1. ABSTRACT

Observatory of ATTR amyloidosis and of patients treated with Vyndaqel® (tafamidis) OBSAMYL study

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Rationale and background
ATTR amyloidosis is a systemic and multi-genotypic condition defined by the presence of extracellular protein deposits in several organs and tissues. Two main phenotypic forms are encountered: hereditary transthyretin amyloid polyneuropathy (TTR-FAP, or ATTR-PN according new nomenclature) which is an autosomal dominant hereditary disease and hereditary transthyretin amyloid cardiomyopathy (TTR-FAC, or hATTR-CM according to new nomenclature). Transthyretin amyloid cardiomyopathy (ATTR-CM) also includes wild-type transthyretin amyloid cardiomyopathy (wtATTR-CM) occurring predominantly in men aged over 60 years, in which amyloid deposits are derived from wild transthyretin. TTR-FAP (ATTR-PN) was estimated at $1/1.10^6$ in general population whereas the French national registry has recorded 482 patients from 1989 to 2014. For TTR-FAC (hATTR-CM), there is a lack of epidemiological data.
Vyndaqel® (tafamidis meglumine 20mg) is a TTR tetramer stabilizer authorized in the EU market since 2011, for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment, TTR-FAP (ATTR-PN). Vyndaqel® (tafamidis 61mg) was under clinical study for ATTR-CM (wild-type and hereditary) at the time of the study start up. Since then, it has obtained a marketing authorization in the EU for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).

Pfizer conducted this non-interventional study as a voluntary PASS, OBSAMYL, to provide new data regarding ATTR-amyloidosis and tafamidis use.

Research question and objectives
Primary objectives
1) To estimate the number of living patients diagnosed with ATTR amyloidosis (hereditary and wild-type), in France, on 1st June 2017, by stage of the disease, and by mutation if applicable
2) To evaluate modalities of tafamidis use, its safety and effectiveness profile for patients who have received tafamidis in a real-life setting in France whether or not the patient is still alive.
Secondary objectives
- To estimate the delay between patient's first symptom and time of diagnosis.
- To describe, for each patient, the number of children, brothers and sisters in France and among adults, the number of people with a TTR genetic test performed
- To estimate the number of cases of patients with pathogenic *TTR* gene mutations among participating centres in France and by mutation in the subgroup of patients with hereditary ATTR amyloidosis

Study design

This is a non-interventional, descriptive, retrospective, national, multicentric and two-parts study.

A census part estimates the number of patients in participating centres diagnosed with ATTR amyloidosis (hereditary and wild-type) and alive as of 1st June 2017 (study point date). This objective comprises all patients with a diagnosis of TTR-FAP (ATTR-PN), TTR-FAC (hATTR-CM), TTR-mixed phenotype and wtATTR-CM diagnosed in France (targeted population) still alive at the study point date (census population).
A tafamidis part, based on secondary data collection, describes the modalities of tafamidis use, its safety and effectiveness profile for patients having received or receiving the product in real-life setting, since its launch in France, whether they are still alive or not at the study point date.

Setting
All centres having the ability to treat patients for this disease have been invited to participate on behalf of the scientific committee. They include the national reference center for amyloidosis, and several regional competence centres
Patients Eligibility for the Census Part:
- Patient ≥18 years old;
- With a diagnosis of hereditary or wild-type ATTR amyloidosis or a pathogenic TTR mutation in participating centres and alive on 1st June 2017;
- Who does not oppose to his/her data collection
No Exclusion criteria
Patients Eligibility for tafamidis part:
Inclusion criteria
- Patient ≥ 18 years old;
- With at least one documented prescription of tafamidis (Vyndaqel®) outside of a clinical trial since its launch in France through an Early Access Programme (EAP)
Exclusion criteria
- Patient who participated and received tafamidis only within an interventional study evaluating the efficacy of tafamidis at time of data collection

Subjects and study size
Census part: The sample size is based on the primary endpoint whose aim is to estimate the number of ATTR amyloidosis patients. As such, no hypothesis has been defined and no sample size calculation has been carried out.
Tafamidis part: at the time of protocol writing a recent market data estimates approximately 300 patients in the tafamidis population[1]

Variables and data sources
All data collected for the purpose of the study are routine data for the disease of interest. They are readily available in patients' medical records in participating centres. As these centres are experts on the disease, additional and specific tools have already been used to collect these data within these centres. An electronic Case Report Form (e-CRF) has been used for data recording. It was the investigator's responsibility to ensure completion

Results

[1] sales data obtained by extraction of GERS database providing analysis of market sales in France to pharmaceutical industry players.

A total of 23 centres participated in this study, including 11 cardiology centres and 12 neurology centres.

