STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: -
ACTIVE INGREDIENT: -

Study No: D1680R00018 / CV181-148
DIAPAZON

Developmental Phase:
Study Completion Date: June 2015
Date of Report: May 2016

OBJECTIVES:

The study was mainly descriptive and evaluated saxagliptin utilization and effect in "actual practice" conditions:

- Description of the population at initiation of saxagliptin *(sociodemographic data, medical history, history of the disease, comorbidities, including renal, hepatic and cardiac function, HbA1c level at treatment initiation),*
- Description of saxagliptin utilization by general practitioners and endocrinologists-diabetologists in France *(indication, initial dosage and dose adjustments, co-prescriptions, blood glucose monitoring, etc.),*
- Evaluation of the retention rate of saxagliptin over a 2-year period and description of discontinuation rate and reasons,
- Description of the changes in HbA1c level, weight and hypoglycaemic episodes over time (2 years) for patients treated with saxagliptin.

The secondary objectives were as follows:

- Description of the distribution of different hypoglycaemic therapeutic strategies used in France and characteristics of T2D patients according to therapeutic strategies (registry data),
- Description of saxagliptin utilization according to patient profile and disease characteristics.

METHODS:

DIAPAZON is a descriptive, observational study conducted among patients suffering from type 2 diabetes mellitus (T2D), conducted in two stages:

- a general registry comprising all adult T2D patients consulting the investigators over the inclusion period covered by the registry, irrespective of the reason for consultation.
- follow-up of an ambispective cohort, for a period of 24 months, which included adult T2D patients having consulted an investigator over the study inclusion period and having initiated treatment with saxagliptin in the 6 months prior to inclusion visit M0 (including visit M0), irrespective of the ongoing hypoglycaemic treatment at the inclusion visit.

Both general practitioners and endocrinologists-diabetologists included patients.

RESULTS:

In total, 33 010 physicians (31 997 general practitioners and 1 013 endocrinologists-diabetologists) were contacted to take part in the study, which enabled 667 participating physicians to be recruited. Almost all participating physicians had at least one patient treated with saxagliptin prior to their participation in the study (93.5%). Among these participating physicians, 332 (49.8%) were active in terms of completion of the registry and 304 (45.8%) were active with regard to inclusion of patients in the ambispective cohort.

Registry:

Out of the 10 170 patients considered evaluable, 61.2% were included by a general practitioner.

Based on the weighted data, half of patients in the registry population were male (54.7%). The patients in the registry population had a mean age of 64.0 years, and their mean body mass index was 29.5 kg/m² (38.9% were obese and 42.7% were overweight).

Mean patient age at diagnosis of T2D was 54.2 years and the mean period between inclusion in the registry and diagnosis of diabetes was 9.9 years.

The last known mean HbA1c value before the appointment was 7.3%. Half of patients in the registry population (55.8%) had an HbA1c level ≥ 7%.

Among patients listed in the registry, saxagliptin was initiated in the past 6 months or during the appointment in 10.5% of cases. The majority of these patients (62.0%) were included in the ambispective cohort. The other patients were not included as they refused to take part (46.2%) or the physician had already included 3 patients (29.4%) or the physician had decided not to (24.1%).

Among the 10 170 patients in the registry population, 91 were receiving non-pharmacological treatment (health and dietary measures and/or bariatric surgery). The patients were mainly treated with OAD only (74.9%). Nearly 20% of patients were receiving treatment including insulin and 5.6% of patients were receiving treatment including a GLP-1 analogue.

In total, 80.9% of patients included by an endocrinologist-diabetologist had an HbA1c level ≥ 6.5% versus 75.6% of patients included by a general practitioner for the last recorded assay.

Patients included by endocrinologists-diabetologists more frequently received treatment combinations including insulin (35.9% vs. 9.3%) whereas those included by general practitioners more frequently received OAD only (88.2% vs. 53.4%).

Ambispective cohort:

The Diapazon study fulfilled its objectives in terms of the number of patients included in the ambispective cohort (1 033): 97.5% initiated saxagliptin with Onglyza® and 2.5% with Komboglyze®.

Seventy-five per cent of patients included in the ambispective cohort were included by a general practitioner.

