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NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	Impact of tafamidis use in Colombian patients diagnosed with ATTR-CM on quality of life during two years of follow-up
Protocol number	B3461112
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Date	27 July 2023
EU Post Authorization Study (PAS) register number	EUPAS105913
Active substance	N07XX08
Medicinal product	Tafamidis
Product reference	INVIMA 2022M-0020673
Marketing Authorization Holder(s) (MAH)	Pfizer SAS Avenida Suba No. 95 – 66 Bogota, D.C
Joint PASS	No.
Research question and objectives	**Research Question** What is the impact of tafamidis use in Colombian patients diagnosed with ATTR-CM on quality of life during two years of follow-up? **Primary Objective** To describe the impact of tafamidis use in Colombian patients diagnosed with ATTR-CM on quality of life during two years of follow-up **Secondary Objectives** • To describe the clinical and demographic characteristics of the patients at the moment of prescription of tafamidis • To determine the treatment patterns to manage ATTR-CM previous to Tafamidis prescription • To evaluate the frequency of hospitalization and its causes during the follow-up period

	• To describe the use of cardiovascular devices during the follow-up of patients recruited in the study • To outline the change in baseline for patients in cardiovascular functionality in patients prescribed tafamidis. • To measure the adherence of the patients to the therapy. • To describe the access barriers during the use of tafamidis **Exploratory objectives** • To analyze the relationship between baseline variables and changes on quality of life and cardiovascular functionality
Country of study	Colombia
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AEM	Adverse event monitoring
AL	Monoclonal immunoglobulin light chains
ARMS	Adherence to Refills and Medications Scale
ATTR	Transthyretin amyloidosis
ATTR-CA	Transthyretin amyloidosis cardiac amyloidosis
ATTR-CM	Transthyretin amyloidosis cardiac cardiomyopathy
ATTRv	Hereditary transthyretin amyloidosis
BNP/NT-proBNP	B-type natriuretic peptide/N-terminal pro b-type natriuretic peptide
CA	Cardiac amyloidosis
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD	Chronic Kidney diseases
CRF	Case report form
CRT-D	Cardiac resynchronization therapy – defibrillator
CRT-P	Cardiac resynchronization therapy – pacemakers
CSA	Clinical study agreement
EDP	Exposure during pregnancy

FDA	Food Drug Administration
GPP	Good Pharmacoepidemiology Practices
HF	Heart failure
HR	Hazzard ratio
ICD	Implantable cardioverter defibrillator
IEC	Independent ethics committee
INVIMA	National Institute for Drug and Food Vigilance
IQRs	interquartile ranges
IPS	Health Provider Institution
IRB	Institutional review board
ISPE	International Society of Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KCCQ	Kansas City Cardiomyopathy Questionnaire
HMG COA	3-hydroxy-3-methylglutaryl coenzyme A
6-MWT	6 minute walk test
99mTc-DPD	Technetium-99m-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid
99mTc-HMDP	99mTc-Hydroxymethylene diphosphonate
NIS	Non-interventional study
NYHA FC	New York Heart Association functional classification
PASS	Post-authorization safety study

PV	Pharmacoviligance
QoL	Quality of life
QRS	Q wave, R wave and S wave
RR	Risk ratio
SAE	Serious adverse events
TTR	transthyretin
wtATTR	wildtype transthyretin amyloidosis

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
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4. ABSTRACT

- **Title:** Impact of tafamidis use in Colombian patients diagnosed with ATTR-CM on quality of life during two years of follow-up

- **Rationale and background**

Cardiac amyloidosis (CA) is a restrictive cardiomyopathy secondary to amyloid deposits, which are misfolded protein fragments, in cardiac tissue(1, 2).

The most common forms of CA are caused by the deposition of monoclonal immunoglobulin light chains (AL) or transthyretin which can be hereditary or acquired (3).

AL is considered a rare disease with an estimated prevalence between 8-12 cases per million(4). The prevalence of CA in patients with heart failure is estimated at 13.7% (95%CI 7.9 – 19.8) according to a meta-analysis collecting studies worldwide (5). In patients with heart failure the preserved ejection fraction, increases to 15.1% (95% CI 9.6-20.6). Analyzing the subgroup of amyloidosis, the prevalence in patients with wild-type transthyretin amyloidosis (wtATTR) was 9.0% (95%CI 5.2 - 12.7) while hereditary transthyretin amyloidosis (ATTRv) was 2.9% (95% CI 0.8-4.9)(5).

The diagnosis of CA is delayed or missed. It has required more than 4 years as is the case of ATTR-CA. Highlighting that 44% of patients with ATTR and 81% with AL are usually evaluated for more than five physicians before diagnosis (6). Patients with preliminary stages of CA are commonly misdiagnosed with other cardiovascular diseases such as hypertensive cardiac disease, hypertrophy cardiomyopathy, or ischemic heart diseases (7).

The diagnosis of this disease is challenging requiring multidisciplinary management. Additionally, the absence of therapies and late presentation of CA has produced a sub-diagnosis of this condition (4). For that reason, red flags have raised suspicion of AL and allowed a diagnosis to be made. Among them, some red flags are heart failure with preserved ejection fraction, down-titration of anti-hypertensive medication, intracardiac thrombosis, stroke and transient ischemic attack, poor tolerance to heart failure therapy, carpal tunnel syndrome, biceps tendon rupture, lumbar spinal stenosis, trigger finger, polyneuropathy, antihypertensive drugs down-titration, autonomic dysfunction, macroglossia, spontaneous bruising, unexplained LV hypertrophy (>12 mm), right ventricular hypertrophy, increased valve thickness, pericardial effusion, apical sparing, biatrial dilation, diastolic dysfunction, elevated BNP/NT-proBNP levels, persistently elevated troponin levels, and atrial fibrillation (7).

CA diagnosis is relevant given that it is associated with significant morbidity and mortality. ATTR-CA diagnosis requires several invasive and non-invasive imaging and tests. Electrocardiography, echocardiography, cardiac magnetic resonance imaging for suspicion of CA. Nuclear scintigraphy allows identifying ATTR amyloid deposits and TTR gene sequence to differentiate between hereditary or acquired ATTR (1). With the availability of scintigraphy, the diagnosis of ATTR-CA has increased exponentially and patients have been diagnosed

earlier in the disease course, also by the increased awareness among physicians and specialties (8).

