DM) and obesity. Due to the potential novelty represented by incorporating tirzepatide to clinical practice, we aim to review practical aspects of tirzepatide use in T2DM and the supporting scientific evidence. A group of

ten endocrinologists involved as investigators in the phase 3 SURPASS clinical trial program followed a nominal group technique, a qualitative research methodology designed as a semi-structured group discussion to reach a consensus on the selection of a set of practical aspects. The scientific evidence for tirzepatide has been reviewed with respect to a number of patients' clinical profiles and care goals. Information of interest related to adverse events, special warnings and precautions, and other considerations for tirzepatide use has been included. Finally, information provided to the patients has been summarized. The practical aspects reported

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herein may be helpful in guiding physicians in the use of tirzepatide and contribute to optimizing the management of T2DM.

Keywords: Tirzepatide; Type 2 diabetes mellitus

Key Summary Points

Tirzepatide is a once-weekly glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist approved in the USA and EU for the treatment of type 2 diabetes mellitus (T2DM) and obesity.

The authorization of tirzepatide for clinical use in T2DM represents a therapeutic novelty and an advance in the field of incretins for T2DM management.

The review of practical aspects of tirzepatide use and the supporting scientific evidence may be useful for the management of this drug in a clinical setting.

INTRODUCTION

Tirzepatide is a novel antidiabetic medication authorized for clinical use in the USA and the European Union (EU) for the treatment of type 2 diabetes mellitus (T2DM) and obesity. According to the EU, tirzepatide is indicated for the treatment of adults with insufficiently controlled T2DM as an adjunct to diet and exercise, in addition to other antidiabetic therapies, or as monotherapy in the event that metformin is considered inappropriate due to intolerance or contraindications [1]. It is a glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 receptor agonist (GLP-1 RA), and a “first-in-class” agent, being the only GIP/GLP-1 RA approved for the treatment of T2DM and obesity.” The authorization of tirzepatide represents a

therapeutic advance in the field of incretins for T2DM management [2].

Tirzepatide’s mode of action enhances insulin secretion and reduces glucagon secretion in a glucose-dependent manner and increases insulin sensitivity. In addition, tirzepatide delays gastric emptying, influences satiety, and appetite, resulting in decreased appetite and food consumption, thus inducing body weight reduction. Weight reduction, mainly due to fat mass reduction, can help to improve insulin sensitivity, although additional mechanisms may be involved [1, 3].

The phase 3 SURPASS clinical trial program [4–8] has evaluated the safety and efficacy of once-weekly subcutaneously injected tirzepatide, as monotherapy or combination therapy, in a broad spectrum of people with T2DM [9]. All five studies demonstrated that tirzepatide treatment achieved sustained statistically significant and clinically meaningful reductions from baseline in hemoglobin A1c (HbA1c) (– 1.87 to – 2.59%, – 20 to – 28 mmol/mol) and in body weight (– 6.2 to – 12.9 kg), compared to either placebo or active comparators (semaglutide 1 mg, insulin degludec and insulin glargine). Body weight reduction was observed during the dose-escalation period, as early as 4 weeks after treatment initiation and was sustained for up to 2 years, the longest period studied to date [7].

Due to the novelty of this medication [2], we aim to review practical aspects of tirzepatide use in T2DM and the supporting scientific evidence. To do so, a scientific committee was formed with ten endocrinologist (Luis Alberto Vazquez, Esteban Jodar-Gimeno, Santiago Tofe-Povedano, Diego Bellido-Guerrero, Marta Botella-Serrano, Alfonso Soto-Gonzalez, Pedro Mezquita-Raya, Elias Delgado, Carmen Fahardo-Montanana, and Cristobal Morales-Portillo) experts in the management of patients with diabetes mellitus and who participated in the phase 3 SURPASS clinical trial program as principal investigators. They reached a consensus on the set of practical aspects to be addressed in this review using the nominal group technique, a qualitative

research methodology designed as a semi-structured group discussion that secures the balanced participation of all group members, encouraging them with an equal opportunity to express their ideas [10–13]. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

The expert group agreed on selecting the following practical aspects and the supporting scientific evidence:

Clinical Profiles of Patients and Tirzepatide Use

One of the approved indications for tirzepatide is the treatment of adults with inadequately controlled T2DM [1]; notwithstanding, a consensus was reached regarding the selection of the following practical aspects related to certain patient profiles, fulfilling this indication, for the use of tirzepatide.