Census population comprised 769 patients, including 629 with a confirmed diagnosis. Among them, 296 were diagnosed with TTR-FAP (ATTR-PN), 39 with TTR-FAC (hATTR-CM), 117 with ATTR-mixed phenotype and 177 patients with wtATTR-CM. Patients' mean age at diagnosis was 63.7 ± 17.8 years, and was the lowest for TTR-FAP (ATTR-PN) patients (54.8 ± 17.4 years) whilst being the highest for wtATTR-CM (80.1 ± 7 years). Two-thirds of population were male.
Most frequent pathogenic TTR mutations were: Val30Met (52% of census population and 67% of TTR-FAP (ATTR-PN) patients) with early onset (before age 50) reported for 50.3% of Val30Met patients, and late onset for 49%, Val122Ile (15% of census population, 72% of TTR-FAC (hATTR-CM) patients and 27% of mixed form patients) and Ser77Tyr (11.6% of census population and 15% of TTR Mixed patients). First symptoms related to amyloidosis were different according to amyloidosis phenotype. For TTR-FAP (ATTR-PN) patients, the most frequent first symptom was paresthesia (67%) while weight loss occurred for 16%. For other phenotypes, most frequent symptom was shortness of breath (from 44% to 58%).
Diagnosis was mainly performed through biopsies, accounting for more than 80% of patients in each phenotype and more frequently for ATTR-mixed phenotype patients (90%). Salivary gland biopsy was the most frequent (74%). Bone scintigraphy was also performed in 94% of wtATTR-CM patients, 82% of TTR-FAC (hATTR-CM) patients, 74% of ATTR-mixed phenotype patients and 68% of TTR-FAP (ATTR-PN) patient.
Time between first symptoms and diagnosis was longer for TTR-FAP (ATTR-PN) patients (median at 2 years) than for other phenotypes (median at 1 year).

Tafamidis population comprised 464 patients, including 367 patients also in the census population. TTR-FAP (ATTR-PN) patients accounted for 52% of the tafamidis population and ATTR-mixed phenotype patients accounted for 21%. TTR-FAC (hATTR-CM) and wtATTR-CM represented 4% and 13% respectively of this population. There were 22 asymptomatic patients at time of diagnosis included in this population (only 4 had no symptoms documented at the time of tafamidis initiation), as well as 27 patients with undetermined ATTR genotype. Among 376 tafamidis patients with complete follow-up, 116 discontinued treatment. For this population the median duration of treatment was estimated to be 4.4 years ($_{95\%}$CI [3.7; 6.3]).
363 TTR-FAP (ATTR-PN) patients were included. For TTR-FAP (ATTR-PN) patients with a complete follow-up, the median duration of treatment was estimated to 6.3 years ($_{95\%}$CI [4.0; 7.5]), with 69 recorded tafamidis discontinuations. The duration of treatment for the 58 patients with a Val30Met Early Onset disease was shorter (4 years) while it reached 6.42 years for the Val30Met Late Onset patients (n= 73) and 6 years for the 65 non Val30Met patients. Among tafamidis discontinuations, patient with Val30Met Early Onset disease were more likely to discontinue tafamidis due to transplantations (13/14 patients with discontinuation). For ATTR-mixed phenotype patients, the median duration reached 3.4 years ($_{95\%}$CI [2.4; 5.2]) with 36 recorded discontinuations. For these two phenotypes, emergence of new symptoms was the main reason for discontinuation (41% and 25% respectively). For TTR-FAC (hATTR-CM) and wtATTR-CM forms, only 2 and 3 discontinuations were reported respectively, considering they had been receiving tafamidis for 1 month as a median. For TTR-FAP (ATTR-PN) and ATTR-mixed phenotype patients still treated at last visit, FAP score (Coutinho classification) remained stable for 70% of them during the whole treatment period.
During the study, 49 adverse events comprising 20 SAEs were reported, experienced by 44 patients. A total of 16 AEs (including 2 SAEs) were considered as associated to tafamidis

discontinuation. SAEs comprised 14 cases of death, none were considered as related to the drug according to the investigator.

Discussion/Conclusion
OBSAMYL study provided national estimations of ATTR diagnosed in expert centres in line with recent data, with 629 recorded prevalent ATTR cases. As amyloid cardiomyopathy can be managed by more generalist sites since Vyndaqel® launch, some prevalent wtATTR-CM could have been missed and would need to be further estimated.
In this study, tafamidis was proposed within 4 months after diagnosis, predominantly within the scope of its indication, in FAP score stage 1, with symptomatic disease, and for all types of mutations. Treatment is continued over the long term, with half of the -FAP (ATTR-PN) patients still being treated after 6 years. More than 70% of patients are stable from a locomotion perspective (FAP score) during treatment. A quarter of the OBSAMYL population discontinued treatment during follow-up for 4 patients, reported treatment discontinuation was associated with adverse events or tolerability.
With the temporary recommendation (RTU) of tafamidis for cardiac amyloidosis in November 2018, patients with TTR-FAC (hATTR-CM) and wtATTR-CM receiving the treatment were enrolled in the study. As a majority of elderly men with a high prevalence of hypertension and carpal tunnel syndrome history, they were in line with the known profile of TTR amyloid cardiopathy and mainly had an NYHA class of II to III in accordance with the treatment indication. The challenge is to earlier diagnosis of their condition to be able to initiate the treatment earlier, when it is expected to be the most effective.

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