In terms of healthcare resources, the ATTR-CA has a relevant impact compared to heart failure patients. One study conducted in four countries using information from databases between 2008 and 2018 found that during the first year after diagnosis, the outpatient visits was higher among ATTR-CM (10.2 [95%IC 10.1-10.4]) than HF patients 5.7 [95%CI: 5.6 -5.9]) and number of hospitalizations (3.3 [CI: 3.2 - 3.4] vs. 2.5 [CI: 2.5 - 2.6]), hospitalization days (21.7 [CI: 21.5 -22] vs. 15.2 [CI: 15 -15.4]), and surgical procedures (1.7 [CI: 1.6 -1.8] vs. 1.06 [CI: 1.00 -1.12]) (9). Colombia does not have information that evaluates the use of resources in CA.

During the last decade, the treatment option for CA was limited to symptom management. Currently, there are other options to manage this disease which can slow disease progression to optimize quality of life and improve survival. There are several types of diseases-modified therapies both researched and approved for use. They depend on the type of CA. For AL-CA, for instance, chemotherapy regimens, immunotherapy and autologous stem cell transplantation are therapeutic options with several limitations such as toxicity or tolerability by patients. While ATTR-CA, the only therapy approved by the Food Drug Administration (FDA) has been tafamidis, a TTR stabilizer. Other therapies called TTR silencers (inotersen and patisiran) are approved only for polyneuropathy, but in CA are in the clinical phase (10).

Tafamidis was approved by the FDA in May 2019 after positive results of the ATTR-ATC study. This study recruited 441 ATTR-CA patients divided into three arms (oral tafamidis 80 mg, tafamidis 20 mg, or placebo). The pooled analysis showed that tafamidis of 80 mg and 20 mg versus placebo were associated with a reduction in all-causes of mortality (29.5% vs 42.9%, HR 0.70; CI 0.51-0.96) and cardiovascular hospitalizations (RR 0.68; CI 0.56-0.81) at 30 months. Other endpoints as functional capacity by six-minute walking test and quality-of-life measured by the Kansas City Cardiomyopathy Questionnaire–Overall Summary scores were notably lower. In terms of tolerability, there were no significant safety problems reported (11). Tafamidis was approved in July of 2022 in Colombia.

Considering that Colombia has already approved tafamidis as an option therapy for ATTR-CM patients, the characteristics of its health care system, the awareness process of the CA in the physicians to diagnostic and treat early, and the limitation of patient compliance to use the therapy, this study intends to measure the quality of life, hospital frequency and mortality during the first two years of follow-up.

- **Research question and objectives**

Research Question

What is the impact of tafamidis use in Colombian patients diagnosed with ATTR-CM on quality of life during two years of follow-up?

Primary Objective

To describe the impact of tafamidis use in Colombian patients diagnosed with ATTR-CM on quality of life during two years of follow-up

Secondary Objectives

- To describe the clinical and demographic characteristics of the patients at the moment of prescription of tafamidis
- To determine the treatment patterns to manage ATTR-CM previous to tafamidis prescription
- To evaluate the frequency of hospitalization and its causes during the follow-up period
- To describe the use of cardiovascular devices during the follow-up of patients recruited in the study
- To outline the change in baseline for patients in cardiovascular functionality in patients prescribed tafamidis
- To measure the adherence of the patients to the therapy
- To describe the access barriers during the use of tafamidis

Exploratory objectives

To analyze the relationship between baseline variables and changes on quality of life and cardiovascular functionality.

- **Study design**

The study will be a non-interventional, descriptive, and longitudinal prospective study with primary data collection that involves sites/investigators. The patients must be diagnosed before enrollment with ATTR-CM and prescribed with tafamidis following the indications approved by National Institute for Drug and Food Vigilance (INVIMA) in Colombia. The patients will be followed up from the index date until patient i) have deceased, ii) have decided to withdraw from the study, iii) have terminated of treatment, iv) have been lost to follow up, or v) finalize the 24 months of following up. The index date will be defined as the date for the first prescription of tafamidis.

The patients who have been prescribed with tafamidis before August of 2023 will be recruited. The quality of life will be evaluated when the patient accepts to participate and signs the informed consent.

Quality of life, adherence, concomitant treatment, hospitalization for any causes, cardiovascular functionality will be measured 24 months after the prescription of tafamidis. Twelve months before the index date, treatments, and frequency of hospitalization for any causes will be measured (Table 1).

There will be two sources of information. Clinical and demographic information at the baseline will be abstracted from the medical record while the data related to hospitalizations, cardiovascular functionality, quality of life, and deaths will be collected directly from the patients using validated questionnaires and structured interviews. Thus, in this case the report form (CRF) will serve as a source document.

The patients will be reached out to every three months±15 days through a phone call by a healthcare professional of the site. During this interview, the professional will perform a standardized interview with structured questionnaires to guarantee that the data collection process will be harmonized among patients. The interview could be in the site if the patient received clinical care there or she decided to move to it. Both collection data are completely accepted in the study.

All assessments described in this protocol will be performed as part of normal clinical practice or standard practice guidelines for the patient population and healthcare provider specialty in Colombia.

- **Population**

The study will be performed in 6 Colombian Health Provider Institution (IPS, in its Spanish acronym) whose population includes patients with ATTR-CM diagnosis in the period established. The patients might be treated at the participant IPS or referred from other Colombian IPS.

Inclusion criteria

The selected patients must meet all the following inclusion criteria for analysis in the study:

1. Patient older than 18 years
2. Spanish speaking patients
3. Patients with diagnosis of ATTR-CM confirmed by the treating Cardiologist
4. Patients prescribed with tafamidis
5. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. Liver or heart transplantation history
2. Pregnancy
3. Breastfeeding
4. Recruited in clinical trials

- **Variables**

  - Demographic characteristics (i.e., age, sex, race)

  - Clinical characteristics (date of symptoms of ATTR-CM, sim of QRS amplitude in I, II and III leads at diagnosis, Sum QRS amplitude in all 6 limb leads at diagnosis, Sum QRS amplitude in all 6 precordial leads at diagnosis, Sokolow-Lyon index at diagnosis, Low QRS voltage at diagnosis, Pseudo-infarct Q waves at diagnosis, atrioventricular conduction disease (block) at diagnosis, left ventricular ejection fraction at diagnosis, N-terminal pro b-type natriuretic peptide at diagnosis, lumbar spinal stenosis, hypertrophic cardiomyopathy over 60 years old, embolic stroke, low flow/low gradient aortic valve stenosis, any cardiovascular device, history of heart block, syncope, NYHA FC, carpal tunnel syndrome, bleeding history, intravitreal deposition, Sum of QRS amplitude in I, II, and III leads at the end of follow-up, Sum of QRS amplitude in all 6 limb leads at the end of follow-up, Sum of QRS amplitude in all 6 precordial leads at the end of follow-up, Sokolow - Lyon index low voltage criteria at the end of follow-up)

