Sponsor
Novartis Pharmaceuticals

Generic Drug Name
Sacubitril/Valsartan

Trial Indication(s)
Heart Failure (HF)

Protocol Number
CLCZ696BIT08

Protocol Title
Real world Experience in HFrEF patients treated with sAc/vaL in Italy

Clinical Trial Phase
NA

Phase of Drug Development
NA

Study Start/End Dates
Study start date: 23/11/2020

Study Completion date: 15/09/2021

Reason for Termination

NA

Study Design/Methodology

The study is a cohort observational, retrospective, non-interventional study.

Study period: Index date: The index date were defined as the first date of the first prescription of Sacubitril/Valsartan during inclusion period and this were used to establish the beginning of the follow-up period. Characterization period: 6 months period before the index date were used to characterize patients. Follow-up period: Any patients has at least 1 year of follow-up. Follow-up period went from index date to June 2020.

Centers

Novartis Investigative Site

Objectives:

Primary objective(s)

- Describe characteristics of the patients treated with Sacubitril/Valsartan, including baseline demographics, pharmacotherapy and clinical characteristics in an Italian specialistic setting, overall and by calendar quarter (relating to time since launch).

Secondary objective(s)

- Explore evolving baseline pharmacotherapy, clinical characteristics in patients that initiate Sacubitril/Valsartan treatment, overall and by calendar quarter (relating to time since launch);
- Evaluate resource utilization in patients that initiate Sacubitril/Valsartan treatment, overall and by calendar quarter (relating to time since launch);
- Describe Sacubitril/Valsartan drug utilization, including daily dose, titration dose, add-on and persistence;
- Proportion and reason for not achieving target titration dose, overall and by calendar quarter (relating to time since launch);
- Proportion, timing and reason for Sacubitril/Valsartan discontinuation;
- Evaluate frequency of cardiovascular (CV) and non-CV death, overall and by calendar quarter (relating to time since launch)

Test Product (s), Dose(s), and Mode(s) of Administration

NA

Statistical Methods

Categorical data were summarized in terms of the number of patients providing data. The frequency counts and percentages of patients in each category are provided. Percentages were calculated using the number of observations with non-missing values as the denominator. Continuous data have been summarized in terms of mean, standard deviation (SD).

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

Consecutive ambulatory patients with a diagnosis of HF that attended the Outpatient Clinics for HF management and who have been prescribed Sacubitril/Valsartan from 01 October 2016 to 30 June 2019 (inclusion period) were included in the study. To allow for at least 1-year follow-up period for any patients, the observation period ended by 30 June 2020.
In detail, all patients attending by outpatient clinics for the diagnosis and treatment of HF in the Italian Centers involved, with:

- • age ≥18 years old AND
- • at least one prescription of Sacubitril/Valsartan from 01 October 2016 to 30 June 2019

were included in the study.

Exclusion criteria

Missing age or sex information

Participant Flow

Among the 9 Centers involved in the study, a total of 948 HF patients with at least one prescription of Sacubitril/Valsartan during all data availability period was detected. Among them, 924 adult HF patients were included in the analyses as they presented at least one prescription of Sacubitril/Valsartan during inclusion period, were without missing age or sex and had 6 months of characterization period and at least 12 months of follow-up available.

Baseline Characteristics

Refer to Primary outcomes results (Demographics)

Primary and Secondary Outcome Result(s)

Demographic characteristics of patients included

	HF patients treated with Sacubitril/Valsartan
N	924
Age, mean (SD)	64.5 (11.9)
Male, n (%)	782 (84.6)

Patients stratified by calendar quarter.