Patients with T2DM and Overweight or Obesity

Overweight and obesity are two of the main modifiable T2DM-related risk factors, strongly associated with insulin resistance, one of the key features in the pathogenesis of T2DM, and one of the barriers to achieving good glycemic control [14].

Participant inclusion criteria across the SURPASS clinical trial program [4–8] included a body mass index (BMI) ≥ 25 kg/m² [5–7], or ≥ 23 kg/m² [4, 8], in addition to stable weight ($\leq 5\%$ fluctuation in either direction) for the previous 3 months. The mean baseline body weight ranged from 86 to 95 kg and the mean BMI ranged from 31.9 to 34.2 kg/m² across the five studies. Tirzepatide showed clinically meaningful weight reductions with an average weight loss ranging from 6.2 to 12.9 kg [9]. Among those participants who received tirzepatide 15 mg, weight loss of at least 5% was achieved by up to 88% (range, 77–88%), weight loss of

at least 10% was achieved by up to 69% (range, 47–69%) while weight loss of at least 15% was achieved by up to 43% (27–43%) [9]. Tirzepatide was included in the recent consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) as a drug with very high efficacy in weight reduction [15].

Weight reduction has been associated with improvement in HbA1c and a decrease in the risk of weight-related complications, with a higher extent of loss related to better outcomes [16]. A body weight reduction of up to 5–10% confers metabolic improvement, whereas a weight loss of $\geq 10\%$ can have disease-modifying effects [16].

Patients with T2DM and Weight-Related Comorbidities

The clinical burden associated with overweight and obesity is high, emerging as one of the leading causes of death [14]. Patients with T2DM and overweight or obesity present a higher risk of weight-associated comorbidities such as osteoarthritis, joint pain, sleep apnea, and impaired health-related quality of life (HRQoL) or functionality [17]. Care of people with diabetes and weight-related comorbidities should include strategies to achieve weight loss [15].

In the phase 3 SURPASS clinical trial program, weight loss in adults with T2DM treated with tirzepatide 5, 10, and 15 mg was associated with an improvement in weight-related and overall HRQoL, with greater improvement observed in participants achieving higher weight loss [18].

Qualitative interviews conducted with tirzepatide-treated patients with T2DM who had recently completed one of two trials (SURPASS-2, SURPASS-3) revealed their satisfaction with their weight loss, and the broad and meaningful impact this had on multiple aspects of their quality of life and daily activities [19].

Tirzepatide is being studied in several weight-related diseases, such as sleep apnea, non-alcoholic steatohepatitis or heart failure (HF) with preserved ejection fraction, thus specific improvements in these weight-related diseases are currently under investigation [20–22].

Patients with T2DM and with Overweight or Obesity and on Insulin Treatment

Tirzepatide improved markers of insulin sensitivity partly due to weight loss [1, 3]. Tirzepatide increased insulin sensitivity by 63%, in the context of a mean weight loss of 11.2 kg [23]. Insulin-resistant patients with T2DM and overweight or obesity receiving insulin treatment would benefit from the efficacy of tirzepatide in reducing body weight, and for such patients, insulin dose reduction would be a feasible objective. In SURPASS 6, patients with T2DM and a mean baseline BMI of 33 kg/m² receiving insulin glargine in combination with metformin were randomized to tirzepatide or insulin lispro. At 52 weeks, compared to insulin lispro, tirzepatide (pooled) achieved better results for HbA1c and weight reduction from baseline, with substantially lower insulin use (from a geometric mean total baseline daily insulin use of 46 IU to 13 IU [0.15 IU/kg] in the tirzepatide group vs. 112 IU (1.2 IU/kg)) in the insulin lispro group), with 8% to 19% of tirzepatide-treated participants completely discontinuing insulin glargine therapy by week 52 [24].