  - Diagnostic characteristics (date of ATTR-CM diagnosis, genotype, scintigraphy at diagnosis, biopsy)

  - Treatment (angiotensin-converting enzyme inhibitors previous diagnosis, Agents acting on the renin–angiotensin system previous diagnosis, HMG COA reductase inhibitors previous diagnosis previous diagnosis, Loop diuretics previous diagnosis, Amiodarone previous diagnosis, Anticoagulation previous diagnosis, Beta blockers previous diagnosis, Calcium channel blockers previous diagnosis, Angiotensin receptor blockers previous diagnosis, Agents acting on the renin–angiotensin system after diagnosis, HMG COA reductase inhibitors after diagnosis, Loop diuretics after diagnosis, Amiodarone after diagnosis, Anticoagulation after diagnosis, Beta blockers after diagnosis, Calcium channel blockers after diagnosis, Angiotensin receptor blockers after diagnosis, angiotensin-converting enzyme inhibitors previous diagnosis, Cardiovascular devices during follow-up, Date of prescription of tafamidis, Date of first administration of tafamidis, Delay of supply of tafamidis, Cause of delay)

- Comorbidities (Heart failure at early age, any cardiac arrhythmias or conduction disorders, type of any cardiac arrhythmias or conduction disorder, diabetes mellitus, hypertension, sleep apnea, chronic kidney diseases, intracardiac thrombosis, stroke, polyneuropathy, orthostatic hypotension, erectile dysfunction, glaucoma)
- Adherence
- Persistence
- Hospitalization
- Quality of Life (KCCQ-OS)
- Cardiovascular functionality (6-MWT and scintigraphy)
- Hospitalization

- **Data sources**

There will be several sources of information. From the medical record provided by the patient will be abstracted the demographic and clinical characteristics related to diagnosis, comorbidities, and treatment at baseline, as well as the previous medications to manage CA. Other sources will be the patient to confirm or complete the information associated with it.

The study will be performed in approximately 6 Colombian Health Provider Institution (IPS, in its Spanish acronym) whose population includes patients with ATTR-CM diagnosis in the period established. These sites will be in four Colombian cities (Bogotá, Medellin, Cali, and Barranquilla) which have a cardiologist with experience in diagnostic and management of ATTR-CM.

During the follow-up, the patient will provide the information about changes in the treatment, issues to supply tafamidis, and hospitalization which can be confirmed with the summary of the medical records of the patient. The quality of life will be measured using the KCCQ scale through call or face to face meeting. 6-MWT and scintigraphy will be abstracted from medical records.

- **Study size**

Sample size is not required for being observational and descriptive study. The expected number of patients eligible for the study is close to fifty considering the number of patients identified with the diagnosis and the access to the treatment.

- **Data analysis**

Frequencies and percentages will be reported for binary and categorical variables, while medians and interquartile ranges (IQRs) will be reported for continuous variables, i.e., HRU. Finally, it will be presented through a tabular display of summary statistics and will be complemented by the generation of graphs, such as histograms, box plots, violin plots, density plots, scatterplots, depending on the nature of the variable.

On the other hand, difference of means (Student or Welch t-test) or medians (Wilcoxon or Kruskal-Wallis´s test) between subgroups will be considered (according to the variable distribution – normal or not), considering the sizes of these groups and trends in the behavior of the measures of centrality and dispersion.

- **Milestones**

Completion of feasibility assessment	12 May 2023
Registration in the EU PAS register	15 October 2023
Start of data collection	15 November 2023
End of data collection	30 July 2025
Start date of data analysis	16 September 2024
Study progress report 1	30 August 2024
Interim report 1	30 July 2024
Interim report 2	15 January 2025
Final study report	15 January 2026

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	12 May 2023
Registration in the EU PAS register	15 October 2023
Start of data collection	15 November 2023
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Study progress report 1	30 August 2024
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7. RATIONALE AND BACKGROUND

Cardiac amyloidosis (CA) is a restrictive cardiomyopathy secondary to amyloid deposits, which are misfolded protein fragments, in cardiac tissue (1, 2).

The most common forms of CA are caused by deposition of monoclonal immunoglobulin light chains (AL) or transthyretin which can be hereditary or acquired (3).

Light chain CA is considered a rare disease with an estimated prevalence between 8-12 cases per million (4). The prevalence of CA in patients with heart failure is estimated at 13.7% (95% CI 7.9 – 19.8) according to a meta-analysis collecting studies worldwide (5). In patients with heart failure preserved ejection fraction, it increases to 15.1% (95% CI 9.6-20.6). Analyzing the subgroup of amyloidosis, the prevalence in patients with wild type transthyretin amyloidosis (wtATTR) was 9.0% (95%CI 5.2 - 12.7) while hereditary transthyretin amyloidosis (ATTRv) was 2.9% (95% CI 0.8-4.9)(5).

The diagnosis of CA is delayed or missed. It has required more than 4 years as is the case of ATTR-CA. Highlighting that 44% of patients with transthyretin amyloidosis (ATTR) and 81% with AL are usually evaluated for more than five physicians before diagnosis (6). The patients with preliminary stages of CA are commonly misdiagnosed with other cardiovascular diseases such as hypertensive cardiac disease, hypertrophy cardiomyopathy, or ischemic heart diseases (7).

The diagnosis of this disease is challenging requiring multidisciplinary management. Additionally, the absence of therapies and late presentation of CA has produced a sub-diagnosis of this condition (4). For that reason, red flags have raised suspicion of AL and allowed a diagnosis to be made. Among them, some red flags are heart failure with preserved ejection fraction, down-titration of anti-hypertensive medication, intracardiac thrombosis, stroke and transient ischemic attack, poor tolerance to heart failure therapy, carpal tunnel syndrome, biceps tendon rupture, lumbar spinal stenosis, trigger finger, polyneuropathy, antihypertensive drugs down-titration, autonomic dysfunction, macroglossia, spontaneous bruising, unexplained left ventricular hypertrophy (>12 mm), right ventricular hypertrophy, increased valve thickness, pericardial effusion, apical sparing, biatrial dilation, diastolic dysfunction, elevated B-type natriuretic peptide/N-terminal pro b-type natriuretic peptide (BNP/NT-proBNP) levels, persistently elevated troponin levels, and atrial fibrillation (7).

