DISEASE REGISTRY REPORT

Compound(s): **Not applicable**

Registry Title: Multinational, Prospective, Observational Study to Assess the Unmet Medical Needs associated with Basal Insulin Use in Patients with Type 2 Diabetes Newly or recently Initiated with Basal Insulin Treatment

Registry number: OBS13780

Registry name: DUNE

Registry initiation date [date first patient in (FPI)]: 25-Feb-2015

Registry completion date [last patient completed/last patient out (LPO)]: 19-Jul-2016

Registry design: Multinational, observational, prospective, single-arm,

Report date: 22-Mar-2017

This registry was performed in compliance with the guidelines for Good Epidemiology Practice. This report has been prepared based on the publication 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) – Guidelines for reporting observational studies – Ann Intern Med. 2007'.

SYNOPSIS

Title of the registry:	Multinational, Prospective, Observational Study to Assess the Unmet Medical Needs associated with Basal Insulin Use in Patients with Type 2 Diabetes Newly or Recently Initiated with Basal Insulin Treatment. Study number: OBS13780
Design:	Prospective, single-arm, observational, study (non-interventional on the therapeutic strategy). This observational study planned to collect information on the current status, characteristics and management of patients with Type 2 diabetes newly initiated or being treated for less than 12 months with basal insulin. The design of this study aimed to mirror real life management of these subjects. There was no fixed study visit schedule during the follow-up period. The visits were done according to clinical practice. The data was recorded at study entry and 12 weeks. The medical history of patients was also collected especially concerning diabetes complications, comorbidities history of severe hypoglycemia , level of HbA1c and individual diabetes goals.,. In order to have available data on various countries/regions, this observational study was international. This strategy enhanced the significance of the results and allowed analyses on a country/region basis because management patterns could vary on a country/regional basis.
Objectives:	**Primary objective** • Describe the proportion of patients achieving HbA1c target (individual or general target of < 7.0% if individual target was not defined) at 12 weeks. • Evaluate the impact of symptomatic hypoglycemia according to its frequency and severity on short term HbA1c target achievement at 12 weeks. **Secondary objective(s)** • Describe the incidence of hypoglycemic events: any symptomatic, severe, documented symptomatic. • Describe the proportion of patients achieving general HbA1c target of < 7.0%. • Describe the proportion of patients achieving HbA1c target of < 7.0% or < 8.0% according to level of risk (defined by patient's characteristics, comorbidities and severe hypoglycemia history at baseline). • Describe the proportion of patients achieving the "12-week HbA1c" objective (defined as the level of HbA1c aimed to be reached by the patient by Week 12, according to the physician). • Describe the proportion of patients achieving at least 0.5% and 1.0% HbA1c reductions from baseline. • Describe the proportion of patients achieving HbA1c target (individual or general target of < 7.0% if individual target was not defined) without symptomatic hypoglycemia. • Describe the proportion of patients achieving the "12-week HbA1c" objective (defined as the level of HbA1c aimed to be reached by the patient by week 12, according to the physician) without symptomatic hypoglycemia. • Describe proportion of patients achieving at least 0.5% and 1.0% HbA1c reduction from baseline without symptomatic hypoglycemia. • Identify baseline factors associated with treatment failure defined as falling to achieve individual (or general target of < 7.0% if individual target was not defined) and general target of < 7.0%. • Assess fear of hypoglycemia by the validated patient –completed Hypoglycemia Fear

	Survey II (HFS-II).
Participants planned:	DUNE study was planned to involve 4000 subjects in approximately 30 countries worldwide during a recruitment period of 4 months. Participating physicians were general practitioners (GPs) who were familiar with insulin management in Type 2 diabetes and specialists. Selection criteria or the study population were the following: **Inclusion criteria** • Male or female, • Age ≥ 18 years, • With Type 2 diabetes, • Newly initiated (at the time of enrolment) with or being treated with basal insulin for < 12 months with or without oral antihyperglycemic drugs and/or GLP-1 receptor agonists, • Had an HbA1c measurement (≥ 7.5 and ≤ 11.0% for newly initiated patients and ≥ 7.5 and ≤ 10.0% for existing basal insulin users) available at enrolment (or within the last month prior to enrolment), • Were willing to perform self-monitoring blood glucose (SMBG) according to physician instruction, • Were willing to complete study patient diary (for SMBG, insulin dose and hypoglycemia), • Agreed to complete the questionnaire, • Had signed informed consent obtained. **Exclusion criteria** • Treated with rapid acting or premix insulin or for whom the physician planned to intensify the treatment with a rapid acting or premix insulin within the following three months, • Start of insulin within 1 year after diabetes diagnosis in patients under 40 years (potential type 1 diabetes patients), • Pregnancy or were planning to become pregnant.
Scientific committee and members:	Kamlesh Khunti , Leicester, UK. Luigi Meneghini , Dallas , USA Didac Mauricio, Lleida , Spain
Publications (reference):	Not applicable.
Introduction - Background/rationale:	Type 2 diabetes is one of the most prevalent chronic conditions and its frequency is increasing, driven primarily by an accelerated incidence of obesity (1). The burden of the disease is significant both on individuals and on society. The associated costs are mainly driven by associated complications of T2DM (2). Type 2 diabetes is a progressive disease with declining beta-cell function which requires a step-wise addition of different therapeutic approaches to achieve good metabolic control. These interventions typically start with lifestyle changes introduced at the time of the diagnosis and followed by adding oral antihyperglycemic drugs and subsequently injectable therapies including full replacement of the severely diminished endogenous insulin secretion (3). Evidence from previous interventional trials in diabetes clearly demonstrated that long term good

glycemic control is associated with a lower risk of the development of late complications (4). This is well-established in the case of microvascular complications. The link between poor glycemic control and macrovascular complications is still the subject of intensive debate although epidemiological studies have consistently demonstrated poorer cardiovascular outcomes with worsening glycemic control (5). Therefore the ultimate aim of the applied therapies is to achieve appropriate glycemic control in order to delay or prevent late complications (3).

Despite the wealth of evidence showing the vital role of good glycemic control in the management of type 2 diabetes, and the increasing number of antidiabetic medications available for managing these patients, a significant proportion of patients still do not achieve the general HbA1c target of 7.0% and thereby remain at increased risk of complications (6).

One of the reasons why target achievement is limited in the diabetes population is the potential impact of hypoglycemia.

Since improvement in metabolic control is typically associated with higher frequency of hypoglycemia, there is a reluctance both from physician and patient perspectives to achieve appropriate glycemic control.

Physicians do not want to expose their patients to increased hypoglycemic risk whilst patients want to avoid the unpleasant experience of a hypoglycemic episode.

Different therapeutic compounds are associated with different levels of hypoglycemia risk (3). Undoubtedly the antihyperglycemic therapeutic approach which has the highest risk of hypoglycemia is insulin therapy. Hence it is not surprising that there is a high level of reluctance to initiate therapy and to optimize the applied therapeutic regime in case of insulin therapy (7).

The high level of clinical inertia leads to late insulin initiation and sub-optimize dosing, . This is clearly associated with suboptimal overall glycemic control in a large proportion of patients with type 2 diabetes (6) (7).

Although there seems to be a clinical consensus that treatment associated hypoglycemia is a key factor for late insulin initiation and reluctance to optimize the applied dose to achieve target HbA1c, the available evidence to substantiate the link between treatment associated hypoglycemia and failure to achieve glycemic target is surprisingly limited (8).

Data confirming the link between fear of hypoglycemia (either de novo or hypoglycemic event triggered) and reluctance to titrate insulin to the optimal dose is mostly limited to type 1 diabetes (9).

There are a few ways to investigate the association between hypoglycemic events and failure to optimize insulin dose in the diabetes population.

One potential method could be to analyze data from randomized controlled trials, which would provide reliable databases to study such a link. The major problem with this methodology way is the applied titration approach in the trials. For the last 10 years, trials in type 2 diabetes are conducted with a treat to target approach, which in the absence of repeated hypoglycemic events, force the investigators to titrate the insulin dose to the optimal level which theoretically ensures that the protocol-specified fasting blood glucose target is reached (10). Therefore this type of study is not appropriate to describe the link between hypoglycemic events and reluctance of up-titration of insulin dose subsequently leading to suboptimal glycemic control.