Patients with T2DM Seeking Normoglycemia

In the SURPASS program, up to 23–62% of participants achieved normoglycemia (HbA1c < 5.7%), vs. participants treated with semaglutide 1 mg (20%), insulin degludec (5%), and insulin glargine (3%) [9]. Normoglycemia was achieved without clinically significant hypoglycemia in 93.6–100% patients when tirzepatide was not combined with insulin (SURPASS 1–4) and in 85.9% patients when tirzepatide was added to insulin (SURPASS-5) [1]. Tirzepatide-treated participants who achieved normoglycemia were slightly younger, with a shorter duration of diabetes and lower HbA1c value at baseline [25].

In addition, tirzepatide enabled participants to maintain a significantly lower blood glucose level throughout the day across all five studies [4–8], with a higher proportion of 24-h period spent within a tight target glucose range and a smaller within-day glucose coefficient of variation vs. insulin degludec, indicating lower glycemic variability [9]. Data from a cohort study in

patients with newly diagnosed diabetes, showed that stringent glycemic control (HbA1c levels < 6.5%) were associated with better outcomes vs. patients with HbA1c between 6.5% to < 7%. Thus, this study is consistent with literature recommending early and intensive treatment to avoid long-term risk of diabetic complications and related mortality [26].

Patients with T2DM with Very Poor Glycemic Control who are far from Reaching HbA1c Therapeutic Goals

A subgroup analysis involving patients with a HbA1c level > 8.5% showed significant and clinically significant mean reductions in the HbA1c level of –3.18 up to –3.46% for tirzepatide at a dose of 15 mg as compared with –2.58% for semaglutide 1 mg, –2.07% for insulin degludec, –1.96% for insulin glargine, –0.82% for placebo in monotherapy, and –1.27% for placebo added to insulin glargine [27]. In a post hoc analysis of SURPASS 2, 3, and 4 assessing tirzepatide in participants whose baseline HbA1c was > 9%, between 65 and 86% of patients randomized to tirzepatide achieved HbA1c < 7%. Consistent with these data, the ADA-EASD 2022 consensus has categorized the glycemic effect of tirzepatide as very high [15, 28].

Patients with T2DM and Cardiovascular (CV) Risk Factors

The holistic patient-centered approach proposed by the ADA-EASD consensus includes CV risk-factor management and cardiorenal protection [15], in addition to glycemic and weight management. With regard to the cardiovascular profile of tirzepatide, clinical trials have shown an improvement in CV risk factors including systolic and diastolic blood pressure (BP), triglycerides, high-, very low, and low-density lipoproteins and waist circumference in participants receiving tirzepatide [4–8]. Improvements in liver fat content and reduced visceral and subcutaneous abdominal adipose tissue volume have been shown with tirzepatide [29]. In the SURPASS 4 trial, which included participants at high CV risk, the hazard ratio for major adverse CV events for

tirzepatide treatment compared with glargine was 0.74 (95% CI 0.51–1.08), indicating CV risk was not increased [7]. The effects of tirzepatide on CV events in patients with T2DM and increased CV risk are under study in the ongoing clinical trial SURPASS-CVOT [30]. Based on ADA-EASD consensus, if the primary goal is cardiorenal risk reduction, in patients with atherosclerotic cardiovascular disease GLP-1 RA or sodium-glucose transporter 2 inhibitors (SGLT2i) with proven CVD benefit are the recommended treatments. In the case of heart failure or chronic kidney disease (CKD), the preferred options are SGLT2i with HF benefits or evidence of reducing CKD progression, respectively [15].

