Sponsor
Novartis Pharmaceuticals

Generic Drug Name
Sacubitril/Valsartan

Trial Indication(s)
Heart Failure

Protocol Number
CLCZ696BUS29

Protocol Title
Role of Sacubitril/Valsartan in Improving Provider Performance in Managing Heart Failure under Medicare Alternative Payment Models

Clinical Trial Phase
NA

Phase of Drug Development
NA

Study Start/End Dates
Study start date: 10 April 2020

Study Completion date: 30 September 2020

Reason for Termination

NA

Study Design/Methodology

This drug utilization study employed a retrospective cohort design using the 100% files of 2015-2018 Medicare enrollment and Part A, B & D claims data in conjunction with publicly available information on providers participating in Bundled Payments for Care Improvement (BPCI) and/or Medicare Shared Savings Program (MSSP).

BPCI Study Design

The unit of analysis for addressing study objectives was a unique Congestive Heart Failure (CHF) episode of care, which encompassed an initial acute inpatient stay plus all Part A & B covered medical services during the 90 days post hospital discharge. Episode index date was defined as the date of a beneficiary's initial acute hospital stay with a qualifying Medicare Severity-Diagnosis Related Group (MS-DRG) for CHF, triggering a CHF episode of care. Beneficiaries were followed longitudinally from episode index date through episode end date to measure their utilization of sacubitril/valsartan and Part A & B expenditures during the CHF episode of care. A 12-month lookback period, based on when the episode was initiated, was utilized to capture beneficiaries' baseline characteristics. For example, episodes initiated on 2/1/2018 will have a 2/1/2017 to 1/31/2018 baseline lookback period. Balancing the need for data recency, all qualifying CHF episodes from 2016-2018 were included in the analysis. Given this is an episode-level analysis, a beneficiary may have contributed multiple CHF episodes to the data analysis. To account for potential within-subject clustering, a generalized linear model with a gamma distribution was applied for estimating the association between sacubitril/valsartan use and CHF episode costs.

MSSP Study Design

The unit of analysis for addressing study objectives was a HF patient's Part A & B expenditures within the MSSP. Given the most recent year of data available at the time the study was conducted was 2018, the study population included HF patients for whom the MSSP participants were accountable in 2018 per Centers for Medicare & Medicaid Services (CMS) assignment. These beneficiaries' utilization of sacubitril/valsartan and annual Part A & B expenditures was measured from January 1, 2018 - December 31, 2018. Data from CY 2017 was leveraged for capturing these patients' baseline characteristics.

Centers

NA

Objectives:

Primary objective(s)

- To evaluate the differences in CHF episode costs between episodes with sacubitril/valsartan use vs. episodes with Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker (ACEI/ARB) and without sacubitril/valsartan between matched cohorts within the framework of BPCI Model 2

Secondary objective(s)

- To evaluate the differences in annual Part A & B expenditures between HF patients assigned to MSSP participants treated with sacubitril/valsartan vs. patients with ACEI/ARB and without sacubitril/valsartan between matched cohorts
- To rank individual BPCI participants (i.e., hospitals) based on their potential for performance improvement through optimized utilization of sacubitril/valsartan for eligible HF patients
  - Participants with low rate of sacubitril/valsartan utilization and poor performance in reducing CHF episode costs represent greatest potential for performance improvement
- To rank individual MSSP participants (i.e., multi-provider groups identified by a unique identifier) based on their potential for performance improvement through optimized utilization of sacubitril/valsartan for eligible HF patients
  - Participants with low rate of sacubitril/valsartan utilization and poor performance in reducing Part A & B expenditures represent greatest potential for performance improvement