Another method is to analyze electronic medical record databases to try to establish the link between recorder and coded hypoglycemic events and failure to achieve appropriate glycemic control. Here, the major issue is the reliability of the medical records to reflect incident hypoglycemic events. Whilst such databases may capture severe events because these are likely to be associated with emergency room (ER) visits or hospitalization which subsequently are reported to primary care physicians, non-severe events are most likely not reflected in such databases. As the frequency of severe hypoglycemia is relatively low with basal insulin therapy in type 2 diabetes, it is highly challenging to establish the link between severe hypoglycemic events and failure to achieve target HbA1c. On the other hand, non-severe events, which are most likely not captured in general practitioners (GP) databases, are more frequent, and can be frightening and unpleasant for the

	patients, and thus may have an unfavorable impact on target achievement. The question is how we can reliably capture non-severe events to demonstrate such relationships in real clinical practice. One potential way to record such non-severe events is to prospectively follow-up patients in clinical practice and request to record any hypoglycemic event they experience in real time manner. One of the main objectives of the current study was to reliably detect hypoglycemic events in uncontrolled type 2 diabetes patients either newly started with basal insulin or being initiated within one year prior to the involvement in the study and try to establish the association between hypoglycemic episodes detected during the observational period of time and short-term glycemic target achievement 12 weeks enrolment. Furthermore the study also aimed to describe the proportion of patients who achieved their individualized HbA1c target, as defined by the physician, and/or general glycemic target of 7.0%. Establishing the association between non-severe hypoglycemic events and failure to achieve glycemic target is not just important to confirm the assumed link between the two outcomes (hypoglycemia is considered as safety outcome whilst achieving target HbA1c is an established glycemic outcome and a surrogate outcome for late diabetes complications) but also important to highlight the importance of non-severe hypoglycemic events to payors. Since hypoglycemia might be associated with other unfavorable clinical and health economics outcomes (11), the study included multiple secondary objectives to describe the potential impact of hypoglycemia, with a special focus on reliably collected non-severe hypoglycemic events, and factors such as weight gain, fear of hypoglycemia, treatment adherence and discontinuation, and health care resource utilization. An e-diary was provided to a subset of patients instead of the paper diary. The purpose of this e-diary substudy was to obtain in real-time information from patients regarding their glucose monitoring, episodes and symptoms of hypoglycemia, fear of hypoglycemia, and adherence to medication/titration algorithms. The e-diary was able to wirelessly integrate the values from the blood glucose meter and send the information to the electronic data collection tool. In addition, it allowed integration of the treatment algorithms and assessment of whether they had been followed. Finally, it allowed questions to be asked in response to episodes of hypoglycemia that the patient could answer in order to provide a more detailed description of the hypoglycemic episode.
Methodology:	**(a) Site and patient selection** GPs and specialists who are familiar with insulin management in type 2 diabetes with capability to enroll at least 10 patients. In order to limit biases of patient selection, each selected Investigator had to include consecutive patients who met the inclusion and exclusion criteria. The recruiting clinicians had to ensure a minimum of 40% of patients newly initiated with basal insulin therapy (ie, starting treatment with basal insulin at the study entry) at the country level. **(b) Data collection** At study entry, each patient was provided with a study patient diary, in order to collect, following the usual physician instructions and recommendations, his/her blood glucose (BG) values (obtained from their own glucose meter) and insulin doses and to report information on symptomatic hypoglycemia events during the study period. Patients included in Denmark, Finland, Norway and Sweden, were provided with an e-diary at study entry as well as a Bluetooth enabled glucose meter. This allowed an automatic data transfer of the BG measurements in the e-diary. As per current practice, the patient was asked to return his/her diary at the time of routine clinical visits and at the end of the study period.

For each patient, the investigator entered the information requested by protocol in an electronic case report form (e-CRF). Details on e-CRF completion were explained to the investigator. Data were collected at study entry and after 12 weeks.

(c) Safety data collection

In this observational study, there was no product exposure studied, and therefore no systematic collection of safety data applied.

Adverse Drug Reactions (ADRs) to any Sanofi product that occurred during the course of the study had to be recorded and transmitted to the Sponsor within 24 hours (for example: ADRs that were discovered at the time of a clinical research associate monitoring visit or telephone communication with the site).

(d) Data management, review, validation

Data quality control (QC) (site monitoring and/or phone QC) was performed at site level, in 10% of the active sites (which had enrolled at least one patient) chosen at random in each country, with a minimum of 1 site per country. If specific issues were identified in some sites or countries, the percentage of QC in the concerned site/country or in all sites/countries had to be appropriately increased and corrective actions set up. QC was performed by qualified designated personnel in each country.

The methodology of data QC (site monitoring and/or phone QC) and appropriate consecutive corrective actions were detailed in the study manual (see Appendix III, Section 3.5).

The computerized handling of the data by the Sponsor could generate additional requests to which the participating Investigator was obliged to respond by confirming or modifying the data questioned.

Data collection and validation procedures were detailed in appropriate operational documents.

The database was locked on 21st September 2016.

(e) Statistical considerations

For detailed statistical considerations, please refer to Appendix III, Section 3.2 Statistical Analysis Plan (SAP).

Analyses were conducted on the total study population and on subgroups of previously insulin-naïve and already basal insulin user patients at baseline.

Variables and evaluation criteria

Primary endpoints:

- Achievement of individualised HbA1c target at 12 weeks (if individual HbA1c target was not defined at baseline, general HbA1c target of <7.0% was considered as relevant for the patient) at week 12.
- Symptomatic hypoglycemia during the course of the study:
    - At least one symptomatic hypoglycemia (yes/no).
    - Frequency of symptomatic hypoglycemia: Reference: 0 or 1 / Category 1: 2 to 5/ Category 2: more than 5.
    - Severity of symptomatic hypoglycemia: Reference: no symptomatic hypoglycemia / Category 1: non-severe symptomatic hypoglycemia (*) / Category 2: severe (**) hypoglycemia.
    - Number of symptomatic hypoglycemia

(*) Non-severe symptomatic hypoglycemia: any event which was associated with typical

hypoglycemic symptoms and did not require third party assistance regardless of blood glucose measurement.

(**) Severe hypoglycemia: any event with or without blood glucose measurement which required third party assistance.

Secondary endpoints:

- Achievement of the general HbA1c target of <7.0% at week 12 (for patients with individual target as well) and <8.0% according to level of risk (defined according to patient characteristics, comorbidities and severe hypoglycemia history at study entry).
- Achievement of the 12-week HbA1c objective (defined as the level of HbA1c that could be reached by the patient by week 12, according to the physician).
- Hypoglycemia events: any symptomatic, severe and symptomatic documented (with blood glucose level ≤ 70 mg/dL and ≤ 54 mg/dL), during the course of the study.
- HbA1c change from baseline to 12 weeks (week 12 – baseline),
- Achievement of individualized HbA1c target (if individual HbA1c target was not defined at baseline, general HbA1c target of <7.0% was considered as relevant for the patient) without symptomatic hypoglycemia, at week 12.
- Achievement of the 12-week HbA1c objective (defined as the level of HbA1c that could be reached by the patient by week 12, according to the physician) without symptomatic hypoglycemia.
- Achievement of at least 0.5 and 1.0% of HbA1c reduction from baseline to week 12 (decrease of HbA1c from baseline to week 12).
- Achievement of at least 0.5 and 1.0% of HbA1c reduction from baseline to week 12 without any symptomatic hypoglycemia.
- Fasting plasma glucose (FPG) change from baseline to week 12 as measured by Self-monitoring blood glucose (SMBG) (week 12 – baseline).
- Weight change from baseline to week 12 (week 12 – baseline).
- Change in basal insulin dose from baseline to week 12 (week 12 – baseline).
- Evolution of concomitant antidiabetic medications.
- Change in the level of fear of hypoglycemia (by HFS II):

  "Behavior" and "Worry" subscales mean scores were determined by computing the mean of item responses. Total HFS scores could also be calculated by computing the mean of all "Behavior" and "Worry" subscales items.

  The hypoglycemia fear endpoint was the change in hypoglycemia fear scores (Behavior, Worry and total HFS scores), from baseline to week 12 (week 12 – baseline).

Data analyses

Continuous data were summarized using the number of available data, mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum, maximum and 95% confidence interval (CI) of the mean.

Categorical and ordinal data were summarized using the number and percentage of patients in each predefined group. If pertinent, 95% CI of the proportion was added using the score method of Wilson without continuity correction.

Missing data were not categorized in the summaries.

Primary analysis

As primary analyses related to primary objectives:

- The primary endpoint was analyzed at week 12. The percentage of patients at target and its 95% confidence interval were presented.
- In addition, the relationship between the primary endpoint (HbA1c at target at week 12) and symptomatic hypoglycemia occurrence was investigated using a multivariate logistic regression model, with patient at target as dependent variable and with factors including at least 1 symptomatic hypoglycemia (Yes/No) the reference being "at least 1 symptomatic hypoglycemia" = Yes, adjusted on demographic and baseline characteristics, to take into account the heterogeneity between the included patients.
- The relationship between the primary endpoint (HbA1c at target at week 12) and symptomatic hypoglycemia (frequency, severity) was investigated using two separate models:
  - a multivariate logistic regression model, with patient at target as dependent variable and with factors including "frequency" of the symptomatic hypoglycemia, adjusted on the region and other factors if necessary, to take into account the heterogeneity between the included patients.
  - a multivariate logistic regression model, with patient at target as dependent variable and with factors including "severity" of the symptomatic hypoglycemia, adjusted on the region and other factors if necessary, to take into account the heterogeneity between the included patients.
- The relationship between the primary endpoint and the number of symptomatic hypoglycemia episodes reported (quantitative aspect) was also investigated, using multivariate logistic regression model adjusted for demographic and baseline characteristics, to take into account the heterogeneity between the included patients.
- Additional sensitivity propensity score adjusted multivariate logistic analyses were performed to take into account possible confounding factors in the relationship between HbA1c target at week 12 and the severity and frequency of symptomatic hypoglycemia. The propensity scores were derived for each patient according to the quintiles of the distribution of predicted probabilities from the multivariate logistic regression model explaining hypoglycemia. These models were fitted through a stepwise approach including initially in the model with all factors measured at study entry. The propensity scores quintiles were finally included in the model as a correction factor for adjusting purposes.

Some of these analyses were repeated in the subgroup of newly insulin treated patients, and in the subgroup of patients already treated, with basal insulin.

