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Italian Titration Approach Study (ITAS) with insulin glargine 300 U/mL in insulin-naïve type 2 diabetes: Design and population

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Abstract *Background and aims:* Fostering patient's self-managing of basal insulin therapy could improve glucose control, by removing patient's and physician's barriers to basal insulin initiation, titration and glucose monitoring. The Italian Titration Approaches Study (ITAS) aims at demonstrating non-inferiority (<0.3% margin) in efficacy of glucose control (change in glycated hemoglobin [HbA1c] after 24 weeks) by the same titration algorithm of insulin glargine 300 U/mL (Gla-300), managed by the (nurse assisted) patient versus the physician, in insulin naïve patients with Type 2 Diabetes Mellitus (T2DM), uncontrolled with previous treatments.
Methods and results: ITAS is a phase IV, 24-week, national, multicenter, open label, randomized (1:1) parallel group study. 458 patients were enrolled, 359 randomized, and 339 completed the study, in 46 Italian centers. Baseline characteristics and previous medications of the ITT population (N = 355) are reported. Mean ± SD age, T2DM duration, HbA1c, FPG and BMI were 64.0 ± 9.8 years, 11.6 ± 7.6 years, 8.79 ± 0.65%, 170.9 ± 42.3 mg/dL, and 30.3 ± 5.6 kg/m^2, respectively. Vascular and metabolic disorders were most frequent (73.8% and 58.3%, respectively). More than 90% of patients were on metformin.
Conclusion: ITAS is the first study to compare two different managers (nurse-assisted patient vs physician) of the same titration algorithm of Gla-300 in insulin naïve patients with T2DM in unsatisfactory glucose control. This study might provide novel evidence on the efficacy/

Acronyms: AE, adverse event; BMI, body mass index; DES, Diabetes Empowerment; DPP-4, dipeptidyl peptidase 4; DSME, diabetes self-management education; DTSQ, Diabetes Treatment Satisfaction Questionnaire; ECG, electrocardiogram; FPG, fasting plasma glucose; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; IA, interim analysis; ITAS, Italian Titration Approaches Study; ITT, Intention-To-Treat; PAID5, Diabetes Related Distress; PD, pharmacodynamic; PK, pharmacokinetic; PP, per protocol; RAAS, renin-angiotensin-aldosterone system; RCT, randomized controlled trial; SAE, serious adverse event; s.c., subcutaneous; SD, standard deviation; SGLT-2, sodium-glucose co-transporter 2; SMPG, self-monitored plasma glucose; START, Self-Titration with Apidra to Reach Target; TEAE, treatment-emergent adverse event; T1DM, Type 1 Diabetes Mellitus; T2DM, Type 2 Diabetes Mellitus.

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effectiveness of patient-managed titration algorithm of Gla-300 in a pragmatic setting and may reduce barriers to basal insulin initiation and its titration.

Introduction

Although many patients with T2DM require insulin therapy to achieve good glucose control, insulin initiation is often delayed because of patient and physician barriers regarding insulin use. Patient empowerment in self-managing insulin therapy may overcome some of the barriers and improve glucose control. In previous studies this approach has proven to be safe and slightly more efficacious than physician-managed titration. Particularly, the AT-LANTUS study, which compared two insulin glargine 100 U/mL (Gla-100) dose titration algorithms, showed that the patient-managed titration algorithm conferred a slight, albeit statistically significant, improvement in glucose control with a low incidence of severe hypoglycemia compared with physician-managed titration [1].

Gla-300 is second generation insulin that has been developed to optimize glycemic control while minimizing the risk of hypoglycemia. Gla-300 provides more even pharmacokinetic (PK) and pharmacodynamic (PD) profiles and a longer duration of action than Gla-100, due to a more gradual and extended release from the s.c. insulin depot, extending blood glucose control well beyond 24 h [2].

