SICKLE CELL DISEASE AND NEW PHARMACOLOGIC AGENTS

BACKGROUND

Sickle cell disease (SCD) is a broad term that describes a group of genetic disorders that impact hemoglobin (Hb) causing red blood cells to become an irregular, sickle shape. These sickle-shaped red blood cells are rigid and can cause blockages slowing the flow of blood. Blood vessel occlusion is the primary pathophysiology associated with SCD resulting in painful vaso-occlusive crises (VOC).[1,2]

In the United States (US), it is estimated approximately 100,000 people are living with SCD.[3] SCD is primarily present in individuals of African, Mediterranean, Central/South American, and Asian descent.[4,5] According to the Centers for Disease Control and Prevention (CDC), SCD impacts an estimated 1 out of every 365 African-American births and 1 out of every 16,300 Hispanic-American births in the US.[4]

VOCs impact nearly all individuals with SCD and can occur as early as 6 months of age. Patients with sickle cell disease-related pain events have been shown to have low health-related quality of life.[6] These SCD-related pain events can be managed with analgesics, however it has been shown that the use of analgesics may be underutilized due to stigma and provider bias.[6]

Prevention of VOCs is key in treating patients living with SCD. For over 20 years, hydroxyurea has been the primary pharmacotherapeutic agent available for preventing SCD complications. Hydroxyurea increases fetal hemoglobin, reduces "sickling" of red blood cells, and improves blood flow.[7] In 2014, the National Heart, Lung and Blood Institute (NHLBI) updated guidelines for the management of SCD.[8] The evidence-based guidelines provided recommendations for the use of hydroxyurea therapy.

Figure 1: Evidence-Based Recommendations for Use of Hydroxyurea Therapy[8]

Evidence-Based Recommendations for Use of Hydroxyurea Therapy	Strength of Recommendation	Quality of Evidence
In adults with sickle cell anemia (SCA) who have ≥3 moderate to severe pain crises associated with sickle cell disease (SCD) during a 12-mo period, initiate treatment with hydroxyurea	Strong	High
In adults with SCA who have sickle cell-associated pain that interferes with daily activities and quality of life, initiate treatment with hydroxyurea	Strong	Moderate
In adults with SCA who have a history of severe or recurrent acute chest syndrome (ACS), initiate treatment with hydroxyurea[a]	Strong	Moderate
In adults with SCA who have severe symptomatic chronic anemia that interferes with daily activities or quality of life, initiate treatment with hydroxyurea	Strong	Moderate
In infants 9 mo of age or older, in children, and in adolescents with SCA, offer treatment with hydroxyurea regardless of clinical severity to reduce complications (eg, pain, dactylitis, ACS, anemia) related to SCD	Strong[b] and moderate[c]	High[b] and moderate[c]
In adults and children with SCD who have chronic kidney disease and are taking erythropoietin, add hydroxyurea therapy to improve anemia	Weak	Low
Discontinue hydroxyurea therapy in women who are pregnant or breastfeeding	Moderate	Low
Use an established prescribing and monitoring protocol to ensure proper use of hydroxyurea and maximize benefits and safety	Strong	High
In persons with HbSβ⁰-thalassemia or HbSC who have recurrent SCD-associated pain that interferes with daily activities or quality of life, consult an SCD expert for consideration of hydroxyurea therapy	Moderate	Low
In persons not demonstrating a clinical response to appropriate doses and duration of hydroxyurea therapy, consult an SCD expert	Moderate	Very low

[a] More information appears in the chapter entitled "Managing Acute Complications of Sickle Cell Disease" in the full guideline.

[b] Strong recommendation and high quality of evidence for persons aged 9 to 42 months.

[c] Moderate recommendation and moderate quality of evidence for children older than 42 months and adolescents.