Calendar quarter	HF patients treated with Sac/Val
4/2016, n (%)	25 (2.7)
1/2017, n (%)	32 (3.5)
2/2017, n (%)	52 (5.6)
3/2017, n (%)	95 (10.3)
4/2017, n (%)	171 (18.5)
1/2018, n (%)	166 (18.0)
2/2018, n (%)	132 (14.3)
3/2018, n (%)	61 (6.6)
4/2018, n (%)	85 (9.2)
1/2019, n (%)	57 (6.2)
2/2019, n (%)	48 (5.2)

CV related and unrelated events and death during follow-up

EVENTS	Patients with available data	Follow-up period
Hospitalization HF-related, n (%)	744	146 (19.6)
Mean (SD) number of hospitalization HF-related by patient during the 1-year period of follow-up	744	0.2 (0.5)
Hospitalization related to other cardiovascular events, n (%)	579	118 (20.4)
Mean (SD) number of hospitalization related to other cardiovascular events by patient during the 1-year period of follow-up	579	0.2 (0.4)
Hospitalization related to non-CV cause, n (%)	461	89 (19.3)
Mean (SD) number of hospitalization related to non-CV cause by patient during the 1-year period of follow-up	461	0.2 (0.5)
Percutaneous Coronary Intervention (PCI)/coronary artery bypass grafting (CABG), n (%)	171	NI
Valvular intervention, n (%)	171	NI
Device implantation (ICD/CRT), n (%)	863	275 (31.9)
ER visits HF-related, n (%)	333	66 (19.8)
Death*, n (%)	924	35 (3.8)

Note. The analyses involving ≤ 3 patients were not reported, as potentially reconductable to single individuals. Therefore, results referred to ≤ 3 patients were reported as NI (not issuable). * 16 patients had the information regarding the CV-related cause of death.

Clinical characteristics at baseline

Clinical characteristic at baseline	Patients with available data	Characterization period
Ischemic heart disease, n (%)	599	232 (38.7)
PCI/CABG, n (%)	599	191 (31.9)
Moderate or severe mitral or aortic valvulopathy, n (%)	599	99 (16.5)
Implanted prosthetic valve, n (%)	229	33 (14.4)
Devices (ICD/CRT), n (%)	863	439 (50.9)
Atrial fibrillation, n (%)	924	214 (23.2)
Prior hospitalization for HF, n (%)	538	194 (36.1)
Previous stroke, n (%)	460	17 (3.7)
Diabetes mellitus, n (%)	924	235 (25.4)
Hypertension, n (%)	924	424 (45.9)
Chronic kidney disease (CKD) , n (%)	597	142 (23.8)
Duration of HF disease (years), mean (sd)	829	304 (36.7)

Abbreviations: PCI/CABG: Percutaneous coronary intervention/coronary artery bypass grafting; ICD/CRT, Implantable Cardioverter Defibrillator/ Cardiac Resynchronization Therapy.

Demographic and clinical characteristics at baseline for patients stratified by calendar quarter of inclusion

	2/2017	3/2017	4/2017	1/2018	2/2018	3/2018	4/2018	1/2019	2/2019
Pts by calendar quarter, n	52	95	171	166	132	61	85	57	48