CA diagnosis is relevant given that it is associated with significant morbidity and mortality. ATTR-CA diagnosis requires several invasive and non-invasive imaging and tests. Electrocardiography, echocardiography, cardiac magnetic resonance imaging for suspicion of CA. Nuclear scintigraphy allows identifying ATTR amyloid deposits and transthyretin (TTR) gene sequence to differentiate between hereditary of acquire ATTR (1). With the availability of scintigraphy, the diagnosis of ATTR-CA has increased exponentially and patients have been diagnosed earlier in the disease course, also by the increased awareness among physicians and specialties (8).

In terms of healthcare resource, the ATTR-CA has a relevant impact compared to heart failure (HF) patients. One study conducted in four countries using information from databases between 2008 and 2018 found that during the first year after diagnosis, the outpatient visits was higher among transthyretin amyloid cardiomyopathy (ATTR-CM) (10.2 [95%IC 10.1-10.4]) than HF patients 5.7 [95%CI: 5.6 -5.9]) and number of hospitalizations (3.3 [CI: 3.2 - 3.4] vs. 2.5 [CI: 2.5 - 2.6]), hospitalization days (21.7 [CI: 21.5 -22] vs. 15.2 [CI: 15 -15.4]), and surgical procedures (1.7 [CI: 1.6 -1.8] vs. 1.06 [CI: 1.00 -1.12]) (9). Colombia does not have information that evaluates the use of resources in CA.

During the last decade, the treatment option for CA was limited to symptom management. Currently, there other options to manage this disease which can slow disease progression to optimize quality of life and improve survival. There are several types of diseases-modified therapies both researched and approved for use. They depend on the type of CA. For AL-CA, for instances, chemotherapy regimens, immunotherapy, and autologous stem cell transplantation are therapeutic options with several limitations such as toxicity or tolerability by patients. While ATTR-CA, the only therapy approved by the Food Drug Administration (FDA) has been tafamidis, a TTR stabilizer. Other therapies called TTR silencers (inotersen and patisiran) are approved only for polyneuropathy, but in CA are in the clinical phase (10).

Tafamidis was approved by the FDA in May 2019 after positive results of the ATTR-CM study. This study recruited 441 ATTR-CM patients divided into three arms (oral tafamidis 80 mg, tafamidis 20 mg, or placebo). The pooled analysis showed that tafamidis of 80 mg and 20 mg versus placebo were associated with a reduction in all causes of mortality (29.5% vs 42.9%, HR 0.70; CI 0.51-0.96) and cardiovascular hospitalizations (RR 0.68; CI 0.56-0.81) at 30 months. Other endpoints such as functional capacity by six-minute walking test and quality-of-life measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ)–Overall Summary score were notably lower. In terms of tolerability, there were no significant safety problems reported (11). Tafamidis was approved in July of 2022 in Colombia.

Considering that Colombia has already approved tafamidis as an option therapy for ATTR-CM patients, the characteristics of its health care system, the awareness process of the CA in the physicians to diagnostic and treat early, and the limitation of patient compliance to use the therapy, this study intends to measure the impact of tafamidis in quality of life, hospital frequency and mortality during the first two years of follow-up in Colombian patients diagnosed with ATTR-CM.

This non-interventional study is designated as a PASS and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

Hypothesis

There are not hypotheses to evaluate.

Research Question

What is the impact of tafamidis use in Colombian patients diagnosed with ATTR-CM on quality of life during two years of follow-up?

Primary objective

To describe the impact of tafamidis use in Colombian patients diagnosed with ATTR-CM on quality of life during two years of follow-up

Secondary objectives

- To describe the clinical and demographic characteristics of the patients at the moment of prescription of tafamidis
- To determine the treatment patterns to manage ATTR-CM before tafamidis prescription
- To evaluate the frequency of hospitalization and its causes during the follow-up period
- To describe the use of cardiovascular devices during follow-up of patients recruited in the study
- To outline the change in baseline for patients in cardiovascular functionality in patients prescribed tafamidis
- To measure the adherence of the patients to the therapy
- To describe the access barriers during the use of tafamidis

Exploratory objectives

- To analyze the relationship between baseline variables and patient and changes of quality of life and cardiovascular functionality

9. RESEARCH METHODS

9.1. Study design

The study will be a non-interventional, descriptive, and longitudinal prospective study with primary data collection that involves sites/investigators. The patients must be diagnosed before enrollment with ATTR-CM and prescribed with tafamidis following indications approved by National Institute for Drug and Food Vigilance (INVIMA) in Colombia. The patients will be followed up from the index date until patient i) have deceased, ii) have decided to withdraw from the study, iii) have terminated of treatment, iv) have been lost to follow up, or, v) finalize the 24 months of following up, the event that happens first. The index date will be defined as the date for the first prescription of tafamidis.

The patients that were prescribed with tafamidis before August of 2023 will be recruited. In the cases where the patients were prescribed before starting the study, all previous information will be collected from the data provided by the patients. The quality of life will be evaluated when the patient accepts to participate and signs the informed consent.

Quality of life, adherence, concomitant treatment, hospitalization for any causes, cardiovascular functionality will be measured 24 months after the prescription of tafamidis. Twelve months before the index date, treatments, and frequency of hospitalization for any causes will be measured (Table 1).

There will be two sources of information. Clinical and demographic information and death at the baseline will be abstracted from the medical record while the data related to hospitalizations, cardiovascular functionality, quality of life will be collected directly from the patients using validated questionnaires and structured interviews. Thus, in this case the report form (CRF) will serve as a source document.

In patients who have been prescribed with tafamidis more than 1 month and have not received the drug by the HMO yet, the first time of administration of tafamidis will be considered in the analysis. It will be considered as limitation of access. Any delay of supply for treatment will be considered limitation of access which will be assessed during the follow-up.

The scale of qualityof life named Kansas City Cardiomyopathy Questionnaire (KCCQ) (12) will be used after the acceptance to participate in the study by the patients with the signing of informed consent. In the statistical analysis will be considered the date to start tafamidis, the date of prescription of tafamidis and the time to start the measurement of QoL.