To determine whether these PK and PD properties confer clinical benefits, Gla-300 was investigated in comparison with Gla-100 in the phase IIIa EDITION program [3,4] and vs insulin degludec 100 U/mL (Deg-100) in the BRIGHT phase IV study [5]. Specifically, the EDITION 3 and BRIGHT studies investigated the safety and efficacy of Gla-300 in insulin-naïve people with T2DM [4,5]. In EDITION 3 Gla-300 demonstrated equivalent glycemic control, with lower risk of confirmed hypoglycemia vs Gla-100 over a six month period [4], a result observed also in the study extension at 12 months [6]. In the BRIGHT study Gla-300 has shown non-inferiority in terms of HbA1c lowering vs Deg-100, and lower risk for confirmed hypoglycemia in the titration period (0–12 weeks) as a prespecified study endpoint [5]. In both studies, dose titration of Gla-300 was managed by the treating physician [3–5].

Due to its PK-PD profile with lower risks of hypoglycemia, Gla-300 could be suitable for patients to efficiently self-manage their own insulin dose titration.

The TAKE CONTROL and INSIGHT studies reported the performance of patient managed titration algorithms of Gla-300 in cohorts of people with T2DM, almost entirely on basal insulin [7,8]. However, no RCT has been specifically devoted to test the outcomes of a patient managed Gla-300 titration algorithm in insulin naïve T2DM patients.

Therefore the Italian Titration Approach Study (ITAS) was undertaken to assess whether patient management is non-inferior to physician management of the same titration algorithm of Gla-300 in reducing HbA1c at 24 weeks (primary endpoint) in Italian insulin-naïve patients with T2DM. In this paper we report the study design, main baseline characteristics and previous anti-hyperglycemic treatments of the enrolled patients.

Methods

Study design and objectives

ITAS (EudraCT Number: 2015-001167-39) is a national (Italy-based), pragmatic, phase IV, 24 week, randomized (1:1), controlled, open-label, parallel-group study, comparing the efficacy and safety of the same titration algorithm of Gla-300, managed by the patient with nurse assistance versus the physician, in T2DM patients naïve to insulin (Fig. 1, Table 1).

Primary aim of this study was to assess the non-inferiority in terms of HbA1c reduction of the (nurse assisted) patient-managed *versus* the physician-managed algorithm for titrating Gla-300 in insulin naïve T2DM patients, inadequately controlled with oral antidiabetic agents and/or non-insulin injectables, after 24 week treatment. Secondary objectives were: to compare the incidence and event rate of hypoglycemia; changes in Fasting Plasma Glucose (FPG); in insulin dose and body weight; percentage of patients at HbA1c target; percentage of patients at HbA1c target without hypoglycemia; percentage of patients at HbA1c target and no weight increase at 24 weeks. Additional trial goals were to assess: patient/physician adherence to dose titration algorithm and correlation with glycemic control; patient reported outcomes; safety and tolerability.

Study population

The main inclusion criteria were: diagnosis of T2DM for at least one year in insulin-naïve adults, with poor glycemic control (HbA1c $\geq$ 7.5% and $\leq$10%), on oral anti-hyperglycemic agents and/or non-insulin injectables and the willingness/ability to self-manage titration algorithm. Sulfonylureas and/or glinides were discontinued at randomization until the end of the study to reduce the hypoglycemic risk and to evaluate the pure effect of Gla-300 (Fig. 1).

The main exclusion criteria were: T1DM diagnosis; age $<$18 years; previous insulin treatment; lack of willingness to stop sulfonylureas and/or glinides; known hypersensitivity/intolerance to insulin glargine or any of its excipients; pregnant and breastfeeding women; women of