Age, mean (SD)	64.6 (10.3)	63.4 (11.4)	63.6 (11.5)	63.5 (11.9)	63.7 (11.0)	64.2 (12.7)	66.7 (12.4)	65.7 (12.8)	69.1 (12.2)
Male, n (%)	44 (84.6)	79 (83.2)	143 (83.6)	145 (87.3)	113 (85.6)	56 (91.8)	68 (80.0)	47 (82.5)	40 (83.3)
Pts with available data on HF disease, n (%)	46 (88.5)	57 (60.0)	110 (64.3)	87 (52.4)	80 (60.6)	37 (60.7)	58 (68.2)	33 (57.9)	20 (41.7)
Duration of HF disease (years), mean (sd)	7.6 (7.5)	8.0 (6.1)	6.6 (6.1)	6.6 (5.7)	6.5 (6.1)	5.6 (5.0)	7.5 (5.1)	6.4 (6.8)	6.1 (6.5)
Pts with available data on clinical characteristics, n (%)	40 (76.9)	39 (41.1)	75 (43.9)	65 (39.2)	63 (47.7)	39 (63.9)	70 (82.4)	53 (93.0)	47 (97.9)
Ischemic heart disease, n (%)	13 (32.5)	19 (48.7)	34 (45.3)	21 (32.3)	24 (38.1)	14 (35.9)	22 (31.4)	9 (17.0)	15 (31.9)
PCI/CABG, n (%)	10 (25.0)	17 (43.6)	29 (38.7)	17 (26.2)	22 (34.9)	8 (20.5)	16 (22.9)	7 (13.2)	10 (21.3)
Diabetes mellitus, n (%)	9 (22.5)	6 (15.4)	29 (38.7)	15 (23.1)	14 (22.2)	9 (23.1)	13 (18.6)	NI	6 (12.8)
Hypertension, n (%)	16 (40.0)	16 (41.0)	45 (60.0)	29 (44.6)	29 (46.0)	22 (56.4)	29 (41.4)	13 (24.5)	9 (19.1)
Pts with available data on clinical examination, n (%)	48 (92.3)	90 (94.7)	165 (96.5)	147 (88.6)	118 (88.5)	49 (89.4)	56 (65.9)	30 (52.6)	15 (31.3)
NYHA Class 2, n (%)	28 (58.3)	35 (38.9)	125 (75.8)	94 (63.9)	85 (72.0)	29 (59.2)	38 (67.9)	18 (60.0)	10 (66.7)
NYHA Class 3, n (%)	18 (37.5)	54 (60.0)	39 (23.6)	53 (36.7)	33 (28.0)	18 (36.7)	18 (32.1)	10 (33.3)	5 (33.3)

Sacubitril/Valsartan dosing pattern during follow-up

	HF patients treated with Sacubitril/Valsartan
Initial dose, n (%) **Patients with available data (N=924)**	
- 24 mg + 26 mg	548 (59.3)
- 49 mg + 51 mg	333 (36.0)
- 97 mg + 103 mg	43 (4.7)
Final dose, n (%) **Patients with available data (N=881)**	
- 24 mg + 26 mg	254 (28.8)
- 49 mg + 51 mg	229 (26.0)
- 97 mg + 103 mg	398 (45.2)
Non-maximum dose, n (%) **Patients with available data (N=881)**	483 (54.8)
Time to maximal dose prescribed (weeks), mean (sd) **Patients with available data (N=146)**	
Time to 97 mg+ 103 mg (weeks), mean (sd) (N=117)	6.9 (6.2)
Time to 49 mg+ 51 mg (weeks), mean (sd) (N=29)	6.2 (6.7)
Time to dose increase (weeks), mean (sd) (N=146)	6.8 (6.3)

Pharmacological treatments for HF during characterization period and 12 months of follow-up

HF DRUG CLASSES	Characterization period (N=686)	Follow-up period (N=686)	P-value
Diuretics	599 (87.3)	566 (82.5)	0.013
Angiotensin-converting enzyme inhibitor	462 (67.3)	27 (3.9)	<0.001
Angiotensin II receptor Blockers	185 (27.0)	20 (2.9)	<0.001
Ivabradine	51 (7.4)	58 (8.5)	0.485
Digitalis glycosides	36 (5.2)	41 (6.0)	0.558
Nitrates	27 (3.9)	26 (3.8)	0.889
	Characterization period (N=553)	Follow-up period (N=553)	
Beta blocking agents, n (%)	533 (96.4)	531 (96.0)	0.753
Aldosterone antagonists, n (%)	425 (76.9)	425 (76.9)	1

Note. Prescription of Sacubitril/Valsartan excluded from the analysis.

Safety Results
Not applicable.

Other Relevant Findings
NA

Conclusion
The present real-world study provided a thorough characterization of patients with HF starting Sacubitril/Valsartan in settings of daily clinical practice in Italy. Patients included referred to 9 Centers geographically distributed throughout the national Italian territory, giving insights on the changing of clinical parameters in the first year of treatment with Sacubitril/Valsartan. Overall, a significant proportion of patients showed an improvement in their clinical characteristics after starting this therapy.

Date of Clinical Study Report
15 February, 2022