Data collection will be conducted with a CRF. This will be validated by two research centers to ensure feasibility of data collection, availability of the data as well as source documents and accurate definition of the study variables. The research staff at the participating centers will be trained in data extraction and completion of CRF.

The patients will be reached out to every three months±15 days through a phone call by a healthcare professional of the site. During this interview, the professional will perform a

standardized interview with structured questionnaires to guarantee that the data collection process will be harmonized among patients. The interview could be in the site, if the patient received clinical care in there or she decided to move to it. Both collection data are completely accepted in the study.

The 6 min walk test (6MWT) and scintigraphy will be conducted based on the decision of cardiologist or responsible physician based on the guideline of the institution or medical practice. This study does not suggest these tests or is limited to them. They will be abstracted from medical records of patients who had measured them (13).

All assessments described in this protocol will be performed as part of normal clinical practice or standard practice guidelines for the patient population and healthcare provider specialty in Colombia where this noninterventional study is being conducted.

9.2. Setting

The study will be performed in approximately 6 Colombian Health Provider Institution (IPS, in its Spanish acronym) whose population includes patients with ATTR-CM diagnosis in the period established. These sites will be in four Colombian cities (Bogotá, Medellin, Cali, and Barranquilla) which have a cardiologist with experience in diagnostic and management of ATTR-CM. The patients can be recruited from the same site or other healthcare institutions, which the site affiliated to the study can invite to participate. In this last scenario, the patients will maintain the clinical care of the original institution, but the information of the study will be collected in the sites affiliated to the study or by their healthcare professionals through virtual interview.

Tafamidis was approved in July 2022 by INVIMA in the treatment of ATTR-CM (14), thus, the patients with diagnosis of ATTR-CM and treated with tafamidis between August 2022 to August 2023 will be invited to participate in the study. At this time, the number of patients expected to participate will be less than 50 patients considering the number of patients diagnosed with ATTR-CM. This cohort study its representative to patients in Colombia without requiring sampling method, considering the estimated number of patients diagnosed with this disease under treatment with tafamidis.

The follow-up period is 24 months since index date with measurement every three months ± 15 days. During this period quality of life, hospitalization frequency, and death will be measured. The endpoint of the study will be death. Additionally, adherence will be measured. For the cardiovascular functionality, it will be abstracted from the medical records 6MWT and scintigraphy during the time of study.

The activities will be included in the following table.

Table 1 List of activities

Visit Identifier	Screening	Month ± 15 days										End of Observation
		- 12	0	3	6	9	12	15	18	21	24	
Visit Window												
Informed consent	X											
Medical history	X											
Demographic			X									
Clinical variable			X									
Previous treatment		X										
KQCC -HRQoL			X	X	X	X	X	X	X	X	X	
Assessments hospitalization		X	X	X	X	X	X	X	X	X	X	
Adherence			X	X	X	X	X	X	X	X	X	
Concomitant treatment(s)			X	X	X	X	X	X	X	X	X	
6MWT*												
Scintigraphy*												

* It will be collected according to the medical criteria, considering that the physician may choose to perform a different test

9.2.1. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

- Patient older than 18 years
- Spanish speaking patients
- Diagnosis of ATTR-CM confirmed by a Cardiologist
- Prescribed with tafamidis
- Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

9.2.2. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

- Liver or heart transplantation history
- Pregnancy

- Breastfeeding
- Recruited in clinical trials

9.3. Variables

Table 2 List of variables

Variable	Role	Data source(s)	Operational definition
Date of birth	Demographic characteristics	Medical record, Interview	dd-mm-yyyy
Age	Demographic characteristics	Medical record, Interview	Time elapsed since the time of birth to signed consent form (years)
Sex assigned at birth	Demographic characteristics	Medical record, Interview	Men, female
Race (ethnicity)	Demographic characteristics	Medical record, Interview	Indigenous, Rrom, Black, None and Other
Date of symptoms of ATTR-CM	Clinical characteristic	Medical record, Interview	dd-mm-yyyy
Date of ATTR-CM diagnosis	Clinical characteristic	Medical record, Interview	dd-mm-yyyy
Genotype	Clinical characteristic	Medical record, Interview	ATTRwt; ATTRv
Scintigraphy at diagnosis (Perugini scale)	Clinical characteristic	Medical record,	Grade 0 – 3
Biopsy	Clinical characteristic	Medical record, Interview	Yes, No
Sampling biopsy	Clinical characteristic	Medical record, Interview	Heart, bone marrow, others
Sum of QRS amplitude in I, II, and III leads at diagnosis	Clinical characteristic	Medical record, Interview	mm
Sum of QRS amplitude in all six limb leads at diagnosis	Clinical characteristic	Medical record, Interview	mm
Sum of QRS amplitude in all six precordial leads at diagnosis	Clinical characteristic	Medical record, Interview	mm
Sokolow-Lyon index low voltage criteria at diagnosis	Clinical characteristic	Medical record, Interview	mm
Low QRS voltage at diagnosis	Clinical characteristic	Medical record, Interview	Yes, No

Pseudo-infarct Q waves at diagnosis	Clinical characteristic	Medical record, Interview	Yes, No
Atrioventricular conduction disease (block) at diagnosis	Clinical characteristic	Medical record, Interview	Yes, No
Genetic counseling	Patient	Medical record, Interview	Yes, No
Left ventricular ejection fraction at diagnosis	Clinical characteristic	Medical record, Interview	%
N-terminal pro b-type natriuretic peptide at diagnosis	Clinical characteristic	Medical record, Interview	(pg/mL)
Heart failure at early age	Clinical characteristic	Medical record, Interview	Yes, No
Any cardiac arrhythmias or conduction disorders	Clinical characteristic	Medical record, Interview	Yes, No
Type of any cardiac arrhythmias or conduction disorders	Clinical characteristic	Medical record, Interview	Cardiac arrhythmias, Cardiac arrest, Paroxysmal tachycardia, Atrial fibrillation and flutter, Conduction disorders, Atrioventricular and left bundle branch block, other conduction disorders
Lumbar spinal stenosis	Clinical characteristic	Medical record, Interview	Yes, No
Hypertrophic cardiomyopathy over 60 years old	Clinical characteristic	Medical record, Interview	Yes, No
Embolic stroke	Clinical characteristic	Medical record, Interview	Yes, No
Low flow/low gradient aortic valve stenosis	Clinical characteristic	Medical record, Interview	Yes, No
Diabetes mellitus	Clinical characteristic	Medical record, Interview	Yes, No
Hypertension	Clinical characteristic	Medical record, Interview	Yes, No
Sleep apnea	Clinical characteristic	Medical record, Interview	Yes, No
Chronic Kidney Diseases	Clinical characteristic	Medical record, Interview	Yes, No
Any cardiovascular device	Clinical characteristic	Medical record, Interview	Yes, No
Which any cardiovascular devices	Clinical characteristic	Medical record, Interview	Cardiac resynchronization