Secondary analyses

As secondary analyses related to secondary objectives

- Descriptive statistics were presented to:
  - Describe the incidence of symptomatic hypoglycemic events: any symptomatic, severe, and documented symptomatic.
  - Describe the proportion of patients achieving general HbA1c target of < 7.0%.
  - Describe proportion of patients achieving HbA1c target of < 7% or <8% according to level of risk (defined by patient's characteristics comorbidities and severe hypoglycemia history at baseline).
  - Describe the proportion of patients achieving the "12-week HbA1c" objective (defined as the level of HbA1c aimed to be reached by the patient by week 12, according to the physician).
  - Describe the proportion of patients achieving at least 0.5% and 1.0% HbA1c improvement from baseline.
  - Describe the proportion of patients achieving HbA1c target (individualized or general target of <7.0% if individual target was not defined) without symptomatic hypoglycemia.

- Describe the proportion of patients achieving the "12-week HbA1c" objective (defined as the level of HbA1c aimed to be reached by the patient by week 12, according to the physician) without symptomatic hypoglycemia.
- Describe baseline and week 12 scores on the behavior and the worry scales of the HFS II and assess changes in these scales.

- A multivariate analysis was performed to:
  - Identify baseline factors as predictive factors, associated with treatment failure defined as failing to achieve individual (or general target of <7.0% if individual target was not defined) and general target of <7.0%.

Some of these analyses were repeated in the subgroup of newly insulin treated patients, and in the subgroup of patients already treated, with basal insulin.

Sample size calculation

The precision calculation was based on the 2-sided 95% confidence interval of the percentage of patients at HbA1c target (defined by HbA1c < 7%) and assuming an expected percentage of patients at HbA1c target at 12 weeks of 27%. The inclusion of 4000 patients would allow to estimate this percentage with a precision of at least 1.5%, taking into account the 15% rate of non-evaluable patients. In addition, the relationship between being at HbA1c target at 12 weeks and symptomatic hypoglycemia occurrence was investigated.

Assuming that the rate of patients achieving glycemic control as targeted by the physician would be around 27%, this sample size would allow to detect an Odds Ratio (OR) of at least 1.3 – the reference being "at least 1 symptomatic hypoglycemia", as a better control was expected for patients with no hypoglycemia- the expected rate of symptomatic hypoglycemia being 20% in naïve patients to 45% in basal users patients, with a power of at least 80% and an alpha risk of 5%.

Due to the level of uncertainty coming from the nature of the study (real life setting) and to explore the likelihood of demonstrating the correlation between symptomatic hypoglycemia and HbA1c target an interim analysis of the results was performed already with patients who had completed the study as of 30th September 2015. Below are provided the potential correlations that might be demonstrated with corresponding power.

Assuming 15% non-evaluable patients and a power > 80% and according to a range of incidence of patients with hypoglycemia from 20% to 45%; the following OR could be detected according to the number of patients available at the time of the interim analysis:

	Expected % of patients with symptomatic hypoglycemia
Sample size available	**20% to 45%**
500	OR from 1.9 to 2.2
1000	OR from 1.56 to 1.73
2000	OR from 1.36 to 1.46
4000	OR from 1.25 to 1.31

The final analysis was planned after the 4000 patients completed the study.

Registry period: This report includes data reported to the DUNE registry from patients included in the study between 26 February 2015 and 31 March 2016. The Registry was completed on 19 July 2016.

RESULTS

The analysis on the evaluable population is presented below. The source tables for this analysis are provided in Appendix II.

Participants (actual):

(a) Overall participation status

The study was implemented in 28 countries, categorized in 3 regions as depicted in Table 1.

Table 1: Number of patients by region, country and site – All patients

Region/ Country	Centers	Included patients	Eligible patients	Evaluable patients
n	**367**	**4095**	**3880**	**3139**
Europe	**271 (73.8%)**	**2605 (63.6%)**	**2459 (63.4%)**	**2113 (67.3%)**
Austria	3 (0.8%)	8 (0.2%)	6 (0.2%)	4 (0.1%)
Czech Republic	10 (2.7%)	124 (3.0%)	118 (3.0%)	105 (3.3%)
Denmark	4 (1.1%)	60 (1.5%)	51 (1.3%)	45 (1.4%)
Finland	4 (1.1%)	19 (0.5%)	16 (0.4%)	15 (0.5%)
Germany	11 (3.0%)	170 (4.2%)	157 (4.0%)	133 (4.2%)
Greece	16 (4.4%)	205 (5.0%)	202 (5.2%)	170 (5.4%)
Hungary	3 (0.8%)	25 (0.6%)	25 (0.6%)	23 (0.7%)
Ireland	1 (0.3%)	22 (0.5%)	20 (0.5%)	20 (0.6%)
Italy	15 (4.1%)	119 (2.9%)	111 (2.9%)	97 (3.1%)
Lithuania	5 (1.4%)	56 (1.4%)	51 (1.3%)	42 (1.3%)
Norway	2 (0.5%)	11 (0.3%)	9 (0.2%)	5 (0.2%)
Poland	10 (2.7%)	120 (2.9%)	118 (3.0%)	105 (3.3%)
Romania	39 (10.6%)	402 (9.8%)	397 (10.2%)	355 (11.3%)
Russia	27 (7.35%)	300 (7.3%)	298 (7.7%)	291 (9.3%)
Serbia	9 (2.5%)	152 (3.7%)	151 (3.9%)	136 (4.3%)
Slovakia	6 (1.6%)	70 (1.7%)	65 (1.7%)	50 (1.6%)
Slovenia	4 (1.1%)	44 (1.1%)	43 (1.1%)	41 (1.3%)
Spain	88 (24.0%)	599 (14.6%)	536 (13.8%)	414 (13.2%)
Sweden	5 (1.4%)	15 (0.4%)	12 (0.3%)	12 (0.4%)
United Kingdom	9 (2.5%)	84 (2.1%)	73 (1.9%)	50 (1.6%)
Middle East countries	**41 (11.2%)**	**545 (13.3%)**	**512 (13.2%)**	**374 (11.9%)**
Kuwait	2 (0.5%)	30 (0.7%)	28 (0.7%)	18 (0.6%)
Lebanon	8 (2.2%)	110 (2.7%)	107 (2.8%)	98 (3.1%)
Saudi Arabia	6 (1.6%)	128 (3.1%)	117 (3.0%)	70 (2.2%)
Turkey	15 (4.1%)	153 (3.7%)	147 (3.8%)	111 (3.5%)
United Arab Emirates	10 (2.7%)	124 (3.0%)	113 (2.9%)	77 (2.5%)
Latin-American countries	**55 (15.0%)**	**945 (23.1%)**	**909 (23.4%)**	**652 (20.8%)**
Brazil	20 (5.4%)	322 (7.9%)	309 (8.0%)	166 (5.3%)
Colombia	15 (4.1%)	122 (3.0%)	114 (2.9%)	80 (2.5%)
Mexico	20 (5.4%)	501 (12.2%)	486 (12.5%)	406 (12.9%)

Source: Appendix II, Table 2.1 – 1

(b) Participation per period of the registry

A total of 4312 patients were screened. Among them, 217 (5.0%) were not included. Reasons for non-inclusion were: form not fulfilled (89 patients), patient or parent's/guardian's refusal (20 patients), investigator's decision (18 patients) and other reasons (90 patients). (See Appendix II, Tables 2.1-2 and 2.1-3).

Among the 4095 included patients, 215 (5.3%) were not considered for the eligible population due to important deviations that were: no HbA1c available within 1.5 months prior to enrolment until 7 days after study entry (117 patients); baseline HbA1c <7.5% or >11% in newly treated patients or >10% in already insulin treated patients (91 patients); patients not initiated with basal insulin at study entry

or within 395 days prior to study entry (40 patients); patients treated with other insulins than basal insulin at study entry (4 patients); patients aged under 40 who started insulin within 1 year after diabetes diagnosis (4 patients), patients aged under 18 (4 patients), pregnancy or patients planning to be pregnant (3 patients) and no informed consent given(2 patients). The eligible population was therefore composed of 3880 patients. Of these, 741 (19.1%) presented with at least one of the following reasons that excluded them from the evaluable population: "basal insulin regimen not maintained during 12 weeks" (245 patients) and "no post-baseline HbA1c value between 12 weeks after the start of basal insulin treatment through 2 weeks after the last dose of basal insulin treatment" (573 patients), so the evaluable population included 3139 patients. (See Appendix II, Table 2.1-3).

Participant characteristics and primary analyses:

(a) Descriptive data

Participating physicians

Among the 367 participating centers, 363 completed the site questionnaire. Median age of participating physicians was 48.5 (range between 26 and 81) years, being 51% female physicians and 59.5% of the centers were public. Characteristics of the investigators are presented in Appendix II, Table 2.7 – 1.

Evaluable patients

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Patient's characteristics

A total of 3139 patients constituted the evaluable population (with 54.7% of them newly insulin treated patients), They had a mean (SD) age of 60.79 (10.69) years and almost half of the patients (49.1%) were male.