In 2017 the FDA approved L-glutamine (Endari®) as the first new therapeutic agent for the treatment of SCD in over two decades.[9] Endari® is indicated to reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older. In 2019 two new agents were approved for the treatment of SCD, crizanlizumab (Adakveo®) and voxelotor (Oxbryta®). Adakveo® is a selectin blocker indicated to reduce the frequency of vaso-occlusive crises in adults and pediatric patients aged 16 years and older with sickle cell disease.[10] Oxbryta® is a hemoglobin S polymerization inhibitor indicated for the treatment of sickle cell disease in adults and pediatric patients 12 years of age and older.[11] Each of these agents has a unique mechanism of action in treating SCD. Although these four agents are the current medications indicated for treatment of SCD, other potential therapies in this disease state are on the horizon. One of the first gene therapy agents for sickle cell treatment received approval from the European Medicines Agency (EMA) in 2019 with an estimated price of €1.575 million ($1.8 million). It is currently under review by the FDA in the US. [12–14]

Determining the place in therapy for each agent is crucial in the treatment of SCD. The Institute for Clinical and Economic Review (ICER) released their Draft Evidence Report for sickle cell disease in February 2020.[15] Their review included data on clinical and cost effectiveness for each of the newer agents approved for use in the United States. Figure 2 is a table describing recently approved therapies for SCD.

Figure 2: Recently Approved Therapies for SCD.[15]

	Date of FDA Approval	FDA Indication	FDA Dosage	How Supplied	WAC*	Cost per Year**
Crizanlizumab (Adakveo®)	11/15/2019	Indicated to reduce the frequency of vaso-occlusive crises in adults and pediatric patients age ≥16 years with SCD	Administer 5 mg/kg (IV) over a period of 30 minutes on week 0, week 2, and every 4 weeks thereafter	100mg/10ml (10mg/ml) single-dose vial	$2,357.14 per 10ml vial	$107,700
Voxelotor (Oxbryta®)	11/25/2019	Indicated for the treatment of SCD in adults and pediatric patients age ≥12 years	1,500 mg orally once daily with or without food	500 mg tablets; 90 count bottle	$10,417.00 per 90 count bottle. ($115.74 per tablet)	$104,357
L-Glutamine (Endari®)	7/7/2017	Indicated to reduce the acute complications of SCD in adult and pediatric patients ≥5 years	5-15 grams orally, twice daily based on body weight	5 gram packets; carton of 60	$1,154.00 per 60 count carton; $19.23 per 5 gram packet	$26,082

Notes: IV - intravenous; SCD - sickle cell disease; WAC - wholesale acquisition cost.
*WAC accessed June 1, 2020
** Cost per Year estimates based on ICER figures[15]

The Mississippi Division of Medicaid requested MS-DUR conduct an analysis of Medicaid beneficiaries diagnosed with SCD. Utilization of therapies for the treatment of SCD was analyzed. Applying key inclusion/exclusion criteria used in clinical trials for both Adakveo® and Oxbryta®, MS-DUR examined claims data to forecast beneficiaries that may be potential candidates for these newly approved therapies.

METHODS

A retrospective analysis was conducted using Mississippi Medicaid fee-for-service (FFS) and coordinated care organization [CCOs: Magnolia (MAG), Molina Health (MOL), and UnitedHealthcare (UHC)] claims for the period of January 1, 2018 to December 31, 2019. Medicaid beneficiaries with SCD were identified using the ICD-10 codes from CMS Chronic Conditions Warehouse (CCW) algorithm.[16] All 25 ICD-10 diagnosis codes as well as the principal diagnosis code of each claim were checked from inpatient, outpatient and medical claim files to identify beneficiaries with SCD. Information on the beneficiaries' race, gender, age, and plan (FFS/UHC/MAG/MOL) were summarized in the analysis. Age and plan were assessed as of the date for first SCD diagnosis claim in the analysis period, referred to as the index SCD diagnosis date hereafter.

RESULTS

A total of 2,331 beneficiaries were identified through claims data as being diagnosed with SCD during the study period.

- 0.33% of the average Medicaid enrollment during the study period (702,956) were diagnosed with SCD.
- 1,914 (82.1%) were 35 years of age or below.
- Females made up 60.9% of those diagnosed with SCD.
- 86.8% were African American.

TABLE 1a: Proportion of Medicaid Beneficiaries with Sickle Cell Disease Diagnosis
(January 2018 - December 2019)

Plan	Average Enrollment	Beneficiaries with SCD	Percent
FFS	181,187	668	0.37%
UHC	226,557	724	0.32%
MAG	257,634	847	0.33%
MOL	37,578	92	0.24%
Total	**702,956**	**2,331**	**0.33%**

Note: SCD - Sickle Cell Diagnosis
Average enrollment calculated over the study period.