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

NA

Statistical Methods

Descriptive analyses were first performed to describe beneficiary characteristics as well as actual CHF episode expenditures for Part A & B services overall and stratified by utilization of sacubitril/valsartan during the episode. Summary statistics such as mean, standard deviation, 5, 25, 50, 75 and 95 percentiles were reported for continuous variables whereas binary and categorical variables were summarized as frequencies and percentages. Following the descriptive analyses, a generalized linear model (GLM) estimated the adjusted difference in CHF episode expenditures between the CHF episodes with sacubitril/valsartan use vs. propensity score (PS) matched control episodes with ACEI/ARB and without sacubitril/valsartan use and the CHF episodes with sacubitril/valsartan use vs. propensity score (PS) matched control episodes without ACEI/ARB and without sacubitril/valsartan use. The adjusted difference in CHF episode expenditures between the sacubitril/valsartan and matched cohorts was estimated. To account for beneficiary level and participant level clustering, GEE or other appropriate statistical techniques were applied.

Descriptive analyses of annual Part A & B expenditures among HF beneficiaries managed by MSSP participants overall was performed and was stratified by beneficiary utilization of sacubitril/valsartan. PS matching was performed to compare HF beneficiaries with sacubitril/valsartan use vs HF beneficiaries with ACEI/ARB and without sacubitril/valsartan use and HF beneficiaries with sacubitril/valsartan use vs HF beneficiaries without ACEI/ARB and without sacubitril/valsartan use. The adjusted difference in annual Part A & B expenditures between the matched cohorts was estimated.

BPCI participants (i.e., hospitals) and MSSP participants (i.e., multi-provider groups identified by a unique identifier) were ranked based on their potential for performance improvement in reducing HF events (i.e., hospital readmissions, ER visits) and subsequently Part A & B expenditures for HF patients. Metrics for rating BPCI/MSSP participants' potential for performance improvement were: 1) current utilization rate of sacubitril/valsartan in eligible patients; 2) shared savings/losses; and 3) current utilization rate of ACEi/ARB/ARNIs in eligible patients. Weights were given to the individual metrics to derive a summary score representing the overall potential for performance improvement through increased utilization of sacubitril/valsartan.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

BPCI Study Population

- The short-term acute care hospitalization (STACH) triggering a CHF episode of care must have included a MS-DRG of 291 (Heart failure and shock with major complication or comorbidity), 292 (Heart failure and shock with complication or comorbidity), or 293 (Heart failure and shock without complication or comorbidity or major complication or comorbidity) (see Annex 3.1 for identification of STACH; see Annex 3.2 for DRG descriptions);
- The start and end date of the CHF episode (based on above admission and episode end date [episode end date is 90-days following discharge from initial STACH stay]) fell within 1/1/2016 – 12/31/2018; and
- The beneficiary must have been enrolled in Part A, B & D throughout the entire CHF episode of care (derived from MBSF)

MSSP Study Population

- Had evidence of an ICD-10 diagnosis code for HF (ICD-10-CM codes: I50.xx) in any position on a Part A or Part B claim in 2018;
- Continuously enrolled in Part A, B & D throughout CY 2018 (performance year) and CY 2017 (baseline period); and
- Assigned to a MSSP participant in CY 2018; beneficiary assignment were ascertained based on the SSP Beneficiary File from CMS

Exclusion criteria

BPCI Study Population

- Beneficiary switched to Medicare Advantage (Part C) during the episode (derived from MBSF);

- Medicare was the secondary payer for the STACH that initiated the CHF episode (Inpatient file variable "NCH Primary Payer Code" not equal to 'C', 'M', 'N', or BLANK);
- Beneficiary had evidence of end-stage renal disease (ESRD) during the baseline year (derived from current reason for entitlement = ESRD in MBSF);
- The initial hospital stay lasted for more than 365 days; and
- Beneficiary died before the episode ends (i.e., validated date of death occurs prior to hospital discharge date)

MSSP Study Population

- Beneficiary enrollment in Medicare Advantage at any point during 2017-2018;
- Medicare was the secondary payer for the beneficiary for any duration of 2017-2018;
- Beneficiary had evidence of ESRD in 2017 or 2018; and
- Beneficiary died in 2017-2018

Participant Flow

BPCI Model 2

A total of 1,614,719 Medicare beneficiaries were identified with an acute hospital stay with a qualifying MS-DRG for HF, which triggered a HF episode of care. Among those beneficiaries, 412,781 systolic HF episodes under the BPCI program between 2016 and 2018 were included based on the inclusion and exclusion criteria.