Table 2: Demographic characteristics – Evaluable population

Variable	Newly insulin treated patients (N = 1716)	Patients already treated with basal insulin (N = 1423)	Total (N = 3139)
% total population	54.7%	45.3%	100%
Gender			
Male	867 (50.5%)	673 (47.3%)	1540 (49.1%)
Female	849 (49.5%)	750 (52.7%)	1599 (50.9%)
Age (years)			
n	1716	1423	3139
Mean (SD)	60.48 (10.91)	61.16 (10.41)	60.79 (10.69)
Median (Range)	61 (19 ; 93)	61 (19 ; 92)	61 (19 ; 93)
Weight (Kg)			
n	1714	1423	3137
Mean (SD)	84.55 (17.90)	82.92 (16.79)	83.81 (17.42)
Median (Range)	82.95 (39 ; 184)	82 (42.8 ; 149)	82 (39 ; 184)
BMI (Kg/m^2)			
n	1712	1422	3134
Mean (SD)	30.57 (5.55)	30.40 (5.43)	30.50 (5.50)
Median (Range)	29.75 (17.30 ; 53.33)	29.75 (17.15 ; 51.95)	29.75 (17.15 ; 53.33)
BMI category (Kg/m^2)			
n	1712	1422	3134
< 25	238 (13.9%)	213 (15.0%)	451 (14.4%)
25 – 30	645 (37.7%)	534 (37.6%)	1179 (37.6%
≥ 30	829 (48.4%)	675 (47.5%)	1504 (48.0%)

Newly insulin treated patients: those subjects not receiving basal insulin prior to study inclusion or who started such treatment no earlier than two weeks before the study inclusion.
Patients already treated with basal insulin: those subjects receiving basal insulin treatment at least 2 weeks before being included in the study.
Source: Appendix II, Table 2.3 – 1

Among all evaluable patients, the highest level of education was secondary for 43.7%, primary for

33.4%, university/higher education for 20.6%, while 76 patients (2.4%) were illiterate (See Appendix II, Table 2.3 – 1).

Regarding employment status, a total of 1286 patients (41.0%) were retired, followed by employed full-time (970 patients [30.9%]), and unemployed (484 patients [15.4%]). Additional details can be found in Appendix II, Table 2.3 – 1).

Most patients (87.6%) lived with another adult, 11.2% lived alone, 0.2% lived in an institution or a community, and 1% reported other situation.

A total of 1478 (47.1%) patients were drivers, of whom 252 (17.1%) were professional drivers. Additional details can be found in Appendix II, Table 2.3 – 1).

Diabetes history and complications

The mean (SD) duration of diabetes was 10.14 (6.98) years. In the previous 6 months, 3.6% patients had experienced at least one severe episode of hypoglycemia, and in the previous month prior to study entry, episodes of symptomatic hypoglycemia were experienced by 7.6% patients (with higher rates in patients already treated with basal insulin [12.0% vs. 4.0%])).

Table 3: Diabetes history and complications – Evaluable patients

Variable	Newly insulin treated patients (N = 1716)	Patients already treated with basal insulin (N = 1423)	Total (N = 3139)
Duration of diabetes (years)			
Mean (SD)	9.79 (6.83)	10.57 (7.14)	10.14 (6.98)
Duration of diabetes (years) categories			
n	1715	1420	3135
< 1 year	103 (6.0%)	70 (4.9%)	173 (5.5%)
1 to 5 years	374 (21.8%)	280 (19.7%)	654 (20.9%)
5 to 10 years	567 (33.1%)	416 (29.3%)	983 (31.4%)
> 10 years	671 (39.1%)	654 (46.1%)	1325 (42.3%)
Time since first antidiabetic medication (years)			
Mean (SD)	9.07 (6.55)	9.65 (6.86)	9.33 (6.70)
Type of patient			
Not basal insulin prior to study inclusion	105 (6.1%)	-	105 (3.3%)
≤ 2 weeks	1611 (93.9%)	-	1611 (51.3%)
12-13 months	-	16 (1.1%)	16 (0.5%)
6-12 months	-	636 (44.7%)	636 (20.3%)
< 6 months	-	771 (54.2%)	771 (24.6%)
Severe episodes of hypoglycemia within the last six months prior to study entry			
N	1716	1423	3139
Yes	37 (2.2%)	75 (5.3%)	112 (3.6%)
No	1679 (97.8%)	1348 (94.7%)	3027 (96.4%)
Episodes of symptomatic hypoglycemia within the last month prior to study entry			
n	1716	1423	3139
Yes	68 (4.0%)	171 (12.0%)	239 (7.6%)
No	1648 (96.0%)	1252 (88.0%)	2900 (92.4%)

Source: Appendix II, Tables 2.3 – 2 and 2.3 – 5

Regarding other diabetes complications: neuropathy was reported in 883 patients (28.1%) (mostly peripheral neuropathy [822 of the 883 patients]); retinopathy was reported in 511 patients (16.3%) (which did not lead to blindness in 470 of the 511 patients) ; and renal function impairment was reported in 406 patients (12.9%) (mostly microalbuminuria [264 of the 406 patients]). (See Appendix II, Table 2.3 – 3).

The most frequent comorbidities reported were: hypertension (66.8% of all evaluable patients), dyslipidemia (60.5%), coronary heart disease (14.9%), fatty liver disease (8.7%), and peripheral vascular disease (5.5%). (See Appendix II, Table 2.3 – 4).

Treatment at study entry

Most patients (78.2% of the evaluable population) were treated with long acting insulin analogues, with one (92.3%) daily injection of basal insulin and a median of 15 units per day. The insulin treatment is summarized in the following table:

Table 4: Treatment at study entry – Evaluable population

Variable	Newly insulin treated patients (N = 1716)	Patients already treated with basal insulin (N = 1423)	Total (N = 3139)
Type of current basal insulin			
Human intermediate-acting insulin	341 (19.9%)	342 (24.0%)	683 (21.8%)
Long-acting basal insulin analogue	1375 (80.1%)	1081 (76.0%)	2456 (78.2%)
Current total basal insulin daily dose (units)			
Mean (SD)	14.23 (7.35)	23.38 (15.29)	18.38 (12.50)
Median (Range)	12 (2 ; 80)	20 (3 ; 280)	15 (2 ; 280)
Number of injections per day			
1	1635 (95.3%)	1262 (88.7%)	2897 (92.3%)
2	81 (4.7%)	157 (11.0%)	238 (7.6%)
3	0 (0.0%)	4 (0.3%)	4 (0.1%)
Recommended way of titration			
Patient-driven	1094 (63.8%)	896 (63.0%)	1990 (63.4%)
Physician-driven	622 (36.2%)	527 (37.0%)	1149 (36.6%)
Frequency of titration			
n	1700	1380	3090
No titration	1 (0.1%)	1 (0.1%)	2 (0.1%)
Every 1 to 3 days	769 (45.2%)	488 (35.1%)	1257 (40.7%)
Every 4 to 6 days	107 (6.3%)	75 (5.4%)	182 (5.9%)
Once a week	545 (32.1%)	493 (35.5%)	1038 (33.6%)
Less than once a week	278 (16.4%)	333 (24.0%)	611 (19.8%)
Recommended dose increment			
n	1689	1365	3054
2 units	1480 (87.6%)	1222 (89.5%)	2702 (88.5%)
3 units	39 (2.3%)	20 (1.5%)	59 (1.9%)
4 units	128 (7.6%)	111 (8.1%)	239 (7.8%)
5 units	18 (1.1%)	4 (0.3%)	22 (0.7%)
6 units	18 (1.1%)	6 (0.4%)	24 (0.8%)
> 6 units	6 (0.4%)	2 (0.1%)	8 (0.3%)
Objective for Fasting Self-Monitoring Blood Glucose mg/dL Mean (SD)	116.78 (15.75)	118.45 (14.75)	117.53 (15.33)

Source: Appendix II, Table 2.3 – 6

Additional details, such as HbA1c levels expressed in mmol/mol, can be found in Appendix II, Table 2.3 – 6.

Previous antidiabetic medications

A total of 2905 (92.5% of the evaluable population) patients reported taking a previous antidiabetic medication before basal insulin start. The most frequent reported were metformin used by 2519 (80.2%) patients, followed by sulfonylureas used by 1523 (48.5%) patients, DPP-IV inhibitors used by 886 (28.2%) patients, GLP1 receptor agonists used by 176 (5.6%) patients and metiglinides used by 137 (4.4%) patients. Additional details on all previous antidiabetic medications used can be found in Appendix II, Table 2.3 – 7).

Laboratory tests

Mean (SD) baseline HbA1c within 1.5 months prior to study entry was 8.88% (0.96). Mean baseline fasting plasma glucose (SD) at study entry was 184.78 mg/dL (60.05), being higher in the group of newly insulin treated patients than in the group of patients already treated with basal insulin group (204.30 vs. 160.24 mg/dL). Mean (SD) baseline fasting self-monitoring blood glucose was 172.82

mg/dL (48.26), being also higher in the group of newly insulin treated patients than in the group of patients already treated with basal insulin (190.12 vs. 153.76 mg/dL). Mean (SD) baseline glomerular filtration rate was 84.49 (28.56) mL/min/1.73m^2). A total of 57.3% of the evaluable population had an individual HbA1c target defined by the physician between 7% and 7.5%. The main reasons to define the target were the age in 2059 (65.6%) patients, followed by patient's acceptability in 1294 (41.2%) and comorbidities in 1184 (37.7%) patients. Individualised target was reported for most of patients; only 8 (0.3%) did not have individual target. Additional details on different units analyzed can be found in Appendix II – Tables 2.3 – 8 to 2.3 – 13.