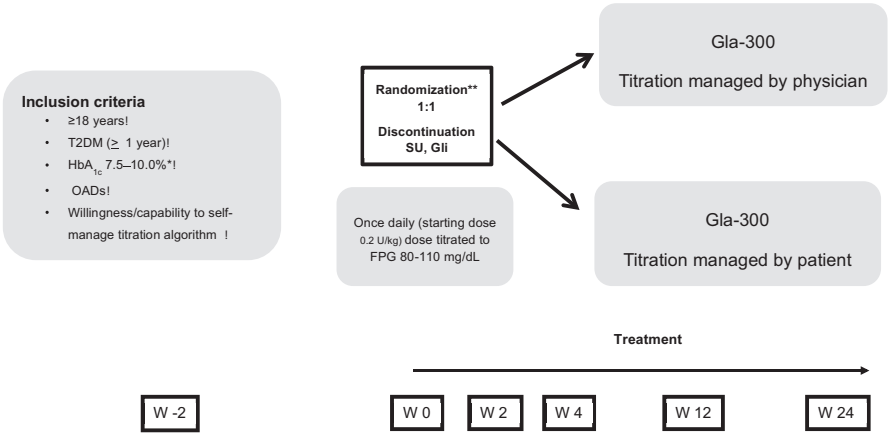

Figure 1 Graphical Study Design. HbA1c, glycated hemoglobin; OAD, oral anti-diabetic drugs; SU, sulfonylureas; Gli, glinides. * HbA1c was measured by a central laboratory. HbA1c was assayed at screening, at 12 weeks, and at endpoint (24 weeks). ** Patients were centrally randomized: the method of assigning patients to treatment group was through the IVRS system (Interactive Voice Response System).

Table 1 Basal Insulin Titration Algorithms (physician- and patient-managed arm).

Median of fasting SMPG values measured on 3 consecutive days, of which the last is the day when titration is to occur	Basal Insulin (Gla-300) dose adjustment (U)[a]	
	Algorithm for Physician (managed by physician)	Algorithm for Patient (managed by patient)
>180 mg/dL	+4	+4
>110–180 mg/dL	+2	+2
80–110 mg/dL	no change	no change
<80 mg/dL	−2	−2
<54 mg/dL or occurrence of ≥2 symptomatic or 1 severe hypoglycemic episode(s) in the preceding week	at physician's discretion	contact physician

[a] Dose should be adjusted every 3–4 days to achieve a target range for fasting SMPG of 80–110 mg/dL. Changes in insulin dose were based on the median of fasting SMPG values measured on 3 consecutive days of which the last is the day when titration is to occur.

childbearing potential not using highly-effective birth control methods or not willing to be tested for pregnancy.

The study was approved by Institutional Review Boards/Ethics Committees at each research site and was performed in accordance with the Declaration of Helsinki and the Guidelines from International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. All participants provided written informed consent.

Study drug (Gla-300) and the glucometer for self-monitoring plasma glucose (SMPG) were provided by Sanofi Milan, Italy.

Randomization and study treatment

Eligible patients entered a run-in period of 2 weeks (±2 days), at the end of which, they were randomized 1:1 to either self-titration or physician-titration arm, following the study titration algorithm (Fig. 1, Table 1). In both study arms insulin dose was adjusted once weekly aiming for a fasting SMPG of 80–110 mg/dL in the absence of hypoglycemia. Dosage was to be increased by 2 U for SMPG >110 and <180 mg/dL and by 4U for SMPG >180 mg/dL, and to be decreased by 2 U if SMPG was <80 mg/dL (Table 1). In the physician-managed titration arm, patients had insulin dose adjustments during subsequent visits/contacts with the physician according to the study titration algorithm, whereas patients self-managing insulin titration received from the study-nurse a specific, detailed, educational session regarding self-adjustment of insulin dose using the same titration algorithm (Table 1). The former patients had visits/contacts mainly to obtain titration prescription from the physician, whereas the patients in the self-titration group had visits/contacts to obtain educational support from the site nurse. Nurse phone calls were scheduled to collect glycemic values and relevant information from self-managed patients and to verify correct algorithm application, but nurses were instructed to exert no influence on insulin titration. Patients were provided with MyStar-Extra glucometer in order to assess and record daily fasting SMPG until it was stable at target. Thereafter, fasting pre-breakfast SMPG was mandatory on at least 3 consecutive days per week; 7-point SMPG profile was performed at Week 12 and Week 24. All patients were instructed to self-administer daily subcutaneous injection of Gla-300 in the evening, from immediately prior to the evening meal until bedtime, at the discretion of the patient/investigator. The time of injection was fixed and maintained as reference for the duration of the study; if necessary, it could vary ±3 h from the fixed time, according to product labeling [9].