TABLE 1b: Demographic Characteristics of Beneficiaries Diagnosed with Sickle Cell Disease
(January 2018 - December 2019)

Characteristic	Total Beneficiaries	Plan							
		FFS		UHC		MAG		MOL	
		N	%	N	%	N	%	N	%
Age Category									
0-17	**1,088**	213	32%	385	53%	451	53%	39	42%
18-35	**826**	251	38%	245	34%	283	33%	47	51%
36-50	**274**	127	19%	67	9%	74	9%	6	7%
51-64	**143**	77	12%	27	4%	39	5%	0	0%
Total	**2,331**	**668**	**100%**	**724**	**100%**	**847**	**100%**	**92**	**100%**
Sex									
Female	**1,420**	392	59%	446	62%	511	60%	71	77%
Male	**911**	276	41%	278	38%	336	40%	21	23%
Total	**2,331**	**668**	**100%**	**724**	**100%**	**847**	100%	**92**	**100%**
Race									
Caucasian	**30**	10	1%	12	2%	8	1%	0	0%
Other	**278**	64	10%	91	13%	111	13%	12	13%
African Amer	**2,023**	594	89%	621	86%	728	86%	80	87%
Total	**2,331**	**668**	**100%**	**724**	**100%**	**847**	**100%**	**92**	**100%**

Note: FFS - Fee-for-Service; UHC - UnitedHealthcare; MAG - Magnolia; MOL - Molina
Patients with Sickle Cell Disease were identified using CCW Chronic Conditions algorithm, and all 25 ICD-10 diagnosis codes, as well as the principal diagnosis code of patients, were checked using claims from inpatient, outpatient and medical claim files. Plan was determined as of the date of index diagnosis date of SCD.

For all beneficiaries with SCD, beneficiaries on Endari®, hydroxyurea, or opioid pain medications were identified during the 24-month study period. Methadone, buprenorphine and buprenorphine-naloxone were excluded from the list of opioid medications as these medications are often used in opioid abuse treatment and have been excluded from opioid pain dosing guidelines.[17] For all the beneficiaries on opioid pain medication, opioid doses were converted into MEDDs (morphine equivalent daily doses) and number of beneficiaries with average and max daily doses were stratified into the following categories: less than 50 MEDD, 50 to 89 MEDD and 90 MEDD or above. Average MEDD is defined as a beneficiary's mean opioid dose level across the duration of their opioid treatment while max MEDD is defined as the maximum opioid dose level at any point during the treatment continuum.

Table 2 displays the utilization of medications among beneficiaries diagnosed with SCD.

- 60.8% (1,417) of beneficiaries diagnosed with SCD had a prescription claim for Endari®, hydroxyurea, opioid medication, or any combination of these medications during the study period.
- Only 2.4% (56) of beneficiaries had a claim for Endari®.
- 27% (629) of beneficiaries diagnosed with SCD had at least one claim for hydroxyurea during the study period.
- 56.5% (1,317) of beneficiaries had claims for opioid pain medication:
    - 83.1% (1,094) of those beneficiaries had an average MEDD of < 50 and
    - 63.1% (831) had a max MEDD of < 50.

TABLE 2: Drug Utilization Stratified by Plan

(January 2018 - December 2019)

Plan*	#Benes on Endari	#Benes on Hydroxyurea	#Benes on Opioid Pain Medication	Opioid Pain Medication											
				Average MEDD ǂ						Max MEDD ǂ					
				< 50 MED		50 -89 MED		90 MED or Higher		< 50 MED		50 -89 MED		90 MED or Higher	
N = 2,331	N = 1,417**			N	%	N	%	N	%	N	%	N	%	N	%
FFS	16	133	275	226	82%	36	13%	13	5%	185	67%	63	23%	27	10%
UHC	11	220	471	396	84%	49	10%	26	6%	293	62%	111	24%	67	14%
MAG	29	273	536	445	83%	66	12%	25	5%	330	62%	125	23%	81	15%
MOL	0	3	35	27	77%	8	23%	0	0%	23	66%	12	34%	0	0%
Total	**56**	**629**	**1,317**	**1,094**		**159**		**64**		**831**		**311**		**175**	

Note: FFS - Fee-for-Service; UHC - UnitedHealthcare; MAG - Magnolia; MOL- Molina

*Patients with Sickle Cell Disease were identified using CCW Chronic Conditions algorithm, and all 25 ICD-10 diagnosis codes as well as the principal diagnosis code of patients were checked using claims from inpatient, outpatient and medical claim files. Plan was determined as of the date of index diagnosis date of SCD.