Table 5: Laboratory tests at study entry – Evaluable population

Variable	Newly insulin Treated patients (N = 1716)	Patients already treated with basal insulin (N = 1423)	Total (N = 3139)
Baseline HbA1c (%) within 1.5 months prior to study entry			
Mean (SD)	9.16 (1.01)	8.57 (0.78)	8.89 (0.96)
Individual HbA1c (%) target set by physician*			
< 6.5%	19 (1.1%)	18 (1.3%)	37 (1.2%)
[6.5% - 7%[	305 (17.8%)	249 (17.5%)	554 (17.6%)
[7% - 7.5%[	994 (57.9%)	806 (56.6%)	1800 (57.3%)
[7.5% - 8%[	286 (16.7%)	241 (16.9%)	527 (16.8%)
[8% - 8.5%[	87 (5.1%)	85 (6.0%)	172 (5.5%)
[8.5% - 9%[	17 (1.0%)	16 (1.1%)	33 (1.1%)
≥ 9%	7 (0.4%)	1 (0.1%)	8 (0.3%)
Patient without target*	1 (0.1%)	7 (0.5%)	8 (0.3%)
Reasons for this target$			
Age	1141 (66.5%)	918 (64.5%)	2059 (65.6%)
Comorbidities	625 (36.4%)	559 (39.3%)	1184 (37.7%)
History of previous severe hypoglycemia	11 (0.6%)	33 (2.3%)	44 (1.4%)
Acceptability patient	689 (40.2%)	605 (42.5%)	1294 (41.2%)
Other	146 (8.5%)	135 (9.5%)	281 (9.0%)
HbA1c (%) objective for week 12*			
< 6.5%	17 (1.0%)	17 (1.2%)	34 (1.1%)
[6.5% - 7%[	248 (14.5%)	227 (16.0%)	475 (15.1%)
[7% - 7.5%[	877 (51.1%)	739 (51.9%)	1616 (51.5%)
[7.5% - 8%[	324 (18.9%)	268 (18.8%)	592 (18.9%)
[8% - 8.5%[	180 (10.5%)	131 (9.2%)	311 (9.9%)
[8.5% - 9%[	42 (2.4%)	29 (2.0%)	71 (2.3%)
[9.0% - 9.5%[	22 (1.3%)	5 (0.4%)	27 (0.9%)
≥ 9.5%	5 (0.3%)	0 (0.0%)	5 (0.2%)
Patient without objective for week 12	1 (0.1%)	7 (0.5%)	8 (0.3%)
Reasons for this target$			
Level of HbA1c	228 (13.3%)	125 (8.8%)	353 (11.2%)
Age	1036 (60.4%)	866 (60.9%)	1902 (60.6%)
Comorbidities	587 (34.2%)	537 (37.7%)	1124 (35.8%)
History of previous severe hypoglycemia	15 (0.9%)	34 (2.4%)	49 (1.6%)
Acceptability patient	647 (37.7%)	573 (40.3%)	1220 (38.9%)
Other	131 (7.6%)	132 (9.3%)	263 (8.4%)
Baseline fasting plasma glucose mg/dL Mean (SD)	204.30 (60.33)	160.24 (49.86)	184.78 (60.05)
Baseline Fasting Self-Monitoring Blood Glucose mg/dL Mean (SD)	190.12 (48.61)	153.76 (39.99)	172.82 (48.26)
Baseline estimated Glomerular Fraction Rate (mL/min/1.73 m^2)$			
Mean (SD)	84.11 (29.42)	84.99 (27.42)	84.49 (28.56)

* If individual HbA1c target was not defined at baseline, general HbA1c target of <7.0% was considered as relevant for the patient.

$ The number in each column could not be added because a patient could have more than one reason.

eGRF: estimated Glomerular Fraction Rate recorded within the month prior to visit.

Source: Appendix II, Tables 2.3 – 8 to 2.3 – 13

Level of risk according to the Steering Committee definition

Most patients (63.1%) of the total population were at high risk. The most frequent reasons for being at the high level risk were: age ≥ 65 years in 1164 (37.1%) patients, followed by duration of diabetes > 15 years in 637 (20.3%) patients, renal function impairment in 485 (15.5%) patients, and coronary heart disease in 467 (14.9%) patients. Additional details can be found in Appendix II, Table 2.3 – 15.

Table 6: Level of risk – Evaluable population

Variable	Newly insulin treated patients (N = 1716)	Patients already treated with basal insulin (N = 1423)	Total (N = 3880)
Level of risk			
Low risk	652 (38.0%)	505 (35.5%)	1157 (36.9%)
High risk	1064 (62.0%)	918 (64.5%)	1982 (63.1%)

Patients at high risk were considered to be those patients ≥ 65 years of age or with evidence of any of the following comorbidities/characteristics: myocardial revascularization procedure; coronary heart disease; stroke; transient ischemic attack; peripheral vascular disease; heart failure; acute myocardial infarction; renal function impairment (including macroalbuminuria, advanced kidney disease and end stage renal failure); severe dementia; diabetic retinopathy leading to blindness; lower extremity amputation for arterial reason; history of severe hypoglycemia; duration of diabetes > 15 years; occupation of the patient: professional driver.
Source: Appendix II, Table 2.3 – 15

Similar characteristics were reported for the global eligible population which is described in Appendix II, Tables 2.3 – 16 to 2.3 – 30

(b) Primary objective

Overall, 861 patients (27.4%) achieved their individual HbA1c target in the predefined groups: 479 (27.9%) patients in the newly insulin treated patients group and 382 (26.8%) patients in the group of patients already treated with basal insulin. Individual HbA1c results are summarized in the following table:

Table 7: Achievement of individual HbA1c target at 12 weeks – Evaluable population

Variable	Newly insulin treated patients (N = 1716)	Patients already treated with basal insulin (N = 1423)	Total (N = 3139)	95% confidence interval
Achievement of individual HbA1c target at 12 weeks#				
n	1716	1423	3139	
Yes	479 (27.9%)	382 (26.8%)	861 (27.4%)	25.874 ; 29.026
No	1237 (72.1%)	1041 (73.2%)	2278 (72.6%)	
Achievement of individual HbA1c target at 12 weeks@				
n	1715	1416	3131	
Yes	479 (27.9%)	382 (27.0%)	861 (27.5%)	25.941 ; 29.100
No	1236 (72.1%)	1034 (73.0%)	2270 (72.5%)	

#if individual HbA1c target was not defined at baseline, general HbA1c target of < 7.0%.
@ not considering those subjects without individual HbA1c target defined
Source: Appendix II, Table 2.4 – 1

In total , 26.2% of the patients who didn't report any hypoglycemia and 33.8% of the patients having reported at least one hypoglycemia achieved their HbA1c target.

Multivariate logistic regression analyses showed an association between the occurrence and frequency of symptomatic hypoglycemia episodes and HbA1c achievement. Table 8 shows the results of the multivariate logistic regression analyses. For the full stepwise factors used in the analyses please refer to Appendix II Tables 2.4.3.1 to 2.4.3.4.

Hypoglycemia occurrence and achievement of HbA1c without occurrence of hypoglycemic episodes are part of the secondary endpoints. Please refer to the corresponding section for the results.

Table 8: Association between achievement of individual target HbA1c at 12 weeks and symptomatic hypoglycemia (occurrence, frequency, severity and number of episodes) – Evaluable population

	Multivariate logistic regression model	
Symptomatic hypoglycemia	**Odd ratio (95% CI)**	**p-value**
Occurrence		<0.001[1]
Yes [reference]		
No	0.645 (0.513;0.810)	
Frequency		<0.001[1]
0 or 1 [reference]		
2 to 5	1.463 (1.080;1.981)	0.014[1]
More than 5	2.690 (1.385;5.224)	0.003[1]
Severity		<0.001[1]
No [reference]		
Non-severe	1.526 (1.208;1.926)	<0.001[1]
Severe	2.148 (0.886;5.207)	0.091[1]
No. of episodes	1.088 (1.030;1.149)	0.002[1]

[1] Forced factors: region, age, duration of diabetes, HbA1c at study entry, use of sulfonylureas and/or metiglinides at study entry, and use of GLP1 receptor agonists at study entry.
Non-forced factors considered: heart failure, previous basal insulin, time since basal insulin, type of basal insulin, previous antidiabetic medications, SMBG, individual HbA1c target set by physician, HbA1c objective for week 12, gender.
Source: Appendix II, Tables 2.4.3.1 to 2.4.3.4

An association between the target achievement and the occurrence of symptomatic hypoglycemic events has been found for the following factors:

- age (global p = 0.037) with patients ≥ 68 years old more likely to achieve the HbA1c target (p = 0.004);
- male population (p = 0.049) more likely to achieve HbA1c target
- patients without history of heart failure (p = 0.010) more likely to achieve the HbA1c target
- duration of diabetes (global p < 0.001) with patients diagnosed for diabetes for less than one year, more likely to achieve the HbA1c target ;
- time since starting basal insulin (global p < 0.001) with patients newly treated more likely to achieve the HbA1c target ;
- patients using long-acting basal analogue (p=0.024) more likely to achieve HbA1c target, than patients using human intermediate-acting insulin;
- patients with HbA1c < 8.01 % at study entry more likely to achieve the HbA1c target comparing to patients with higher values (global p < 0.001);

Additional details can be found in Appendix II, Tables 2.4.3.1 and 2.4.3.2.

The results of this analysis were also confirmed by the analyses adjusted on propensity scores for the association between individual target HbA1c at week 12 and hypoglycemia. For further details please see Appendix II, Tables 2.4.3.18, 2.4.3.22 and 2.4.3.26.

Table 9: Association between achievement of individual target HbA1c at 12 weeks and symptomatic hypoglycemia –Sensitivity analyses adjusted for propensity score– Evaluable population

	Propensity score Multivariate model
	Odd ratio (95% CI)
Symptomatic hypoglycemia occurrence	
Yes [reference]	
No	0.709 (0.571;0.881)[1]
Frequency of symptomatic hypoglycemia	
0 or 1 [reference]	
≥ 2	1.376 (1.056;1.791)[2]

[1] Multivariate model adjusted by propensity scores quintiles, propensity factors: weight, depression, time since basal insulin, type of basal insulin, previous antidiabetic medications, SMBG, HbA1c at study entry, duration of diabetes.
[2] Multivariate model adjusted by propensity scores quintiles, propensity factors: weight, type of basal insulin, previous antidiabetic medications, SMBG, duration of diabetes.
Source: Appendix II, Tables 2.4.3.18, 2.4.3.22.