Treatment with Gla-300 should be initiated at 0.2 U/kg/die as per label, and then adjusted, at least weekly, but not more than every 3–4 days as needed, to achieve a fasting SMPG goal of 80–110 mg/dL [9]. In both study groups changes in the insulin dose should be based on the median of the fasting SMPG values measured on 3 consecutive days, of which the last was the day when titration was scheduled, according to the study algorithm (Table 1).

Until week 12, visits/contacts were weekly, and then every two weeks until week 24; four of these visits were held at the center.

Rescue therapy, if needed, either by adding a new anti-hyperglycemic drug and/or by increasing the dose of an existing anti-hyperglycemic non-study drug, was based on the Investigator's judgment, considering primarily the patient's individual clinical needs, but also local guidelines and Gla-300 labeling [9].

All study data were entered by the Investigator through an *ad hoc* electronic Case Report Form (e-CRF).

Endpoints and safety assessment

The primary efficacy endpoint was the change in HbA1c from baseline to Week 24 (delta HbA1c 0.3% non-inferiority margin). The principal secondary endpoint was the incidence (%) of participants with at least one confirmed (≤3.9 mmol/L [70 mg/dL]) and/or severe nocturnal (00.00–05.59) hypoglycemic event from baseline to Week 24. Other main secondary endpoints included hypoglycemic events per patient-years during the study treatment period; percentage of patients with HbA1c < 7.0% and 8.0% with and without hypoglycemia; change from baseline to endpoint in FPG, body weight and insulin dose. Modifications of Diabetes Related Distress (PAID5) and of Diabetes Empowerment (DES) were also evaluated in both study groups. Diabetes Treatment Satisfaction Questionnaire (DTSQ) was also administered at randomization (Status) and end of trial (Change).

Safety and tolerability analyses were based on all hypoglycemic events, skin reaction at injection site, hypersensitivity reactions, any other adverse events (AE) or serious adverse events (SAE) and other safety parameters such as clinical laboratory data, vital signs, body weight and ECG.

All hypoglycaemic episodes were recorded in the patient's diary or documented in the "hypoglycemia section" of the eCRF.

Statistical analysis

Sample size determination

A sample size of 318 subjects (159 in the patient-managed titration group and 159 in the physician-managed titration group) ensures that the upper confidence limit of the two-sided 95% CI for the mean difference between the 2 algorithm approaches is lower than 0.3% in HbA1c with 80% power, assuming that SD is 0.95%, and that the true difference between the two dosing regimens of Gla-300 is zero in HbA1c. Assuming a 10% drop-out rate, 354 participants are to be randomized.

Demographic variables, as well as disease characteristics at baseline are summarized in the randomized population by titration group and overall. No statistical test was planned for between-group differences in demographics and disease characteristics at baseline. Summaries of previous medications are generated separately for antidiabetic therapies and for other therapies. No statistical tests were performed.

The efficacy analysis will be based on the Intention-To-Treat (ITT) population that include all randomized patients who receive at least one dose of study drug and have a baseline assessment of primary efficacy variable, irrespective of compliance with the study protocol and procedures. Patients will be analyzed according to the titration group allocated by randomization. The Per Protocol (PP) population, that is all patients in the ITT population without major protocol deviations, will be used for the supportive analysis of the primary efficacy endpoint.

Primary endpoint analysis

The change in HbA1c from baseline to endpoint at Week 24 will be analyzed on the ITT population applying a Linear Mixed-Effect Model with titration approach and center as fixed effect and the HbA1c baseline value as covariate.

To assess the non-inferiority of patient-driven *versus* physician-driven titration, the upper bound of the CI for the estimated difference in the mean change of HbA1c from baseline to endpoint at week 24 between the two titration approaches will be compared with the predefined non-inferiority margin of 0.3% in HbA1c. Non-inferiority will be proved if the upper bound of the two-sided 95% CI of the difference for the ITT population is <0.3%.