Therapeutic Goals

HbA1c Target

A reasonable HbA1c target for most adults with adequate life expectancy is $\leq 7\%$ [15]. Based on the American Association of Endocrinology, for most patients, an optimal HbA1c is $\leq 6.5\%$ or as close to normal if it is safe and achievable [31]. Studies have found that stringent glycemic control during the first year after diagnosis can be associated with lower risks of diabetic complications and mortality in the future [26]. Decisive factors such as early detection and patient age followed by early and intensive treatment may be necessary to avoid irremediable long-term risk due to glycemic complications [32, 33]. Less stringent HbA1c targets can be considered in cases of limited life expectancy, advanced renal disease, severe comorbid conditions, or long T2DM disease duration [31]. Up to 81–97% participants in the SURPASS clinical trial program receiving tirzepatide achieved the treatment goal recommended by ADA and EASD, HbA1c $< 7\%$ [15], which is significantly higher than active comparators (81% semaglutide 1 mg, 61% insulin degludec, 51% glargine). More patients treated with tirzepatide achieved HbA1c $\leq 6.5\%$ (66–95%) compared with semaglutide 1 mg (66%), insulin degludec (44%) or insulin glargine (32%). Compared to semaglutide

1 mg, all three doses of tirzepatide were linked to significantly higher proportions of patients who achieved HbA1c target values of $< 5.7\%$ (29–51% tirzepatide vs. 20% semaglutide) [1]. Normoglycemia was achieved in a significant proportion of tirzepatide treated participants, without an increase in the risk of hypoglycemia, and was associated with an overall improvement in markers of metabolic health [25].

Body Weight Reduction Target

Weight management should be a focus for patients with T2DM and overweight or obesity, according to the ADA-EASD consensus report [15]. A target of at least 5% weight loss can be expected to have clinical benefits, whereas a substantial ($> 10\%$) weight loss and weight loss early in the course of T2DM increase the chance of disease remission [15, 16]. In the SURPASS program, up to 69% of patients achieved a goal of $\geq 10\%$ weight loss, and up to 43% experienced weight loss of $\geq 15\%$ [1]. Body weight reduction was mainly driven by fat mass loss, thereby improving body composition [1, 23].

HRQoL and Functionality

A holistic and multifactorial approach in T2DM management, with an overall goal of maintaining HRQoL and avoiding complications is recommended [15, 34]. Tirzepatide may contribute to achieving such therapeutic goals, since across the SURPASS clinical program improvements in multiple domains of HRQoL and functionality were consistently observed [4–8].

Time to Achieve Therapeutic Goals and Reassess Targets

The ADA-EASD consensus indicates that the reassessment of individual targets and their achievement at regular intervals is key, recommending proactive care and thus avoiding inertia [15]. The American Association of Clinical Endocrinology Consensus Statement recommends attaining the treatment goal “as soon

as possible". Clinicians should continuously evaluate treatment goals at each visit, ideally ≤ 3 monthly intervals, and consider making therapeutic changes to achieve targets more rapidly [31, 35]. In addition, some patients may require medication reduction or discontinuation, as in the case of side effects or ineffectiveness [15]. Facilitating the communication, access to the medical center, and interactions between health care professionals (HCPs) and patients positively impacts treatment adherence and clinical outcomes [36, 37].

In a clinical trial setting, the median time to reach HbA1c $< 7\%$ was 8.1 weeks with tirzepatide 5 mg dose vs. 12 weeks with semaglutide 1 mg; and the median time to reach the weight loss target ($\geq 5\%$ weight loss) was 16 weeks with tirzepatide 5 mg dose vs. 24 weeks with semaglutide 1 mg [38]. Those patients that achieved early (at 8 weeks) weight loss of $\geq 5\%$ had a greater substantial reduction in weight at the end of the trial vs. those that did not reach this early weight loss target across all tirzepatide doses (mean bodyweight change from baseline (kg) was -12.4 (5 mg), -15.7 (10 mg) and -18.0 (15 mg) for early weight loss compared to -5.8 (5 mg), -8.3 (10 mg) and -10.4 (15 mg) for non-early weight loss groups) [39]. The starting dose of tirzepatide is 2.5 mg once weekly [1]. After 4 weeks, the dose should be increased to 5 mg once weekly [1]. If needed, dose increases can be made in 2.5 mg increments after a minimum of 4 weeks on the current dose [1]. The recommended maintenance doses are 5, 10 and 15 mg, with a maximum dose of 15 mg once weekly [1]. This information can be useful to guide treatment titration with tirzepatide and frequency of patient follow-up visits.