Secondary analyses:

- **Symptomatic hypoglycemia during the study**

Overall a total of 503 (16.0%) patients reported to have experienced at least one symptomatic hypoglycemia during the course of the study. Mean (SD) number of symptomatic hypoglycemia per patient during the study was 0.45 (1.66) episodes and 90.3% of patients had a frequency in symptomatic hypoglycemia ≤1. A total of 477 (15.2%) patients had non-severe symptomatic hypoglycemia and 26 (0.8%) patients had severe hypoglycemia. Symptomatic hypoglycemia is summarized in the following table:

Table 10: Symptomatic hypoglycemia during the course of the study – Evaluable population

Variable	Newly insulin treated patients (N = 1716)	Patients already treated with basal insulin (N = 1423)	Total (N = 3139)
At least one episode of symptomatic hypoglycemia			
n	1716	1421	3137
Yes	243 (14.2%)	260 (18.3%)	503 (16.0%)
No	1473 (85.8%)	1161 (81.7%)	2634 (84.0%)
Number of symptomatic hypoglycemia per patient			
n	1716	1421	3137
Mean (SD)	0.37 (1.36)	0.55 (1.96)	0.45 (1.66)
Median (Range)	0.00 (0,21)	0.00 (0;39)	0.00 (0;39)
Frequency of symptomatic hypoglycemia			
n	1716	1421	3137
0 to 1	1569 (91.4%)	1263 (88.9%)	2832 (90.3%)
2 to 5	128 (7.5%)	131 (9.2%)	259 (8.3%)
More than 5	19 (1.1%)	27 (1.9%)	46 (1.5%)
Severity of symptomatic hypoglycemia			
No symptomatic hypoglycemia	1473 (85.8%)	1161 (81.7%)	2634 (84.0%)
Non-severe symptomatic hypoglycemia*	235 (13.7%)	242 (17.0%)	477 (15.2%)
Severe hypoglycemia**	8 (0.5%)	18 (1.3%)	26 (0.8%)

*non-severe symptomatic hypoglycemia: any event which was associated with typical hypoglycemic symptoms and did not require third party assistance regardless of blood glucose measurement (only non-severe episodes reported).
**severe hypoglycemia: any event with or without blood glucose measurement which required third party assistance.

Multivariate logistic regression results for the propensity score analyses performed with hypoglycemia as dependent variable showed association between occurrence of hypoglycemia and predictive factors with patients more likely to have at least one hypoglycemia in the following conditions : lower weight (p<0.001), patients treatment with basal insulin for more

than 6 months (p=0.014), use of human intermediate-acting insulin (p<0.001) , lower SmBG values (0.021), shorter duration of diabetes (p =0.003), depression at study entry (0.011).

. For further details please see Appendix II, Tables 2.4.3.15, 2.4.3.19 and 2.4.3.23.

- **Achievement of HbA1c target of < 7.0% or 8.0% at week 12 according to level of risk**

Overall, a total of 319 (27.6%) patients achieved the general target of < 7.0% HbA1c after 12 weeks of treatment and 728 (62.9%) patients achieved the general target of < 8.0% HbA1c after 12 weeks of treatment in patients at low risk. Similar results were found for patients at high risk with 22.5% patients achieving the HbA1c target < 7.0% and 64.7% patients achieving the HbA1c target < 8.0%.

Table 11: Achievement of general HbA1c targets < 7.0% and < 8.0% at 12 weeks in patients at low and high risk – Evaluable population

Low risk patients	Newly insulin treated patients (N = 652)	Patients already treated with basal insulin (N = 505)	Total (N = 1157)
Achievement of general HbA1c target < 7.0% at 12 weeks			
n	652	505	1157
Yes	176 (27.0%)	143 (28.3%)	319 (27.6%)
No	476 (73.0%)	362 (71.7%)	838 (72.4%)
Achievement of general HbA1c target < 8.0% at 12 weeks			
n	652	505	1157
Yes	401 (61.5%)	327 (64.8%)	728 (62.9%)
No	251 (38.5%)	178 (35.2%)	429 (37.1%)
High risk patients	**Newly insulin treated patients (N = 1064)**	**Patients already treated with basal insulin (N = 918)**	**Total (N = 1982)**
Achievement of general HbA1c target < 7.0% at 12 weeks			
n	1064	918	1982
Yes	257 (24.2%)	188 (20.5%)	445 (22.5%)
No	807 (75.8%)	730 (79.5%)	1537 (77.5%)
Achievement of general HbA1c target < 8.0% at 12 weeks			
n	1064	918	1982
Yes	693 (65.1%)	589 (64.2%)	1282 (64.7%)
No	371 (34.9%)	329 (35.8%)	700 (35.3%)

Source: Appendix II, Tables 2.5 – 2 and 2.5 – 3.

Details on the eligible population can be found in Appendix II, Tables 2.5 – 28 and 2.5 – 29.

- **Achievement of the 12-week HbA1c objective**

Less than half (40.4%) of the population achieved the HbA1c objective after 12 weeks of treatment. Achievement in the newly insulin treated patients group was 42.2% and 38.3% in the group of patients already treated with basal insulin. Reasons for not achieving the objective were mainly lack of adherence to lifestyle recommendations (in 60.1% patients), followed by lack of adherence to titration (in 43.5% patients), and other reasons (in 24.0% patients).

Table 10: Achievement of the 12-week HbA1c objective – Evaluable population

	Newly insulin treated patients (N = 1716)	Patients already treated with basal insulin (N = 1423)	Total (N = 3139)
Achievement of the 12-week HbA1c objective			
n	1716	1416	3132
Yes	724 (42.2%)	542 (38.3%)	1266 (40.4%)
No	992 (57.8%)	874 (61.7%)	1866 (59.6%)
Reasons for non-achievement			

Lack of adherence to titration	432 (43.5%)	380 (43.5%)	812 (43.5%)
Lack of adherence to lifestyle recomm..	618 (62.3%)	503 (57.6%)	1121 (60.1%)
Hypoglycemia events	40 (4.0%)	40 (4.6%)	80 (4.3%)
Intercurrent disease	39 (3.9%)	47 (5.4%)	86 (4.6%)
Other	213 (21.5%)	235 (26.9%)	448 (24.0%)

Source: Appendix II, Table 2.5 – 6.

Details on the eligible population can be found in Appendix II, Table 2.5 – 30.

- **HbA1c target achievement without symptomatic hypoglycemia**

Achievement of 12-week HbA1c objective without symptomatic hypoglycemia was reached by, 1034 (33.0%) patients. The rate was higher in the newly insulin treated patients group than in the group of patients already treated with basal insulin (35.8% and 29.7% patients, respectively). When individual targets were analyzed, the proportion of patients who achieved the individualized HbA1c target without symptomatic hypoglycemia was 22.0% for the overall population, being again higher in the newly insulin treated patients groups (23.5% vs. 20.2%, respectively).

Table 11: HbA1c target achievement without symptomatic hypoglycemia – Evaluable population

	Newly insulin treated patients (N = 1716)	Patients already treated with basal insulin (N = 1423)	Total (N = 3139)
Achievement of 12-week HbA1c objective without symptomatic hypoglycemia			
n	1716	1416	3132
Yes	614 (35.8%)	420 (29.7%)	1034 (33.0%)
No	1102 (64.2%)	996 (70.3%)	2098 (67.0%)
Achievement of the individual HbA1c target without symptomatic hypoglycemia			
n	1716	1135	3139
Yes	403 (23.5%)	288 (20.2%)	691 (22.0%)
No	1313 (76.5%)	1135 (79.8%)	2448 (78.0%)

Source: Appendix II, Tables 2.5 – 8 and 2.5 – 9.

Details on the eligible population can be found in Appendix II, Tables 2.5 – 32 and 2.5 – 33.

- **HbA1c improvement 0.5% and 1.0% at week 12**

Overall, the proportion of patients who achieved at least an improvement of 0.5% from baseline to week 12 was 73.7% (2312 patients). Of them a total of 190 (%) 6 patients achieved this improvement without any symptomatic hypoglycemia. It should be noted that the proportion of patients who achieved this improvement was higher in the newly insulin treated group with respect to the group of patients already treated with basal insulin (80.0% vs. 66.1% for the 0.5% improvement, and 67.4% vs. 52.6% for the improvement without symptomatic hypoglycemia, respectively).

Improvement of 1.0% in HbA1c from baseline to week 12 was achieved by a total of 1687 patients (53.7%) overall and 1372 patients (43.7%) did so without symptomatic hypoglycemia. The newly insulin treated patients group again showed higher proportion in achievement. The following table summarized these results:

Table 12 : HbA1c improvement 0.5% and 1.0% at week 12 – Evaluable population

	Newly insulin treated patients (N = 1716)	Patients already treated with basal insulin (N = 1423)	Total (N = 3139)
Achievement of at least 0.5% from baseline to week 12			
n	1716	1423	3139
Yes	1372 (80.0%)	940 (66.1%)	2312 (73.7%)
No	344 (20.0%)	483 (33.9%)	827 (26.3%)
Achievement of at least 0.5% from baseline to week 12 without any symptomatic hypoglycemia			
n	1716	1423	3139
Yes	1157 (67.4%)	749 (52.6%)	1906 (60.7%)
No	559 (32.6%)	674 (47.4%)	1233 (39.3%)

Achievement of at least 1.0% from baseline to week 12			
n	1716	1423	3139
Yes	1086 (63.3%)	601 (42.2%)	1687 (53.7%)
No	630 (36.7%)	822 (57.8%)	1452 (46.3%)
Achievement of at least 1.0% from baseline to week 12 without any symptomatic hypoglycemia			
n	1716	1423	3139
Yes	909 (53.0%)	463 (32.5%)	1372 (43.7%)
No	807 (47.0%)	960 (67.5%)	1767 (56.3%)

Source: Appendix II, Tables 2.5 – 7 and 2.5 – 10.