Secondary endpoints analysis

The incidence of patients with at least one confirmed (≤3.9 mmol/L [70 mg/dL]) and/or severe nocturnal hypoglycemic event from baseline to Week 24 will be presented in the two trial arms. The cumulative incidence and the annual incidence rate of hypoglycemia will be computed by type and time in each study arm. All statistical comparisons between the two titration groups will be based on 95% Confidence Intervals.

Continuous variables (FPG, mean fasting SMPG based, body weight) will be analyzed using the same Linear Mixed-Effect model described above using the baseline value as a covariate.

The change in PAID5 and in DES total score will be computed and will be analyzed through a Linear Mixed-Effect model, including in the model the effect of the titration approach and the baseline total score as covariates. DTSQ at the end of the treatment will be reported through descriptive statistics in each study arm.

Safety data analysis

Safety analyses will be based on the safety population. A summary of treatment-emergent AEs (TEAEs), serious TEAEs and TEAEs of special interest will be presented by titration approach.

Interim analysis (IA)

A descriptive IA was planned when half of the randomized patients completed 12 weeks of treatment, in order to have early information on protocol and insulin titration compliance in both titration groups in relation to main efficacy outcome and safety issues.

Results

Study enrollment started in September 2015 and ended in March 2017. At total of 458 patients were enrolled, 359 randomized, of whom 339 (94.4%) completed the trial in 46 Italian centers.

Nine patients (2.5%) discontinued the study due to consent withdrawal, 4 (1.1%) were lost to follow-up, 2 (0.6%) discontinued the study due to AE and 5 (1.4%) discontinued for other reasons. The main reason for screening failures of the 99 (21.6%) patients not randomized was HbA1c values outside the prespecified interval for inclusion in the study (i.e. <7.5% or >10%), after central laboratory report.

Baseline characteristics of the ITT population (N = 355, 62.0% males) are reported in Table 2. The mean ± SD age was 64.0 ± 9.8 years, known duration of T2DM 11.6 ± 7.6 years, HbA1c 8.79 ± 0.65%, FPG 170.9 ± 42.3 mg/dL and BMI 30.3 ± 5.6 kg/m^2 (weight 83.4 ± 17.5 kg).

According to patient reported medical history, the most frequent underlying medical conditions were: vascular (73.8%), metabolism and nutrition (58.3%) disorders, surgical and medical procedures (34.1%), cardiac (23.9%), nervous system (16.3%) and renal and urinary (13.2%) disorders. The previous medications of the ITT population at baseline are shown in Table 3. As to cardiovascular medications at baseline, 59% of patients were on renin-angiotensin-aldosterone system (RAAS) agents, namely ACE inhibitors or ARB, and 54% of patients were on lipid lowering agents (Table 3).

Previous glucose lowering treatments are reported in Fig. 2. Metformin treatment was present (alone or in combination with other agents) in more than 92.1% of patients. Sulfonylureas and glinides were used in about 27.9% and 8.5% of patients respectively. Other classes of glucose lowering medications in use at baseline were: DPP-IV inhibitors (32.1%), GLP-1 receptor agonists (8.7%) and SGLT2 inhibitors (10.7%). Few patients were treated with pioglitazone (6.5%) or acarbose (3.1%).

The IA was performed in 223 patients (107 randomized in the patient managed and 116 in the physician managed group), who received at least one dose of the study drug: no relevant differences in the main efficacy and safety parameters were reported (data not shown). Due to the observational nature of this IA, no interventions/adjustments were pre-planned such as stopping the study or modifying the sample size, and therefore no adjustment of the alpha level was made.

Table 2 Baseline characteristics and patient reported medical history of the intention-to-treat population (n = 355).