**1,417 unique beneficiaries were on one or more of the 3 therapies.

ǂ MEDD - Morphine Equivalent Daily Dose

Inpatient sickle cell related hospitalizations on or after index SCD diagnosis date were identified. Each hospitalization's length of stay was calculated. Hospitalizations within 3 days of a previous hospitalization were considered as the same hospitalization event. Average number of hospitalizations per beneficiary, average length of stay per beneficiary and average length of stay per hospitalization event (stay) were reported stratified by plan. For each plan, the average length of stay per hospitalization event was calculated by dividing the total days of hospitalization across all beneficiaries enrolled in that plan by the total number of hospitalization events across all beneficiaries in that plan. Sickle cell-related hospitalization events were identified from inpatient claims with a primary diagnosis for one of the sickle cell-related events, consistent with literature.[18] For sickle cell-related hospitalizations, average cost per beneficiary and average cost per stay were reported, stratified by plan for the entire study period. In calculating sickle cell-related hospitalizations in each plan, the average cost per stay was calculated by dividing the total cost across all beneficiaries enrolled in that plan by the total number of hospitalization events across all beneficiaries in that plan.

TABLE 3.1: Cost and Length of Stay of Sickle Cell-related Hospitalization Stratified by Plan
(January 2018 - December 2019)

Plan at Index Sickle Cell Diagnosis	#Benes	Hospitalization Cost		Length of Stay (LOS) in days		No. of Hospitalizations
		Average Cost/Bene	Average Cost/Stay	Average LOS/Bene	Average LOS/Stay	Average Hospitalizations /Bene
FFS	**153**	$22,840.1	$5,424.9	27.6	9.8	4.3
UHC	**246**	$20,271.7	$5,479.2	4.9	1.5	3.7
MAG	**272**	$22,768.3	$5,531.1	24.3	5.1	4.3
MOL	**6**	$6,395.7	$3,999.4	5.8	3.4	1.5

Note: FFS - Fee For Service, UHC - UnitedHealthcare, MAG - Magnolia, MOL - Molina
Plan was determined as of the index Sickle Cell Diagnosis. Patients with Sickle Cell Disease were identified using CCW Chronic Conditions algorithm, and all 25 ICD-10 diagnosis codes as well as the principal diagnosis code of patients were checked using claims from inpatient, outpatient and medical claim files. SCD-related hospitalizations were calculated using inpatient claims that had a primary diagnosis code for a sickle cell related event [Kauf, Teresa L., et al. "The cost of health care for children and adults with sickle cell disease." American Journal of Hematology 84.6 (2009): 323-327.]

- 28.8% (671) of beneficiaries diagnosed with SCD had a sickle cell-related hospitalization during the study period.
- The average cost per sickle cell-related hospitalization across all plans was $5,356.51.
- Over $14.5 million was spent on sickle cell-related hospitalizations during the study period.

Moreover, for beneficiaries with a diagnosis for SCD in the study period, all-cause and SCD-related costs post index SCD diagnosis were determined. Costs included amount paid by Medicaid for hospitalizations, non-hospitalization medical events, and prescription drug use. Months of Medicaid eligibility post index diagnosis were assessed to standardize costs to per member per year (PMPY) metrics while reporting the plan stratified results. (Table 3.2)

TABLE 3.2: All-Cause and Sickle Cell Disease (SCD)-related costs for Beneficiaries with a SCD Diagnosis
(January 2018 - December 2019)