Details on the eligible population can be found in Appendix II, Tables 2.5 – 31 and 2.5 – 34.

- **Documented symptomatic hypoglycemic events during the course of the study**

Overall, 393 patients (12.6%) reported at least one documented hypoglycemic event ≤ 70 mg/dL during the course of the study. Higher proportions were found in the group of patients already treated with basal insulin (14.9% vs. 10.8%, respectively). More than 90% of patients had a frequency of these hypoglycemic events between 0 and 1.

On the other hand, a total of 136 patients (4.4%) reported at least one documented hypoglycemic event ≤ 54 mg/dL during the course of the study. In this case the proportion between the two groups was similar as it is summarized in the following table:

Table 13 : Hypoglycemic events during the study – Evaluable population

Variable	Newly insulin treated patients (N = 1716)	Patients already treated with basal insulin (N = 1423)	Total (N = 3139)
Any symptomatic documented hypoglycemic event (≤ 70 mg/dL)			
n	1701	1412	3113
Yes	183 (10.8%)	210 (14.9%)	393 (12.6%)
No	1518 (89.2%)	1202 (85.1%)	2720 (87.4%)
Frequency of symptomatic documented hypoglycemic event (≤ 70 mg/dL)			
n	1701	1412	3113
0 to 1	1592 (93.6%)	1298 (91.9%)	2890 (92.8%)
2 to 5	94 (5.5%)	94 (6.7%)	188 (6.0%)
More than 5	15 (0.9%)	20 (1.4%)	35 (1.1%)
Any symptomatic documented hypoglycemic event (≤ 54 mg/dL)			
n	1701	1411	3112
Yes	69 (4.1%)	67 (4.7%)	136 (4.4%)
No	1632 (95.9%)	1344 (95.4%)	2976 (95.6%)
Frequency of symptomatic documented hypoglycemic event (≤ 54 mg/dL)			
n	1701	1411	3112
0 to 1	1679 (98.7%)	1393 (98.7%)	3072 (98.7%)
2 to 5	20 (1.2%)	16 (1.1%)	36 (1.2%)
More than 5	2 (0.1%)	2 (0.1%)	4 (0.1%)

Source: Appendix II, Table 2.5 – 1.

Details on the eligible population can be found in Appendix II, Table 2.5 – 25.

- **Hospitalizations and emergency room visits**

For the evaluable population a total of 72 patients (2.3%) reported at least one hospitalization during the course of the study. There were a total of 80 hospitalizations. The most frequent reason for hospitalization was intercurrent disease reported 42 times in 37 patients. Regarding emergency room visits, a total of 69 patients (2.2%) reported a total of 78 visits to the emergency room, with intercurrent disease again being the most frequent cause reported (40 times in 35 patients). Additional details can be found in Appendix II, Table 2.5 – 11, and for the eligible population in Table 2.5 – 35.

- **Patient adherence**

Regarding adherence to treatment, 40.4% patients reported high adherence, 37.6% patients reported medium adherence and 22.0% patients reported low adherence to treatment in the

evaluable population. Additional details can be found in Appendix II, Table 2.5 – 12, and for the eligible population in Table 2.5 – 36.

- **Change from baseline to week 12 in basal insulin**

Mean basal insulin dose increased at week 12 with respect to baseline value (7.13 [SD: 11.02] units), a higher increase was shown in the newly insulin treated patients than in the patients already treated with basal insulin (8.99 vs. 4.87 units). Additional details can be found in Appendix II, Table 2.5 – 18.

Mean basal insulin at week 12 for all patients who were still on the initial basal insulin at week 12 or using another basal insulin dose at week 12 was 25.46 (SD: 16.10) units. Additional details can be found in Appendix II, Table 2.5 – 19.

- **Basal insulin treatment discontinuation and insulin titration**

Basal insulin was discontinued in 40 (1.3%) patients, with most patients (26 patients) reporting insufficient control as the main reason for discontinuation. . Additional details on basal insulin treatment discontinuation can be found in Appendix II, Table 2.5 – 20.

Regarding insulin titration, a total of 1416 (45.1%) patients reported an increase of basal insulin dose of 1 to 5 steps, and 830 (26.4%) patients didn't report any titration With regards to decrease in titration, a total of 2409 (76.9%) did not report decrease in doses, while 599 (19.1%) patients reported a decrease titration of 1 to 5 steps. Additional details can be found in Appendix II, Table 2.5 – 21.

- **Concomitant antidiabetic medications**

A total of 2011 (64.1%) patients reported at least one concomitant antidiabetic medication other than basal insulin during the study. The most frequently reported antidiabetic medications were: sulfonylureas reported in 1091 (34.8%) patients, followed by DPP-IV inhibitors in 748 (23.8%) patients, and metformin in 343 (10.9%) patients. Additional details can be found in Appendix II, Table 2.5 -22.

Regarding medications discontinued before week 12 visit, these were reported by 253 (8.1%) patients. The most frequently discontinued antidiabetic medication reported were: sulfonylureas in 141 (4.5%) patients, DPP-IV inhibitors in 49 (1.6%) patients and metformin in 48 (1.5%) patients. Additional details can be found in Appendix II, Table 2.5 – 23.

- **Change from baseline to week 12 in laboratory tests and body weight**

Laboratory tests revealed a decrease with respect to the baseline value in HbA1c, fasting plasma glucose and self-monitoring blood glucose. It should be noted that greater decreases were found in the newly insulin treated patients group. Body weight and BMI remained stable throughout the study.. The following table summarizes these changes:

Table 13: Laboratory tests during the study – Evaluable population

Mean (SD)	Newly insulin treated patients (N = 1716)	Patients already treated with basal insulin (N = 1423)	Total (N = 3139)
HbA1c (%)			
Baseline	9.14 (1.01)	8.56 (0.77)	8.88 (0.96)
Week 12	7.75 (1.19)	7.74 (1.17)	7.74 (1.18)
Change (week 12 – Baseline)	-1.39 (1.31)	-0.82 (1.13)	-1.13 (1.26)
Fasting plasma glucose (mg/dL)			
Baseline	203.54 (59.71)	160.06 (50.28)	184.11 (59.74)
Week 12	142.83 (45.90)	136.90 (42.42)	140.18 (44.47)
Change (week 12 – Baseline)	-60.71 (67.78)	-23.16 (57.34)	-43.93 (66.01)
Self-monitoring blood glucose (mg/dL)			
Baseline	190.12 (48.61)	153.76 (39.99)	172.82 (48.26)
Week 12	139.11 (41.42)	134.77 (34.00)	137.05 (38.13)
Change (week 12 – Baseline)	-51.01 (53.31)	-18.98 (39.86)	-35.77 (50.01)
Body weight (Kg)			

Baseline	84.51 (17.88)	82.90 (16.78)	83.78 (17.41)
Week 12	84.79 (17.77)	82.99 (16.71)	83.97 (17.32)
Change (week 12 – Baseline)	0.28 (3.15)	0.09 (2.72)	0.19 (2.96)

Source: Appendix II, Tables 2.5 – 13 to 2.5 – 17.
SMBG: mean of the fasting self-monitored blood glucose values recorded on the last 3 measures within the month prior to visit.

Additional details can be found in Appendix II, Tables 2.5 – 13 to 2.5 – 17, and for the eligible population in Tables 2.5 – 37 to 2.5 – 41.

- **Hypoglycemia Fear Survey II**

As summarized in the table below, slight changes in the HFS II survey were found when baseline and 12-week values were compared with slight decrease in total and worry score.

Table 14: HFS II Survey: Change from baseline to week 12 – Evaluable population

Mean (SD)	Newly insulin treated patients (N = 1716)	Patients already treated with basal insulin (N = 1423)	Total (N = 3139)
HFS-II – Total score			
Baseline	22.75 (22.95)	24.60 (22.40)	23.59 (22.72)
Week 12	21.39 (20.70)	20.66 (19.54)	21.06 (20.19)
Change (week 12 – Baseline)	-1.36 (17.01)	-3.94 (17.43)	-2.53 (17.25)
HFS-II – Behavior			
Baseline	9.60 (10.26)	10.84 (10.34)	10.16 (10.31)
Week 12	9.64 (9.64)	9.46 (9.34)	9.55 (9.50)
Change (week 12 – Baseline)	0.03 (8.38)	- 1.38 (8.43)	-0.61 (8.43)
HFS-II – Worry			
Baseline	13.17 (15.30)	13.74 (14.94)	13.43 (15.14)
Week 12	11.79 (13.30)	11.24 (12.81)	11.54 (13.08)
Change (week 12 – Baseline)	-1.38 (11.94)	-2.51 (12.09)	-1.89 (12.02)

Source: Appendix II, Table 2.5 – 24

Additional details can be found in Appendix II, Table 2.5 – 24, and for the eligible population in Table 2.5 – 48.