			therapy – defibrillator (CRT-D), Cardiac resynchronization therapy – pacemakers (CRT-P), implantable cardioverter defibrillator (ICD)
History of heart block	Clinical characteristic	Medical record, Interview	Yes, No
NYHA FC	Clinical characteristic	Medical record, Interview	I, II, III, IV
Syncope	Clinical characteristic	Medical record, Interview	Yes, No
Carpal tunnel syndrome	Clinical characteristic	Medical record, Interview	Yes, No
Bleeding history	Clinical characteristic	Medical record, Interview	Yes, No
Intracardiac thrombosis	Clinical characteristic	Medical record, Interview	Yes, No
Stroke	Clinical characteristic	Medical record, Interview	Yes, No
Polyneuropathy	Clinical characteristic	Medical record, Interview	Yes, No
Orthostatic hypotension	Clinical characteristic	Medical record, Interview	Yes, No
Erectile dysfunction	Clinical characteristic	Medical record, Interview	Yes, No
Glaucoma	Clinical characteristic	Medical record, Interview	Yes, No
Intravitreal deposition	Clinical characteristic	Medical record, Interview	Yes, No
angiotensin-converting enzyme inhibitors previous diagnosis	Treatment	Medical record, Interview	Yes, No
Agents acting on the renin–angiotensin system previous diagnosis	Treatment	Medical record, Interview	Yes, No
HMG COA reductase inhibitors previous diagnosis	Treatment	Medical record, Interview	Yes, No
Loop diuretics previous diagnosis	Treatment	Medical record, Interview	Yes, No
Amiodarone previous diagnosis	Treatment	Medical record, Interview	Yes, No

Anticoagulation previous diagnosis	Treatment	Medical record, Interview	Yes, No
Beta blockers previous diagnosis	Treatment	Medical record, Interview	Yes, No
Calcium channel blockers previous diagnosis	Treatment	Medical record, Interview	Yes, No
Angiotensin receptor blockers previous diagnosis	Treatment	Medical record, Interview	Yes, No
Agents acting on the renin–angiotensin system after diagnosis*	Treatment	Medical record, Interview	Yes, No
HMG COA reductase inhibitors after diagnosis*	Treatment	Medical record, Interview	Yes, No
Loop diuretics after diagnosis *	Treatment	Medical record, Interview	Yes, No
Amiodarone after diagnosis*	Treatment	Medical record, Interview	Yes, No
Anticoagulation after diagnosis *	Treatment	Medical record, Interview	Apixaban, dabigatran, rivaroxaban, warfarin
Beta blockers after diagnosis*	Treatment	Medical record, Interview	Yes, No
Calcium channel blockers after diagnosis*	Treatment	Medical record, Interview	Yes, No
Angiotensin receptor blockers after diagnosis*	Treatment	Medical record, Interview	Yes, No
angiotensin-converting enzyme inhibitors previous diagnosis*	Treatment	Medical record, Interview	Yes, No
Glomerular filtration rate at diagnosis*	Clinical characteristics	Medical record, Interview	>40, <40
Cardiovascular devices during follow-up	Treatment	Medical record, Interview	Cardiac resynchronization therapy – defibrillator (CRT-D), Cardiac resynchronization therapy – pacemakers (CRT-P), implantable cardioverter defibrillator (ICD)
Date of prescription of tafamidis	Treatment	Interview	ddmmyyyy

Date of first administration of tafamidis	Treatment	Interview	ddmmyyyy
Delay of supply of tafamidis	Treatment	Interview	Yes, No
Cause of delay	Treatment	Interview	Authorization, Treatment not available in the supplier, error of prescription, other
Adherence	Outcomes	Interview	%
Sum of QRS amplitude in I, II, and III leads at the end of follow-up	Clinical characteristic	Medical record, Interview	mm
Sum of QRS amplitude in all six limb leads at the end of follow-up	Clinical characteristic	Medical record, Interview	mm
Sum of QRS amplitude in all six precordial leads at the end of follow-up	Clinical characteristic	Medical record, Interview	mm
Sokolow-Lyon index low voltage criteria at the end of follow-up	Clinical characteristic	Medical record, Interview	mm
Persistence	Outcomes	Interview	Yes, No
Hospitalization	Outcomes	Interview	Yes, No
Cause of the hospitalization	Outcomes	Interview	Cardiovascular, Other
Date of hospitalization	Outcomes	Interview	Date of admission: dd-mm-yyyy Date of discharge: dd-mm-yyyy
Day(s) of hospitalization	Outcomes	Interview	Days
Quality of life (KCCQ-OS score per visit)	Outcomes	Interview	Score
6MWT[$]	Outcomes	Site	Meters
Scintigraphy (Perugini scale)[$]	Outcomes	Site	Grade 0 - 3

* Per visits, according to schedule of the study
[$] According to medical criteria, considering that the physician may choose to perform a different test

9.3.1. Definitions

Kansas City Cardiomyopathy Questionnaire (KCCQ) Score: It is a Patient-reported outcome composed by 23-item, KCCQ that takes 4-6 min to complete. A self-administered questionnaire will be used to measure the patient's perception of their health status within a 2-week recall period. The domains of this scale are: Symptom, Physical function, Social Limitation, self-efficacy, Symptom stability, and Quality of Life. The clinical summary is calculated including the domain Physical limitation and Symptoms. The overall summary score combines total symptoms, physical and social limitation, and Quality of life. The score for each domain has a range from 0-100 where 0 is considered worst health and 100 the best health. Changes in the Overall summary of 5, 10 and 20 points have been considered small but clinically important, moderate to large, and large to very large changes, respectively (**12**). The scale has been translated and validated to Spanish of Colombia (15).