MSSP

A total of 4,361,831 beneficiaries had an ICD-10 diagnosis code for HF in any position on a Part A or Part B claim between January 1, 2018 and December 31, 2018. After applying the inclusion and exclusion criteria the analytic sample included 312,611 beneficiaries with systolic HF episodes under the MSSP CY 2018.

Baseline Characteristics

BPCI Model 2

Variable	Treatment Group 1: Received SAC/VAL (N = 13,775 episodes)	Treatment Group 2: Received ACE/ARB and did not receive SAC/VAL (N = 41,325 episodes)	Treatment Group 1: Received SAC/VAL (N = 12,324 episodes)	Treatment Group 3: Did not receive ACE/ARB and did not receive SAC/VAL (N = 36,972 episodes)
Male (%)	8,084 (58.69)	23,950 (57.96)	7,124 (57.81)	20,704 (56.00)
Mean age at index (SD)	73.05 (11.78)	73.35 (12.23)	74.20 (11.24)	74.54 (11.96)
Race (%)				
White	10,082 (73.19)	30,296 (73.31)	9,284 (75.33)	27,769 75.11)
Black	2,739 (19.88)	8,161 (19.75)	2,248 (18.24)	6,770 (18.31)
Other	850 (6.17)	2,533 (6.13)	704 (5.71)	2,165 (5.86)
Unknown	104 (0.75)	335 (0.81)	88 (0.71)	268 (0.72)

MSSP

Variable	Treatment Group 1: Received SAC/VAL (N = 17,604 beneficiaries)	Treatment Group 2: Received ACE/ARB and did not receive SAC/VAL (N = 52,812 beneficiaries)	Treatment Group 1: Received SAC/VAL (N = 8,820 beneficiaries)	Treatment Group 3: Did not receive ACE/ARB and did not receive SAC/VAL (N = 26,460 beneficiaries)
Male (%)	11,195 (63.6)	33,752 (63.9)	4,863 (55.1)	14,598 (55.2)
Mean age at index (SD)	74.9 (9.7)	75.0 (10.1)	77.2 (9.2)	77.6 (10.6)
Race (%)				
White	14,691 (83.5)	44,073 (83.5)	7,560 (85.7)	22,887 (86.5)
Black	2,015 (11.5)	6,006 (11.4)	873 (9.9)	2,475 (9.4)
Other	693 (3.9)	2,107 (4.0)	315 (3.6)	902 (3.4)
Unknown	205 (1.2)	626 (1.2)	72 (0.8)	196 (0.7)

Primary and Secondary Outcome Result(s)

BPCI Model 2

When controlling for baseline characteristics and for duration of therapy, BPCI HF episode Part A/B costs for systolic HF patients treated with SAC/VAL were $899 less than those treated with ACEi/ARBs (95% CI: -$1,687, -$111, p=0.03) and $10,102 less than patients receiving no treatment (95% CI: -$11,167, -$9,037, p<0.01). Mean CHF episode rehospitalization and skilled nursing facility costs for patients receiving SAC/VAL were $946 (95% CI: -$1,584, -$308) and $298 (95% CI: -$422, -$174) less than the those treated with ACEI/ARBs and $4,517 (95% CI: -$5,344, -3,691) and $3,769 (95% CI: -$4,407, -$3,491) less than those on neither therapy.