Discussions:

The DUNE study included 3139 evaluable patients from 28 countries worldwide: 1716 patients newly insulin treated and 1423 patients already treated with basal insulin. More than half of these patients (67.3%) were included in Europe, 20.8% were included in Latin America countries, and 11.9% patients were included in Middle East countries.

More than half of the investigators practiced in public centers (59.5%).

Patients' characteristics

The evaluable patients included a good balance between male (50.9%) and female (49.1%), similar in both groups. Median age of patients was 61 years ranging between 19 and 93 years. Most patients had an abnormal BMI (37.6% between 25 and 30 Kg/m^2 and 48.0% had a BMI ≥ 30 Kg/m^2).

Mean duration of diabetes was 10.1 years with a mean time since first antidiabetic medication of 9.3 years (with a higher proportion of patients with duration of more than 10 years in those already treated with basal insulin [46.1%] than newly insulin treated patients [39.1%]). Severe episodes of hypoglycemia in the 6 months before the start of the study were reported by 3.6% of patients, while symptomatic episodes of hypoglycemia were experienced by 7.6% patients in the previous month with higher rates in the group of patients already treated with basal insulin (12.0%) with respect to the group of newly insulin treated patients (4.0%).

Less than half of the patients (1260 patients, 40.1%) presented with any diabetes complication at study entry. Among the most frequent reported complications were: peripheral neuropathy in 822 patients (26.2% of the evaluable population), diabetic retinopathy not leading to blindness in 470

patients (15.0%), and microalbuminuria in 264 patients (8.4%) with higher figures in the patients already treated (9.6%) compared to patients newly treated (7.4%)..

Most patients (82.6%) reported comorbidity or relevant past history with hypertension in 66.8% patients, dyslipidemia in 60.5% patients, and coronary heart disease in 14.9% patients being most frequently reported. The study included a high proportion of patients (63%) classified at high risk (aged >65 years with diabetes- or age-related comorbidities).

The majority of evaluable patients (78.2%) were treated with long-acting basal analogue insulin. The majority of patients were treated with one daily injection of basal insulin, at a median daily dose of 15 units per day.

More than 90% patients reported having taken a previous antidiabetic medication before basal insulin start . The most frequent reported were metformin in 80.2% patients, followed by sulfonylureas in 48.5% patients, DPP-IV inhibitors in 28.2% patients, GLP1 receptor agonist in 5.6% patients and metiglinides in 4.4% patients.

Patients at study entry had a baseline HbA1c (obtained within 1.5 months prior study entry) of 8.9%, a fasting plasma glucose of 184.8 mg/dL (higher in the group of newly insulin treated patients [204.30 mg/dL] than in the group of patients already treated with basal insulin [160.24 mg/dL]), a fasting self-monitoring blood glucose of 172.8 mg/dL (again higher in the group of newly insulin treated patients [190.1 mg/dL and 153.8 mg/dL, respectively]), and a glomerular fraction rate of 84.5 mL/min/1.73m^2.

More than half of the population (57%) had an individual HbA1c target defined by the physician of 7% to 7.5%. The major reasons underlying physicians' decisions on HbA1c targets were age (65.6%), patient's acceptability (41.2%) and comorbidities (37.7%).

Primary objective

The percentage of patients who achieved HbA1c target (individual or general target of < 7.0% if individual target was not defined) at 12 weeks was one of the two primary endpoints. Despite a substantial fall in HbA1c levels, with a mean (± SD) HbA1c level of 7.7% (± 1.18) at week 12, only 27.4% of the patients achieved their HbA1c at target after 12 weeks. These figures were consistent with those reported in previous studies performed in real life settings (12).

Multivariate logistic regression analyses showed an association between the occurrence and frequency of symptomatic hypoglycemia episodes and HbA1c achievement, with a lower percentage of patients achieving their HbA1c target in patients without hypoglycemia than in patients with hypoglycemia. This was also confirmed with the propensity scores analyzed.

Secondary objectives

Symptomatic hypoglycemia

Symptomatic hypoglycemia was reported in 503 (16.0%) patients (higher rates in the group of patients already treated with basal insulin (18.3%) than in the group of newly insulin treated patients (14.2%)), which was less than the expected incidence of patients with hypoglycemia (between 20 and 45%). Documented symptomatic hypoglycemia (blood glucose ≤ 70 mg/dL) episodes were reported in 393 (12.6%) patients and severe hypoglycemia in 26 (0.8%) patients. The majority of patients (90.3%) reported ≤ 1 episode of symptomatic hypoglycemia.

Multivariate logistic regression analyses on propensity scores with hypoglycemia as dependent variable showed similar results than those reported for the primary variable.

Achievement of HbA1c target after 12 weeks

The proportion of patients at low risk who achieved < 7.0% HbA1c after 12 weeks was 27.6%,. Lower rate was reported for patients at high risk (22.5%). When an achievement of < 8.0% was analyzed, the proportion increased up to more than 60% of responders in the two categories (low and high risk).

A total of 40.4% (1266 patients) of the population achieved the HbA1c objective set by the physician after 12 weeks of treatment. Reasons for not achieving the objective were mainly lack of adherence

	to lifestyle recommendations (60.1%), followed by lack of adherence to titration (43.5%) as considered by the physician. A total of 691 (22%) patients achieved their HbA1c target at 12 weeks without any episode of symptomatic hypoglycemia. HbA1c decrease Regarding improvement in HbA1c, the majority of patients (73.7%) achieved at least an improvement of 0.5% (with higher rates in the group of newly insulin treated patients than in the group of patients already treated with basal insulin [80.0 % vs 66.1%, respectively]). Of the total population, a total of 60.7% of patients achieved this 0.5% improvement without any symptomatic hypoglycemia episode. More than half of the patients (53.7%) achieved an improvement of 1% in HbA1c after 12 weeks (63.3% in the group of patients newly treated and 42.2% in the group of patients already treated), with 43.7% of the total population who achieved this improvement without any episode of symptomatic hypoglycemia. Changes in basal insulin Basal insulin regimen was discontinued in 40 (1.3%) patients: the main reason for discontinuation that patient was insufficiently controlled. By week 12, daily insulin dose increased to a mean of 23 U and 28 U (0.27 and 0.34 U/Kg) in newly treated and already treated patients, respectively. Regarding insulin titration, a total of 1416 (45.1%) patients reported between 1 to 5 steps of insulin dose increase over the 12 –week study period , and 830 (26.4%) patients didn't report any insulin dose increase.. Additional details can be found in Appendix II, Table 2.5 – 21. Antidiabetic medications A total of 2011 (64.1%) patients reported at least one concomitant antidiabetic medication other than basal insulin during the study. The most frequently reported antidiabetic medications were sulfonylureas, DPP-IV inhibitors and metformin. Regarding medications discontinued before week 12 visit, these were reported by 253 (8.1%) patients. The most frequently discontinued antidiabetic medication reported were sulfonylureas, DPP-IV inhibitors and metformin in 48 (1.5%) patients. Laboratory tests Regarding change from baseline to 12 weeks in laboratory tests, there was a decrease in HbA1c, fasting plasma glucose and self-monitoring blood glucose. A higher decrease was found in the group of newly treated patients, showing the benefits of basal insulin. Body weight Body weight remained unchanged during the course of the study. Quality of life The HFS-II survey showed slight decrease in total and worry score after 12 weeks of treatment,. This observational study has some limitations: the centers were not selected at random but by their capacity to recruit a high number of patients. The patients included in the DUNE study may therefore not be fully representative of the global population of patients with Type 2 diabetes. The rather short duration of the study should be noticed with potential impact in term of insulin dose optimization and HbA1c achievement. The modest increase in insulin doses over the 12 week – period may have also contribute to the low hypoglycemia incidence . The observed number of symptomatic hypoglycemia episodes lower than expected per protocol, can be also at least partially explained by the patient-based collection of the events .

Conclusions:	DUNE is a global observational study including a large sample of patients across many countries with a good representation. It showed that in real life settings , while HbA1c levels fell substantially, a high proportion of Type 2 diabetes patients newly or recently initiated with basal insulin treatment do not achieve individual HbA1c target after 12 weeks. Patients with symptomatic hypoglycemia were more likely to have reached their HbA1c target than those with no hypoglycemia. This suggests that other factors may contribute to individualized glycemic targets.
Date of report:	22-MAR-2017

APPENDICES

APPENDIX I – ADMINISTRATIVE AND LEGAL CONSIDERATIONS

1.1 ETHICAL CONSIDERATIONS

1.1.1 Ethical principles

This registry was conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) including all subsequent amendments.

1.1.2 Laws and regulations

This registry was conducted in compliance with all international guidelines, and national laws and regulations of the country(ies) in which the registry was performed, as well as any applicable guidelines.

Each participating country locally ensured that all necessary regulatory submissions (eg, IRB/IEC) were performed in accordance with local regulations including local data protection regulations.

Regulatory authorities' submissions by country are presented in Section **3.7** (Appendix III).

1.2 DATA PROTECTION

The patient's personal data and physician's personal data which were to be included in the Company's databases were treated in compliance with all local applicable laws and regulations.

When archiving or processing personal data pertaining to the physician and/or to the patients, the Company took all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

1.3 RECORD RETENTION

The physician was responsible for the retention of the registry documentation until the end of the registry. In addition, the physician had to comply with specific local regulations and recommendations regarding patient record retention.

1.4 THE COMPANY AUDITS AND INSPECTIONS BY COMPETENT AUTHORITIES (CA)

The physician agreed to allow the Company's auditors and Competent Authorities' inspectors to have direct access to records of the registry for review, it being understood that all personnel with