Perugini grading scale: It is a semi-quantitative method of scoring cardiac uptake following injection of 99mTc-DPD, 99mTc-Pyrophosphate or 99mTc-HMDP scintigraphy (16). It is classified as:

- grade 0: no cardiac uptake and normal rib uptake
- grade 1: cardiac uptake which is less than rib uptake
- grade 2: cardiac uptake with intensity similar rib uptake
- grade 3: cardiac uptake greater than rib uptake with mild or absent rib uptake

6 Minute walk test: It is considered as an alternative to cardiopulmonary exercise test for risk stratification in patients with Heart Failure. It is a simple test that requires no specialized equipment or physicians. It assesses the functional capacity while the patient walks on a flat, solid surface in a period of 6 min (13).

Hospitalization: It is defined as a nonelective admission to an acute care setting for medical therapy that results in at least a 24-hour stay (17).

Cardiovascular causes of hospitalization: The following diseases were considered as cardiovascular causes of hospitalization only it was considered the primary diagnosis (17):

- Heart failure
- Arrhythmia: When the patient is hospitalized by bradyarrhythmia, atrial, or ventricular rhythm disorders of the heart.
- Transient ischemic attack
- Stroke

- Myocardial infarction
- Unstable angina
- Pulmonary embolism or peripheral arterial/vascular disease
- Peripheral emboli
- Venous thrombosis
- Other vascular reasons or complications.

Persistence: It will be calculated counting the days number covered to discontinuation from the index date to the end of the follow-up period. Discontinuation is considered as the end of the day of supply of the previous prescription.

Adherence: It will be measured by report through the Popit Sense device (18). This device identifies remotely in real-time when medications are taken. The information is gathered in Popit Cloud. The information needs to be downloaded through the Popit App into the smartphone. This outcome is measured only to patients that have access to the Popit Sense device. The Popit Sense devices are provided by the Pfizer Patient program to patients that are part of this program.

9.4. Data sources

There will be several sources of information. From the medical record provided by the patient will be abstracted the demographic and clinical characteristics related to diagnosis, comorbidities, and treatment at baseline, as well as the previous medications to manage CA. Other sources will be the patient to confirm or complete the information associated with it.

During the follow-up, the patient will provide the information about changes in the treatment, issues to supply tafamidis, and hospitalization which be confirmed with the summary of the medical records of the patient. The quality of life will be measured using the KCCQ scale through call or face to face meetings. 6-MWT and scintigraphy will be abstracted from medical records.

Adherence will be measured using the information available in the Popit sense device. It is only available in patients that use this device. If the patient does not have access to Popit, it will not be a limitation to participate in the study, only that this variable will be not measured for them.These scales have been validated (12) and translated to Spanish of Colombia (14).

9.5. Study size

Sample size is not required for being observational and descriptive study. The expected number of patients eligible for the study is close to fifty considering the number of patients identified with the diagnosis and the access to the treatment based on the national database of MiPres in Colombia in which each prescription of treatments outside of National Formulary must be registered (19).

9.6. Data management

9.6.1. Case report forms (CRFs) /Data Collection Tools (DCTs)/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each patient included. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initiated, and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

9.6.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should

be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study or as required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data analysis

9.7.1. Statistical Hypotheses

This is a descriptive, prospective, and observational study. There is no formal hypothesis being tested. The study will describe the clinical and demographic characteristics of ATTR-CM patients. Also, it will describe previous treatments, cardiovascular devices, and comorbidities.

Adherence, persistence, and frequency of hospitalization will be described during the time exposure of treatment.

The change of baseline in the quality of life measured every 3 and 6 months respectively for 24 months.

9.7.2. Statistical Decision Rules

Given that no hypotheses are tested, a – priori defined statistical decision rules are not applicable.

9.7.3. Population Analysis

9.7.3.1. Total population

The analyses will be conducted for all the eligible patients.

9.7.3.2. Subgroup analysis

Analyses will be performed for the following sub-groups:

- Age
- Sex assigned at birth
- Genotype of ATTR-CM
- Scintigraphy at diagnosis

- Clinical characteristics
- Comorbidities
- Cardiovascular devices NYHA at start of tafamidis
- Any delay of supply (Yes or No)
- Time of treatment with tafamidis (Interval between date of diagnosis to date of start treatment with tafamidis)
- Time with tafamidis before enrollment in the study

9.7.4. Handling of Missing Data

There will be no imputation or replacement of missing data. All analyses will be conducted on observed cases. All patients will be included in the descriptive analysis limited with the information recollected. The missing data will be included in the study report. Analysis with case complete will not be conducted.

9.7.5. Statistical Methods

To achieve the objectives described above, the following methods will be used:

9.7.5.1. Descriptive statistics

Frequencies and percentages will be reported for binary and categorical variables, while medians and interquartile ranges (IQRs) will be reported for continuous variables, i.e., HRU. Finally, it will be presented through a tabular display of summary statistics and will be complemented by the generation of graphs, such as histograms, box plots, violin plots, density plots, scatterplots, depending on the nature of the variable.

On the other hand, difference of means (Student or Welch t-test) or medians (Wilcoxon or Kruskal-Walli´s test) between subgroups will be considered (according to the variable distribution – normal or not), considering the sizes of these groups and trends in the behavior of the measures of centrality and dispersion.

9.7.5.2. Bivariate and multivariable analysis

This study does not evaluate any hypothesis. As exploratory analysis and if it is feasible with the number of patients enrolled and distribution of the studied variables, the analysis of the association of baseline characteristics with quality of life and cardiovascular functionality using bivariate and multivariate regression models will be conducted. In terms of distribution of studied continuous variables, a normal test will be conducted in order to determine if it requires a parametric or no parametric test. The test of normality used will be used, frequency distribution (histogram), boxplot, P-P plot (probability-probability plot), and Q-Q plot

(quantile-quantile plot) to assess normality visually and Kolmogorov-Smirnov (K-S) test and Shapiro-wilk test to evaluate directly (20).

For bivariate analysis, no-parametric tests are necessary due to the variables being of dependent nature by being repeated measures during the follow-up. For continuous variables, paired t-test and Wilcoxon signed ranks test will be used (21).

For multivariable analysis, mixed models will be used, repeated measures analysis of covariance with an unstructured covariance matrix, being patient as random effects and visit and baseline characteristics as fixed effects (22,23).

9.8. Quality control

Quality control for each project is performed by a specific audit team member assigned to the Study and the Monitoring and Data Quality Oversight plan (24).