Adverse Events (AEs), Special Warnings, Precautions, and other Considerations for use

Acute Pancreatitis

In the phase 2 and 3 clinical trials, a low incidence of pancreatitis was reported (0.24% tirzepatide vs. 0.13% comparators), however patients

with a history of pancreatitis were not included [40].

Patients should be informed of identifiable symptoms of pancreatitis, such as stomach and back pain. If pancreatitis is suspected, tirzepatide should be discontinued out of caution. In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone would not be predictive of acute pancreatitis [1].

Diabetic Retinopathy

Diabetic retinopathy was reported in $< 1\%$ participants across the five phase 3 SURPASS clinical trials [4–8]. Patients with a history of proliferative diabetic retinopathy, maculopathy, or non-proliferative diabetic retinopathy requiring acute treatment were not included in tirzepatide clinical trials and thus it should be used with caution in these patients and with appropriate monitoring [1]. Based on the ADA standard of medical care, retinopathy status should be assessed when intensifying glucose-lowering therapies such as those using GLP-1 RA. In addition, if any level of diabetic retinopathy is present, retinal examinations should be repeated at least annually. If retinopathy is progressing, examinations will be required more frequently [41].

Acute Gallbladder Disease

Acute gallbladder disease (cholecystectomy, biliary colic, and cholelithiasis) was reported by 0.6% of tirzepatide-treated patients (vs. none with placebo). If cholelithiasis is suspected, diagnostic studies and follow-up are recommended [42].

Blood Pressure

Weight loss in patients with T2DM is related with BP reduction and less use of antihypertensive medication [43]. Tirzepatide has been associated with improvements in BP during the phase 3 SURPASS clinical trial program [44]. Treatment with tirzepatide was associated with a mean reduction in systolic and diastolic BP of 6

to 9 mmHg and 3 to 4 mmHg vs. a mean reduction of 2 mmHg with placebo in each systolic and diastolic BP. The highest baseline category (>140 mmHg) had the largest reductions, while those in the systolic BP category <122 mmHg showed no further decrease [45]. The induced BP reduction was primarily mediated through weight loss, with different degrees of contributions from weight loss-independent effects, and independent from the use of antihypertensive medication [45, 46].

Concomitant Antidiabetic Medication

Tirzepatide in combination with sulphonylurea (SU) or insulin may increase the risk of hypoglycemia, so it can be considered a dose reduction of these concomitant medications. To adjust the dose, blood glucose self-monitoring is necessary following a stepwise approach [1]. Clinically significant hypoglycemia was reported in 10–14% (0.14–0.16 events/patient year) of patients when tirzepatide was combined with sulphonylurea and in 14–19% (0.43–0.64 events/patient year) of patients when tirzepatide was combined with basal insulin. In case of tirzepatide use in monotherapy or in combination with other oral antidiabetic drugs, the rate was up to 0.04 events/patient year [1].

The patients included in the SURPASS-5 clinical trial with a baseline HbA1c level $\leq 8\%$, reduced the insulin dose by 20% after randomization [8]. There are no specific recommendations on how much the dose of the sulphonylurea should be reduced when used in combination with tirzepatide, however other authors have proposed a reduction in the dose of SU by 50% if HbA1c is $<8.5\%$, when used in combination with SGLT2i [47].

Gastrointestinal (GI) AEs

The most common AEs reported with tirzepatide are GI, which include nausea, vomiting, and diarrhea [1]. GI events were mostly mild or moderate in severity, and higher during the dose-escalation period and generally decreased over time [1]. The incidence of these GI effects was similar to that reported with semaglutide

1 mg [5]. Permanent treatment discontinuation due the described GI AEs was low ($<6\%$ of patients discontinued treatment due to nausea, vomiting, or diarrhea) [1, 48].

To mitigate GI events, the same considerations as with GLP-1 RA treatment could be taken into account, i.e., patients can be advised to eat smaller portions with less fat content; when GI AEs persist, the short-term prescription of omeprazole and/or antiemetic drugs could be considered; a reduction in the dose and a slower dose titration could be considered [49].