Characteristics		Mean (SD)
Age, years		64.0 (9.8)
Sex, N (%)	Male	220 (62.0)
	Female	135 (38.0)
Time from diabetes diagnosis, years		11.6 (7.6)
HbA1c, %		8.79 (0.65)
FPG, mg/dL		170.9 (42.3)
Weight, kg		83.4 (17.5)
BMI, kg/m^2		30.3 (5.6)
Underlying conditions		Number (%)
Vascular disorders		262 (73.8)
Metabolism and nutrition disorders		207 (58.3)
Surgical and medical procedures		121 (34.1)
Cardiac disorders		85 (23.9)
Nervous system disorders		58 (16.3)
Renal and urinary disorders		47 (13.2)
Eye disorders		45 (12.7)
Gastrointestinal disorders		40 (11.3)
Endocrine disorders		38 (10.7)
Reproductive system and breast disorders		33 (9.3)
Benign, malignant and unspecified neoplasms		32 (9.0)
Psychiatric disorders		24 (6.8)
Musculoskeletal and connective tissue disorders		23 (6.5)
Respiratory, thoracic and mediastinal disorders		22 (6.2)
Hepatobiliary disorders		20 (5.6)
Infections and infestations		15 (4.2)
Investigations		11 (3,1)
Injury, poisoning and procedural complications		13 (3.7)
Skin and subcutaneous tissue disorders		9 (2.5)
Blood and lymphatic system disorders		7 (2.0)
Ear and labyrinth disorders		6 (1.7)
Congenital, familial and genetic disorders		5 (1.4)
Immune system disorders		4 (1.1)
General disorders and administration site conditions		4 (1.1)

Data presented are number (percentages) unless otherwise indicated. Percentages are calculated based on the number of patients with available data. A patient could report more than one relevant medical condition Pathologies collected in medical or surgical history, both in the past and still active at study entry, were coded using MedDRA dictionary version 20.1 and presented by System Organ Class and Preferred Term.

Discussion

Most T2DM patients currently remain in sub-optimal control despite the availability of several non-insulin therapies. Therapeutic inertia appears to be more pronounced when considering addition of insulin, particularly in insulin-naïve people [10]. In Italy about 45% of patients achieves HbA1c <7% and the proportion of patients without insulin therapy despite poor glucose control (HbA1c >9%) is approximately 35–45% [11]. The latest epidemiological report shows only a partial improvement with a 51% of patients achieving HbA1c <7% and about 27% with HbA1c > 9% not treated with insulin [12].

Poor metabolic control can be partly attributed to delayed initiation of insulin, lack of dose adjustment and

Table 3 Previous medications of the intention-to-treat-population at baseline (n = 355).

Patients with at least one previous medication	*n*	%
Drugs used in diabetes	350	98.59
Agents acting on the renin-angiotensin system	209	58.87
Lipid modifying agents	191	53.80
Antithrombotic agents	169	47.61
Beta blocking agents	108	30.42
Drugs for acid related disorders	73	20.56
Calcium channel blockers	71	20.00
Diuretics	49	13.80
Thyroid therapy	37	10.42
Urologicals	23	6.48
Cardiac therapy	21	5.92
Antigout preparations	20	5.63
Psychoanaleptics	19	5.35
Antihypertensives	18	5.07
Drugs for obstructive airway diseases	11	3.10
Vitamins	11	3.10
Analgesics	9	2.54
Psycholeptics	9	2.54
Antianemic preparations	6	1.69
Ophthalmologicals	6	1.69
Antibacterials for systemic use	4	1.13
Antidiarrheals, intestinal antiinflammatory/antiinfective agents	4	1.13
Other	23	6.48

Data presented are number (percentages). Percentages are calculated based on the number of patients with available data. Prior medications: defined as therapies starting prior to the study entry. One patient could report more than one prior medications.

delayed intensification [13]. The reasons why both people with diabetes and physicians often refrain from insulin initiation are complex. Both doctors and patients often are concerned with hypoglycaemia, weight gain and adherence [14]. Other barriers may be psychological, including fear of injections and/or self-measuring blood glucose [15], and fear that quality of life will worsen considerably [16].