Propensity-score matched Medicare Parts A & B cost outcomes in BPCI Model 2 systolic HF episodes in 2016-2018, by service and treatment group

Cost Outcome	Treatment Group 1 Adjusted Mean Costs	Treatment Group 2 Adjusted Mean Costs	Adjusted Mean Difference	95% CI	Treatment Group 1 Adjusted Mean Costs	Treatment Group 3 Adjusted Mean Costs	Adjusted Mean Difference	95% CI
Total Episode Parts A + B Costs	$16,164	$17,063	-$899	(-$1,687, -$111)	$16,486	$26,588	-$10,102	(-$11,167, -$9,037)
All-Cause Rehospitalizations	$7,293	$8,239	-$946	(-$1,584, -$308)	$7,417	$11,934	-$4,517	(-$5,344, -$3,691)
HF-Related Rehospitalization	$3,337	$3,361	-$24	(-$467, $419)	$3,407	$1,482	-$4,889	(-$2,073, -$891)
All-Cause ER Visits	$308	$362	-$54	(-$83, -$24)	$292	$391	-$99	(-$130, -$69)
HF-Related ER Visits	$46	$52	-$6	(-$16, $5)	$44	$50	-$6	(-$16, $3)
All-Cause Physician Office Visits	$494	$446	$48	($30, $65)	$504	$409	$95	($74, $116)
HF-Related Physician Office Visits	$78	$57	$21	($18, $24)	$78	$49	$29	($26, $32)
All-Cause SNF Admissions	$936	$1,234	-$298	(-$422, -$174)	$995	$4,764	-$3,769	(-$4,047, -$3,491)
HF-Related SNF Admissions	$258	$316	$59	(-$119, $1)	$261	$1,256	-$995	(-$77, $42)
All-Cause Distinct Home Health Service Days	$1,370	$1,425	-$55	(-$114, $4)	$1,480	$1,497	-$17	(-$77, $42)
HF-Related Distinct Home Health Service Days	$754	$715	$40	(-$4, $83)	$804	$746	$58	($14, $103)

Notes: -Abbreviations: CI = Confidence Interval, ER = Emergency Room, HF = Heart Failure, HHA = Home Health Agency, SNF = Skilled Nursing Facility

Of the 143 hospitals that participated in BPCI with CHF, the average cost for a CHF episode between 2016 and 2018 was $20,465. For episodes that initiated and were completed in 2016, the average episode cost was $19,997, compared to an average episode cost of $20,026 in 2017 and an average episode cost of $21,217 in 2018. The average historical benchmark was $18,626 and the average peer group benchmark was $18,115. When comparing average CHF episode costs to the two benchmarks, 21% of hospitals (30 hospitals) achieved savings compared to the historical benchmark and 32% of hospitals (46 hospitals) achieved savings compared to the benchmark. The descriptive analysis showing these results is outlined in the following Table.

BPCI Model 2 Historical and Peer Group Benchmarks

Category	Results
2016-2018 Average CHF Episode Cost	$20,465
2016 Average CHF Episode Cost	$19,997
2017 Average CHF Episode Cost	$20,026
2018 Average CHF Episode Cost	$21,217
Average Historical Benchmark	$18,626
Average Peer Group Benchmark	$18,115

For utilization of CHF therapies, an average of 2.84% of episodes attributed to BPCI hospitals utilized SAC/VAL, with a range of 0% to 9.9%. Comparatively, an average of 45.36% of episodes utilized ACEi/ARB/ARNI, with a range of 32.76% to 65.22%. The descriptive analysis showing these results is outlined in the following Table.

BPCI Model 2 Hospital SAC/VAL Utilization

Category	Results
Average Hospital SAC/VAL Utilization (Range)	2.84% (0% to 9.09%)
Number of Hospitals Above/Below Average SAC/VAL Utilization	65/78
Average Hospital ACE/ARB/ARNI Utilization (Range)	45.36% (32.76% to 65.22%)
Number of Hospitals Above/Below Average ACE/ARB/ARNI Utilization	69/74

MSSP

The SAC/VAL group had total Medicare Parts A/B costs that were $908 less than the ACEi/ARB group (95% CI: -$1,695, -$121, p=0.02) and $9,806 less than the no treatment group (95%CI: -$11,508, -$8,105). Mean annual rehospitalization and skilled nursing facility costs for patients receiving SAC/VAL were $1,726 (95% CI: -$2,272, -$1,180) and $202 (95% CI: -$328, -$82) less than the those treated with ACEI/ARBs and $7,232 (95% CI: -$8,433, -$6,032) and $2,235 (95% CI: -$2,625, -$1,844) less than those on neither therapy.