Information to Patients

Disease Information

HCPs from the prescription team, including the trained nurses from the diabetes unit and certified diabetic educators (CDEs), play a key role in appropriately educating the patients, not only regarding their clinical management and treatment but also self-management skills, which are necessary for an optimal T2DM control [40].

Gastrointestinal Adverse Events

The information required for patients starting treatment with tirzepatide could be similar to that provided to patients starting with GLP-1 RA [49]. In accordance with recommendations for GLP-1 RA usage, dietetic recommendations reinforcing nutritional aspects and a healthy lifestyle could be encouraged [50, 51]. General recommendations include eating habits improvements, such as eating smaller portions more frequently, more slowly, adapting food composition to individual requirements, by increasing fluid intake, reducing fats, and avoiding sweet, spicy or processed meals containing dressings or sauces that are not home-cooked [52]. In case of developing GI AEs, as already mentioned, the patient should know that they are commonly mild to moderate and generally transient [52]. Nevertheless, if they persist, patients should contact their prescription team [52]. Finally, patients should be advised of the potential risk of dehydration due to GI AEs and

take precautions to avoid fluid depletion and electrolyte disturbances. This should particularly be considered in the elderly, who may be more susceptible to such complications [1].

Body Weight Reduction

Since tirzepatide treatment is associated with weight loss and in a relevant percentage of patients weight reduction can be >10–15% [1]. Patients should be informed about this treatment effect, which is mainly driven by fat mass loss [1], and related to glycemic improvement [35]. Regular physical activity and minimization of a sedentary lifestyle should be encouraged [15, 53, 54].

CONCLUSIONS

Tirzepatide is a novel single-molecule GIP and GLP1 receptor agonist approved for the treatment of T2DM, which has recently been included in clinical guidelines [15]. The availability of this review, focusing on practical aspects of tirzepatide use and the supporting scientific evidence may be useful for HCPs in their daily practice.

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Declarations

Conflict of Interest. Luis A. Vázquez is advisory board member for Eli Lilly, has received speaker honoraria from AstraZeneca, Eli Lilly, and Novo Nordisk, has received research grants to institution from Eli Lilly, Novartis and Novo Nordisk, and is minor shareholder of Eli Lilly. Santiago Tofé-Povedano has received consulting, speaker and research honoraria from Eli Lilly, Novo Nordisk, AstraZeneca and GlaxoSmithKline. Diego Bellido-Guerrero is advisory board member for Eli Lilly, Novo Nordisk, Sanofi, Nestle HS, Persan Pharma, has received speaker honoraria from Novo Nordisk, Sanofi, Eli Lilly, Boehringer, Persan Pharma, Nutricia, AstraZeneca and is collaborator in national health research projects (FIS) and has participated in clinical trials of Eli Lilly, Sanofi, Bayer, Adventia Pharma, AstraZeneca, Novartis, Abbott. M.B.S has participated in clinical trials and has received speaker honoraria from Eli Lilly, Novo Nordisk, Abbot and AstraZeneca. Alfonso Soto-González is advisor on scientific boards for Novo Nordisk and Eli Lilly, has received speaker honoraria from MSD, Novo Nordisk, Eli Lilly and AstraZeneca, is collaborator in national health research projects (FIS) and has participated in clinical trials of Eli Lilly, Novo Nordisk, AstraZeneca, Bayer, Boehringer, Amgen, Pfizer and Novartis. Pedro Mezquita-Raya is advisor on scientific boards for Abbott, AstraZeneca, FAES and Novo Nordisk; lectures for AstraZeneca, Eli Lilly, FAES, Fresenius and Novo-Nordisk and performs research activities for Eli Lilly and Novo Nordisk. Elías Delgado has received unrestricted research support from AstraZeneca, Novo Nordisk, Sanofi, Pfizer, and Roche and has received consulting fees and/or honoraria for membership on advisory boards and speaker's bureau from AstraZeneca, Novo Nordisk, Lilly, Sanofi, GlaxoSmithKline, Pfizer, Almirall, Novartis, Abbott Laboratories, Esteve, and Merck Sharp & Dohme. Carmen

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Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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