Review of the data collected in the study for accuracy and consistency throughout the execution of the study is essential to ensure data quality and integrity. It will be led by a vendor responsible to monitor the collection of data and the established requirements in this protocol. Three monitoring is planned during the collection data. Each monitoring involves the validation of eligibility criteria, sign of informed consent, consistency, and accuracy of data from the data sources as is descriptive in the Monitoring and Data Quality Oversight plan. Additionally, a review of consistency of the behavior of collected data will be conducted after finalizing the collection data. It consists of validated outliers, data that are not consistent with the variable or missing data. In the case of any query of the data, it will be clarified to the sites (24).

Quality control practices include, but are not limited, to:

- Consistency checks of the anonymized database.
- Review of records and variables with less completeness.
- Having qualified individuals who did not have a role in the study review data analyses and any final study report documentation for accuracy.
- Statistical and econometric programming will be performed by experienced personnel with significant quantitative health care research experience and a thorough understanding of study design and analytic methods.
- Scripts will be reviewed by a second person with understanding of the study to ensure accuracy and validity of the code. This implies auditing all software programs and results both with respect to computer output and final tables.
- Ensuring proper documentation of data sources and key analytical steps.

- All results will be evaluated for theoretical and logical soundness by multiple personnel, performing internal consistency checks of data presentations.
- Aligning dissemination materials with external requirements.

9.9. Limitations of the research methods

This study has the following limitations:

- The information of the patient in the baseline will be limited to data available in the clinical records and awareness of the patient.
- The complete information of hospitalizations will depend on the access to medical records provided by the patients.
- The number of patients recruited will likely be small which affects the subgroup analysis.
- The patients may have already started treatment prior to start of the study. This could make it difficult to adequately measure baseline QoL.
- Availability of 6 Minute walk test and scintigraphy for all patients during the follow-up due to the management of ATTR-CM patients have not been standardized.
- Although the official language of Colombia is Spanish, the languages and dialects of ethnic groups are also recognized as official. However, only around 5% of the population recognizes itself as belonging to an Indigenous or Rrom group (25).

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

10.2. Patient consent

The informed consent documents and any patient recruitment materials must be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the institutional review board (IRB)/independent ethics committee (IEC) before use, and available for inspection.

The investigator must ensure that each study patient is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the patient's personal data. The investigator further must ensure that each study patient is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

Whenever consent is obtained from a patient's legally acceptable representative, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the

capacity to provide assent, as determined by the IRB/IEC. If the investigator determines that a patient's decisional capacity is so limited that he or she cannot reasonably be consulted, then, as permitted by the IRB/IEC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents must record why the patient did not provide consent (e.g., minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (e.g., parent, spouse), and that the patient's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

10.3. Patient withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document patient outcome, if applicable. The investigator would inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved adverse events.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

10.4. Institutional review board (IRB)/Independent ethics committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained by the investigator. Copies of IRB/IEC approvals should be forwarded to Pfizer.

10.5. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society of Pharmacoepidemiology (ISPE), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making, International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS).

The study will be submitted to the IEC in the category of research minimal risk. The ethical principles of justice, beneficence, non-maleficence, and confidentiality of information

established by the Declaration of Helsinki will be followed, in accordance with Resolution No. 8430 of 1993 of the Ministry of Health of Colombia.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

REQUIREMENTS

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure. These events are defined in the section "Definitions of safety events."

Safety event	Recorded on the CRF	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	None
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE) Note: Any associated AE is reported together with the exposure scenario.

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE (refer to section "Serious Adverse Events" below).

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to tafamidis**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on

previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For safety events that are considered serious or that are identified in the far-right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of tafamidis or the time of the patient's informed consent if s/he is being treated with tafamidis at study start, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (e.g., patient changes his/her mind about participation, failed screening criteria">), the reporting period ends on the date of the decision to not enroll the patient.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to tafamidis, the SAE also must be reported to Pfizer Safety.

Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each AE. For AEs with a causal relationship to tafamidis follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that tafamidis caused or contributed to an AE. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether tafamidis caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that *tafamidis* did not cause the event, this should be clearly documented on the *CRF* and the NIS AEM Report Form.

DEFINITIONS OF SAFETY EVENTS

Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an AE);
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;

- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Serious adverse events

A SAE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute AEs);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance (PV) personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)

Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) tafamidis, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to tafamidis (maternal exposure).

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to tafamidis to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

For exposure during pregnancy in studies of pregnant women, data on the exposure to drug during pregnancy, are not reportable unless associated with serious or non-serious adverse events.

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed, with the exception of those studies conducted in pregnant women (as described in above), for which data on the exposure are not reportable unless associated with serious or non-serious adverse events.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with tafamidis this information must be submitted to Pfizer, irrespective of whether an AE has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to tafamidis in a pregnant woman (e.g., a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP Supplemental Form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow-up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and misses abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);
- Confusion with regard to invented name (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.

- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
  - An identifiable reporter;
  - A suspect product;
  - The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

11.1. Single reference safety document

The prescribing information will serve as the single reference safety document during the course of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study.

The single reference safety document should be used by the investigator for prescribing purposes and guidance.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of the study will be published in international or national congress and index journal.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

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14. LIST OF TABLES

15. LIST OF FIGURES

None.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Impact of tafamidis in Colombian patients diagnosed with ATTR-CM on quality of life during two year of follow-up

EU PAS Register® number: EUPAS105913
Study reference number (if applicable): NA

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	9.2.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	8
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g., cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.2	Does the protocol specify whether the study is based on primary, secondary, or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	☒	
3.4	Does the protocol specify measure(s) of association? (e.g., risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7.5.2
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g., adverse events that will not be collected in case of primary data collection)	☒	☐	☐	10

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2
	4.2.2 Age and sex	☒	☐	☐	9.2
	4.2.3 Country of origin	☒	☐	☐	9.2
	4.2.4 Disease/indication	☒	☐	☐	9.2
	4.2.5 Duration of follow-up	☒	☐	☐	9.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g., operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3
5.2	Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☒	☐	☐	9.1
5.3	Is exposure categorised according to time windows?	☒	☐	☐	9.3
5.4	Is intensity of exposure addressed? (e.g., dose, duration)	☒	☐	☐	9.3
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.3

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3	Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.3
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.3

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.3

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.1;9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☐	☐	☐	

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Juan Manuel Reyes

Date: dd/Month/year 27/July/2023

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

No applicable.