The proportion of patients followed up at 24 months was 73.6%. Out of the 273 patients (26.4%) prematurely withdrawn from the study, 94.1% were considered lost to follow-up, 3.7% had discontinued saxagliptin and 2.2% were deceased. It should be noted that 24 active physicians withdrew from the study while the study was in progress, probably further to the change of sponsor. This led to the study being discontinued for 56 patients. These patients were considered lost to follow-up, which represents 21.8% of all patients lost to follow-up.

The mean patient follow-up period for this analysis at 2 years was 20.9 months.

Sociodemographic data and disease history

More than half of patients included in the cohort population were male (58.7%).

The mean age of patients at the time of diagnosis of T2D was 54.3 years.

At initiation of treatment with saxagliptin, mean patient age was 61.2 years (12.6% were aged over 75 years) and mean body mass index was 29.8 kg/m²: 39.7% were overweight and 44.2% were obese. Mean time since diagnosis of T2D at initiation of treatment with saxagliptin was 7.1 years.

The mean value for the last known HbA1c value prior to initiation of saxagliptin was 8.0%, measured in the months leading up to initiation of saxagliptin. More than three-quarters of patients had an HbA1c value greater than or equal to 7%, and 92.7% of patients had an HbA1c value greater than or equal to 6.5%.

Cardiovascular risk factors, complications and comorbidities

At initiation of saxagliptin, the majority of patients presented treated dyslipidaemia (62.0%) and/or treated hypertension (HT) (63.2%). Approximately 20% of patients in the cohort were smokers or had stopped smoking within the past 3 years.

At initiation of saxagliptin, 87.1% of patients were receiving treatment in the context of primary cardiovascular prevention. Furthermore, 4.2% of patients presented angina pectoris. A small proportion of patients had a history of myocardial infarction (5.1%), lower extremity peripheral obliterative arteriopathy (4.0%), stroke (2.5%) or heart failure (1.6%).

Among those patients for whom this information was available (66.0%), microvascular disease, i.e. retinopathy or moderate or severe renal impairment, or microalbuminuria/proteinuria, was identified in 26.9% of patients.

Creatinine clearance was available for 79.6% of patients in the cohort: 11.4% presented moderate renal impairment and 0.2% severe renal impairment.

Among those patients for whom this information was available (81.1% and 80.2% of patients, respectively), a small proportion presented microalbuminuria (8.8%) or proteinuria (1.7%).

Lastly, other comorbidities corresponding to hepatic impairment (0.7%) or a history of acute pancreatitis were observed (0.5%). Only one patient had presented chronic pancreatitis for 5 years.

*Antidiabetic treatment **before** initiation of saxagliptin*

Before initiation of their treatment with saxagliptin, almost all patients were exclusively treated with OAD (91.3%); 5.2% received insulin or a GLP1 analogue; 2.8% of patients in the cohort were not receiving any treatment.

As regards OAD monotherapy (66.4% of patients), 83.8% were receiving metformin; for dual OAD therapy (28.9%), 66.1% were receiving the combination metformin + sulfonylurea.

*Treatment **at initiation** of saxagliptin*

The participating physicians were the physicians having initiated treatment with saxagliptin for almost all patients in the cohort (97.4%).

Almost all patients were exclusively receiving treatment with OAD (95.1%).

The combination saxagliptin + metformin was prescribed to more than half of patients (52.9%). The other main treatments were: saxagliptin monotherapy (15.1% of patients), saxagliptin + metformin + sulfonylurea (15.6% of patients) and saxagliptin + sulfonylurea (6.1% of patients).

The main reasons for initiating treatment with saxagliptin were inadequate glycaemic control (81.4%) and intolerance to the previous treatment (19.1%).

Differences observed according to physician specialist field

The patients included by endocrinologists-diabetologists were more often female (49.0% *vs.* 38.8%), more often in work (41.3% *vs.* 36.0%), with a higher level of education (45.6% *vs.* 38.8%), more often overweight or obese (86.2% *vs.* 83.0%), and their condition was slightly more severe than for patients included by general practitioners. Regardless of the physician's specialist field, almost all patients were receiving treatment exclusively comprising OAD (endocrinologists-diabetologists 91.5% and general practitioners 96.3%).