Diabetes self-management education (DSME) is an integral aspect of the latest guidelines for management of T2DM [17], suggesting that DSME helps patients to manage their diabetes treatment and to adopt positive behavioral changes to optimize clinical outcomes. Insulin titration algorithms can simplify regimen complexity, and thereby help patients to manage glucose control more conveniently and effectively. For example, patient-led titration using simple algorithms resulted in greater HbA1c reductions *versus* physician-led adjustment of Gla-100 (−1.22% *versus* −1.08%, $p < 0.001$; AT.LANTUS Study) [1] in T2DM patients already treated with insulin; more recently, similar results were reported using Gla-300 in a mixed insulin-naïve and treated T2DM population [2,3]. Moreover, in patients with T2DM on basal bolus therapy, the START (Self-Titration with Apidra to Reach Target) study showed, that a simple patient-managed titration algorithm of the meal insulin doses is as effective as a physician-managed algorithm [18]. In this context, the diabetes nurse plays a key role. A recent cluster randomized controlled trial in Australia revealed that a “Stepping Up” model, which involved nurse-led insulin initiation, resulted in increased insulin initiation rates, greater HbA1c reductions and no deterioration in emotional wellbeing [19].

ITAS is a large prospective, randomized study of glucose control management performed in Italy in insulin naïve subjects with T2DM.

About 22% of screened patients were not randomized because outside of the HbA1c interval for inclusion, as the central lab reporting was divergent from the previous local data used by the Investigator for recruitment, as often observed in the screening phases of clinical trials. Compared to EDITION 3 (878 participants) [6] and BRIGHT study (929 participants) [7], patients enrolled in the present study (ITT population: N = 355) were slightly older (64.0 ± 9.8 *versus* 57.7 ± 10.1 and 60.5 ± 9.7 years old), with slightly longer duration of disease (11.6 ± 7.6 *versus* 9.8 ± 6.4 and 10.6 ± 6.3 years) and lower BMI (30.3 ± 5.6 *versus* 33.0 ± 6.7 and 31.5 ± 4.4 kg/m^2), but with similar HbA1c at baseline (8.79 ± 0.65 *versus* 8.54 ± 1.06 and 8.64 ± 0.82%). Use of sulfonylureas at baseline was quite lower in ITAS (27.9%) than EDITION-3 (59%) and BRIGHT

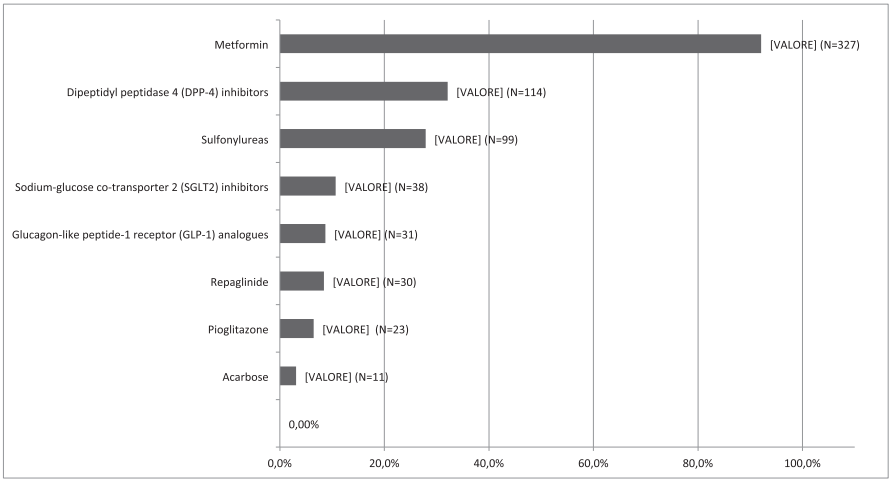

Figure 2 Previous diabetes medications of study population at baseline. Intention-To-Treat-population: % (N) are reported. Prior medications: defined as therapies starting prior to the study entry. One patient could report more than one prior medications.

studies (65.7%). Specifically, according to the Italian Standards of Diabetes Therapy, use of sulfonylureas and glinides in combination with metformin should be considered only after the new anti-diabetic drugs and limited to those ones with the most favorable safety profile [20].

On the other hand, ITAS patients appear to be representative of Italian people with type 2 diabetes and their management [21]. Of note, ITAS confirms that initiation of basal insulin therapy in T2DM occurs only about 10 years after the diabetes diagnosis and after years of poor glucose control, as previously reported in different world geographical areas [22].