Plan at Index Sickle Cell Diagnosis	#Benes	All-cause Cost (PMPY*)		SCD-related Cost** (PMPY*)	
		Average Cost/Bene	Total (annualized)	Average Cost/Bene	Total (annualized)
FFS	**638**	$24,534.1	$15,652,755.8	$11,508.4	$7,342,359.2
UHC	**724**	$19,351.5	$14,010,486.0	$11,059.5	$8,007,078.0
MAG	**847**	$26,696.8	$22,612,189.6	$15,052.5	$12,749,467.5
MOL	**92**	$12,922.5	$1,188,870.0	$1,124.4	$103,444.8

Note: PMPY - Per Member Per Year
FFS - Fee For Service, UHC - UnitedHealthcare, MAG - Magnolia, MOL - Molina
Plan was determined as of the index Sickle Cell Diagnosis. Patients with Sickle Cell Disease were identified using CCW Chronic Conditions algorithm, and all 25 ICD-10 diagnosis codes as well as the principal diagnosis code of patients were checked using claims from inpatient, outpatient and medical claim files.
Number of beneficiaries in each plan may differ from the number of beneficiaries in the descriptive table due to loss of Medicaid eligiblility in the follow-up period.
*PMPY costs assessed by taking into account number of months of Medicaid eligibility in the follow-up period.
**SCD-related costs were calculated using medical claims that had a primary diagnosis code for a sickle cell related event and pharmacy claims for hydroxyurea, endari, or iron chelation agents [Kauf, Teresa L., et al. "The cost of health care for children and adults with sickle cell disease." American Journal of Hematology 84.6 (2009): 323-327.]

- DOM spent over $53 million annually to care for beneficiaries diagnosed with SCD, with approximately $28 million annually being spent directly on sickle cell-related costs.

When forecasting to identify potential candidates for therapy with either Adakveo® or Oxbryta®, MS-DUR looked to clinical trial data utilized in gaining FDA approval for both of these products. In the clinical trials cited in the ICER Report, there were some common criteria across both the SUSTAIN (Adakveo®) and HOPE (Oxbryta®) noted.[15,19,20]

- **Age ≥ 12 years** - The minimum age approved for Adakveo® is 16 years and for Oxbryta® is 12 years. Anyone below the age of 12 years was excluded as a potential candidate for either Adakveo® or Oxbryta®.
- **Stable Hydroxyurea use** - In trials for both medications, the majority of participants had been maintained on a stable hydroxyurea dose for 3 months prior to enrollment and continued on hydroxyurea therapy during the trials. For this analysis, beneficiaries were considered as being on stable hydroxyurea dosing if they had been on the same dose of hydroxyurea for 90 days or more, allowing for compliance gaps of up to 60 days. Number of beneficiaries on stable hydroxyurea dose enrolled in each plan (as of their index SCD diagnosis date) were reported.
- **Receipt of chronic transfusion** – Both the SUSTAIN and HOPE trials excluded participants that had received chronic red-cell blood transfusions. MS-DUR ran 2 analyses, with and without chronic transfusion as an exclusion criteria. For all the beneficiaries on stable hydroxyurea dosing, beneficiaries undergoing blood transfusion were identified according to CPT codes for blood transfusion.[21] Beneficiaries were classified as having "chronic transfusion" if they had transfusions every 6 weeks or less.
- **Number of pain crises experienced**– The SUSTAIN trial included participants with 2-10 acute pain crises during the previous 12 months, while the HOPE trial included participants with 1-10 acute pain crises in the previous 12 months. Pain crisis events were identified during the study period using ICD-10 codes for pain crisis events as described by Stettler et.al. [22] Number of beneficiaries having 1, 2, 3 or more pain crisis events during the study period were reported, stratified by plan.

MS-DUR used these criteria to forecast the number of possible beneficiaries that may be prescribed therapy with one of the two new agents.