Propensity-score matched Medicare Parts A & B cost outcomes for Medicare beneficiaries with systolic HF among MSSP participants in 2018, by service and treatment group

Cost Outcome	Treatment Group 1 Adjusted Mean Costs	Treatment Group 2 Adjusted Mean Costs	Adjusted Mean Difference	95% CI	Treatment Group 1 Adjusted Mean Costs	Treatment Group 3 Adjusted Mean Costs	Adjusted Mean Difference	95% CI
Parts A & B Costs for the Performance Period	$17,781	$18,690	-$908	(-$1,695, -$121)	$20,963	$30,769	-$9,806	(-$11,508, -$8,105)
Parts A & B HF-Related Costs for the Performance Period	$2,684	$1,996	$688	($442, $933)	$3,236	$3,831	-$595	(-$1,079, -$110)
All-Cause Rehospitalizations	$6,143	$7,869	-$1,726	(-$2,272, -$1,180)	$7,713	$14,946	-$7,232	(-$8,433, -$6,032)
HF-Related Rehospitalization	$1,444	$1,267	$177	(-$32, 385)	$1,895	$2,418	-$523	(-$905, -$141)
All-Cause ER Visits	$473	$521	-$48	(-$87, -$10)	$548	$726	-$178	(-$243, -$114)
HF-Related ER Visits	$36	$39	-$3	(-$12, $5)	$41	$48	-$7	(-$22, $9)
All-Cause Physician Office Visits	$989	$891	$98	($78, $118)	$1,061	$976	$85	($53, $117)
Primary Care Physician Office Visits	$107	$114	-$7	(-$14, $0)	$126	$152	-$26	(-$37, -$15)
Cardiologist Physician Office Visits	$220	$180	$40	($34, $46)	$221	$166	$55	($47, $64)
All-Cause SNF Admissions	$618	$820	-$202	($323, $82)	$1,046	$3,281	-$2,235	(-$2,625, -1,844)

Of the 548 ACOs in the Medicare Shared Savings Program in 2018, the average historical expenditures were $197,212,913. The average benchmark was $200,325,637. When comparing expenditures to the benchmark, 37% of ACOs (205) achieved savings. The descriptive analysis showing these results is outlined in the following Table.

ACO Historical Expenditures and Benchmark

Category	Results
Average ACO Historical Expenditures	$197,212,913
Average ACO Benchmark	$200,325,637

On average 7.26% of ACO patients were diagnosed with CHF, with a range of 2.99% to 21.91%. For utilization of CHF therapies, on average 2.97% of CHF patients in ACOs utilized SAC/VAL, with a range of 0% to 10.70%. Comparatively, an average of 58.86% of CHF patients in ACOs utilized an ACEi/ARB/ARNI, with a range of 38.57% to 70.73%. The descriptive analysis showing these results is outlined in the following Table.

ACO SAC/VAL Utilization

Category	Results
Average % of ACO Patients with HF (Range)	7.26% (2.99% to 21.91%)
Average ACO SAC/VAL Utilization (Range)	2.97% (0% to 10.70%)
Number of ACOs Above/Below Average SAC/VAL Utilization	286/262
Average ACO ACE/ARB/ARNI Utilization (Range)	58.86% (38.57% to 70.73%)
Number of ACOs Above/Below Average ACE/ARB/ARNI Utilization	282/266

Safety Results
This study utilized de-identified secondary administrative claims data. Adverse events/adverse reactions were not captured.

Other Relevant Findings
None

Conclusion
This study supports clinical trials that demonstrate that adherent sacubitril/valsartan treatment is associated with fewer inpatient hospitalizations. This study is the first study to provide further evidence that innovative therapies for HF, such as SAC/VAL, could provide benefit in reducing expensive medical events in the context of APMs, such as the BPCI and MSSP, and could, in turn, improve health system and APM performance.

Date of Clinical Study Report
15 December 2020