Only baseline data of the study population are reported in this paper, as per goal of this report. This study will provide further information about the acceptance of Gla-300 in insulin-naïve patients, within a European clinical setting, with a comparative assessment of the efficacy of patient- (nurse assisted) *versus* physician-managed basal insulin titration algorithm. It is worthy to notice that in the patient/nurse driven arm the nurse educational support itself could positively affect the outcome, as frequency of contacts is *per se* a potential factor that improves motivation and adherence.

Moreover, ITAS may provide original insights into its simple, widely applicable titration algorithm for Gla-300, which can easily be translated into clinical practice. Pragmatic randomized trials, such as ITAS, and real-world studies will be instrumental in assessing the effectiveness of different allocation (nurse assisted patient vs physician) of the locus of control of basal insulin therapy in type 2 diabetes.'

Conflicts of interest

None declared.

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Appendices

List of centers participating to the ITAS Study

N. 380001, Perugia, Bolli Geremia; **N. 380002,** Novara, Aimaretti Gianluca; **N. 380003,** Pistoia, Anichini Roberto; **N. 380004,** Alessandria, Ansaldi Egle; **N. 380005,** Padova, Avogaro Angelo; **N. 380006,** Roma, Baroni Marco G.; **N. 380007,** Parma, Bonadonna Riccardo; **N. 380008,** Verona, Bonora Enzo; **N. 380009,** Cuneo, Borretta Giorgio; **N. 380010,** Bergamo, Bossi Antonio Carlo; **N. 380011,** Torino, Broglio Fabio; **N. 380012,** Roma, Bulzomì Rocco; **N. 380013,** Roma, Buzzetti Raffaella; **N. 380014,** Napoli, Capaldo Brunella; **N. 380015,** Chieti, Consoli Agostino; **N. 380017,** Messina, Cucinotta Domenico; **N. 380018,** Foggia, De Cosmo Salvatore; **N. 380019,** Pisa, Del Prato Stefano; **N. 380020,** Ravenna, Di Bartolo Paolo; **N. 380021,** Lucca, Di Carlo Alberto; **N. 380022,** Livorno, Di Cianni Graziano; **N. 380023,** Catania, Di Mauro Maurizio; **N. 380024,** Siena, Dotta Francesco; **N. 380026,** Milano, Genovese Stefano; **N. 380027,** Napoli, Gentile Sandro; **N. 380028,** Roma, Giaccari Andrea; **N. 380029,** Palermo, Giordano Carla; **N. 380030,** Padova, Lapolla Annunziata; **N. 380031,** Roma, Leonetti Frida; **N. 380032,** Roma, D'Angelo Paola; **N. 380033,** Bologna, Marchesini Giulio; **N. 380034,** Desio (MB), Marelli Giuseppe; **N. 380035,** Como, Muratori Fabrizio; **N. 380036,** Roma, Napoli Angela; **N. 380037,** Napoli, Napoli Raffaele; **N. 380038,** Milano, Piatti Piermarco; **N. 380039,** Partinico (PA), Provenzano Vincenzo; **N. 380040,** Savigliano (CN), Oleandri Salvatore; **N. 380041,** Grossetto, Rizzo Loredana; **N. 380042,** Cremona, Ruggeri Patrizia; **N. 380043,** Lecce, Serra Rosalia; **N. 380044,** Foggia, Serviddio Gaetano; **N. 380045,** Palmi (RC), Stagno Gaudenzio; **N. 380048,** San Donà di Piave, Vinci Carmela; **N. 380049,** Roma, Ventura Claudio; **N. 380050,** Negrar, Zenari Luciano; **N. 380051,** Napoli, Foglia Angelo; **N. 380052,** Napoli, Giugliano Dario; **N. 380053,** Oristano, Mastinu Francesco; **N. 380056,** Caserta, Starnone Vincenzo; **N. 380057,** Messina, Di Benedetto Antonino; **N. 380058,** Catania, Privitera Filippo; **N. 380059,** Fermo, Tortato Elena.

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