Compliance with therapeutic indications

In total, 56.4% of prescriptions complied with the therapeutic indications applicable ***at the time of the analysis (Q1 2014).*** In increasing order of magnitude, the reasons for non-compliance were:

- the antidiabetic treatment before initiation did not correspond to the information stipulated in the SmPCs (57.4%), with 36.4% of combinations not mentioned in the SmPCs,
- the HbA1c value was below the defined limits[1] (22.6% of patients),

- the combination of treatments prescribed at initiation of saxagliptin did not comply with the SmPCs (16.7% of patients),
- and initiation of saxagliptin in patients previously treated with metformin only was not due to intolerance to the latter (10.3% of patients).

Compliance with the therapeutic indications and conditions for reimbursement according to the CNAMTS definition

In total, according to the definition used by the CNAMTS, 92.7% of prescriptions at initiation of saxagliptin complied with the therapeutic indications for the product, this percentage being similar regardless of the investigator's specialist field.

A 76.7% proportion of prescriptions at initiation of saxagliptin complied with the conditions for reimbursement. This proportion was higher for patients included by endocrinologists-diabetologists (79.8%) than for patients included by general practitioners (75.6%).

The proportion of prescriptions complying with both the therapeutic indications and the conditions for reimbursement corresponded to 76.7%.

Treatment retention

During the two-year follow-up period, 112 patients (10.8%) discontinued treatment with saxagliptin, mainly further to inadequate glycaemic control (52.1%).

The proportion of patients having discontinued treatment with saxagliptin was 3 times higher among patients included by an endocrinologist-diabetologist (21.2% *vs*. 7.4% among patients included by a general practitioner).

The retention rate at 2 years of follow-up estimated by the Kaplan-Meier method was 78.6%. This percentage was higher among patients included by a general practitioner (83.6% *vs*. 58.3% among patients included by an endocrinologist-diabetologist).

Changes in HbA1c

The mean HbA1c level decreased from 8.0% immediately before prescription of saxagliptin to 7.2% after 6 months of follow-up, and was maintained at this level (7.0%) for up to 2 years of follow-up. These values are confirmed by a repeated-measure model particularly adjusting the HbA1c values on the prescribed treatments.

The proportion of patients with an HbA1c value < 7% increased, from 21% immediately before prescription of saxagliptin to 49.0% two years after initiation of saxagliptin.

Changes in weight

After 2 years of follow-up, the patients in the ambispective cohort presented mean weight loss of 2.0 kg. A repeated-measures model particularly adjusted to weight at inclusion evidences mean weight loss of 1.8 kg after two years of follow-up.

Hypoglycaemia and adverse events

During the two-year follow-up period, 294 hypoglycaemic episodes were reported with saxagliptin; these episodes concerned 70 patients (6.8%). Out of these 294 hypoglycaemic episodes, 143 were reported with saxagliptin in the absence of concomitant insulin-secreting treatment (insulin, sulfonylurea or glinide); these concerned 41 patients (4.0%).

In total, 7 severe hypoglycaemic episodes (requiring the intervention of a third party and/or hospitalisation) were reported for saxagliptin. These severe hypoglycaemic episodes concerned 6 patients (0.6%), including 1 also receiving treatment with a sulfonylurea and 1 also receiving insulin. The other 5 severe hypoglycaemic episodes (two episodes in one patient) required the intervention of a third party. It should be noted that the criterion for third-party intervention causing the episode to be classed as severe consists of information reported to the physician by the patient. All of these patients were included by a general practitioner.

During the two-year follow-up period, 228 patients (22.1%) presented at least 1 AE; 23 patients (2.2%) at least one AE related to saxagliptin and 11 patients (1.1%) at least one AE having resulted in discontinuation of saxagliptin.

During the two-year follow-up period, 84 patients (8.1%) presented at least one serious AE. Out of the 130 serious AE reported, 6 AE reported for 2 patients were considered to be related to saxagliptin.

Development or exacerbation of comorbidities

During the two-year follow-up period, the development of new comorbidities was observed in slightly over 10% of patients in the cohort, mainly represented by the development of renal impairment (9.0% of patients).

Exacerbation of at least one concomitant disorder was observed for 21 patients in the cohort (2.4%). Of these, 15 patients presented exacerbation of renal impairment.