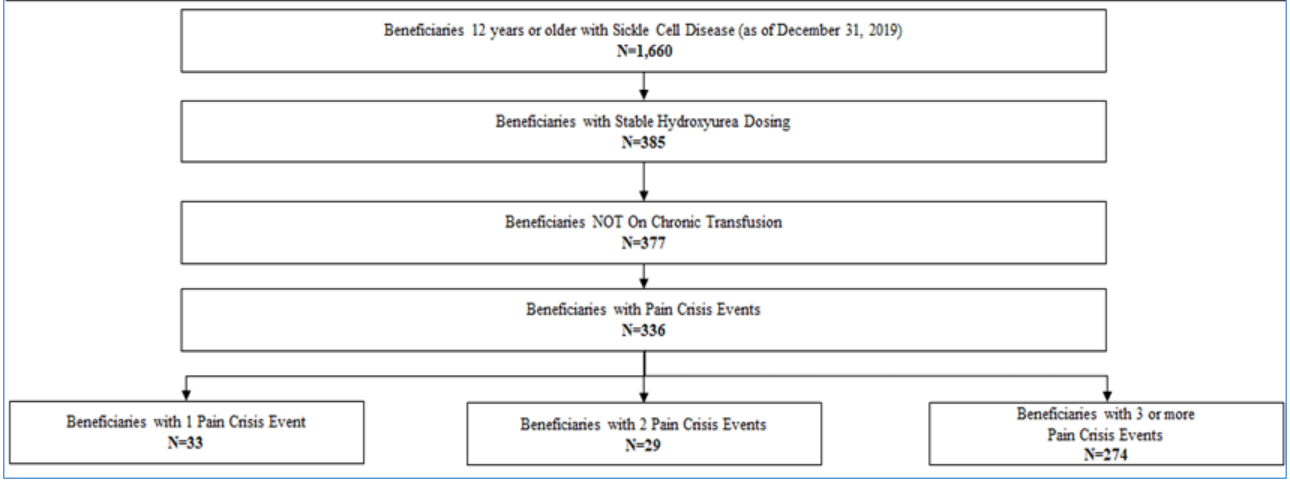
Table 4/Figure 3 describe potential beneficiaries **excluding** those receiving chronic transfusions.

TABLE 4: Description of Pain Crisis Events in Beneficiaries ≥ 12 Years on Stable Hydroxyurea Doses and NOT on Chronic Blood Tranfusion
(January 2018 - December 2019)

Plan	Beneficiaries on Hydroxyurea N= 446	Beneficiaries on Stable Hydroxyurea Dose* N = 385	Beneficiaries NOT on Chronic Blood Transfusion** N= 377	Beneficiaries with Pain Crisis by Number of Pain Crises in During Study Period*** N= 336			
				1	2	3	Total
FFS	105	91	90	10	11	56	**77**
UHC	143	123	121	9	8	90	**107**
MAG	197	170	165	14	10	127	**151**
MOL	1	1	1	0	0	1	**1**
Total	**446**	**385**	**377**	**33**	**29**	**274**	**336**

Notes: FFS - Fee-for-Service; UHC - UnitedHealthcare; MAG - Magnolia; MOL - Molina
*Stable Hydroxyurea dosing was identified as beneficiaries on the same dose of hydroxyurea for 90 days or more, allowing for compliance gaps of up to 60 days
**Blood Transfusion was identified according to CPT codes for blood transfusion and were classified as a "Chronic Transfusion" if the beneficiary had tranfusions every 6 weeks or less; CPT Codes for blood transfusion were referenced from CPT Codes for Transfusion Service Testing retrieved from https://abo20.lstream.org/images/HS_Manual/CPT_Codes.pdf and Kalman, R., Mack, J.P. (2018). Blood products and coagulation. Critical Care Secrets E-Book, 373
***Pain crisis identified using ICD-10 codes as used in Stettler, N., McKiernan, C. M., Melin, C. Q., Adejoro, O. O., & Walczak, N. B. (2015). Proportion of adults with sickle cell anemia and pain crises receiving hydroxyurea. JAMA - Journal of the American Medical Association, 313(16), 1671–1672. https://doi.org/10.1001/jama.2015.3075

FIGURE 3: Sample Attrition for Beneficiaries ≥ 12 Years with Stable Hydroxyurea Dosing and NOT on Chronic Transfusion Having Pain Crisis Events
(January 2018 - December 2019)



- Excluding beneficiaries that were considered as receiving chronic transfusions, a total of 336 beneficiaries across all pharmacy programs could be considered as potential candidates for either Adakveo® or Oxbryta®.

Table 5/Figure 4 describe potential beneficiaries **including** those receiving chronic transfusions.

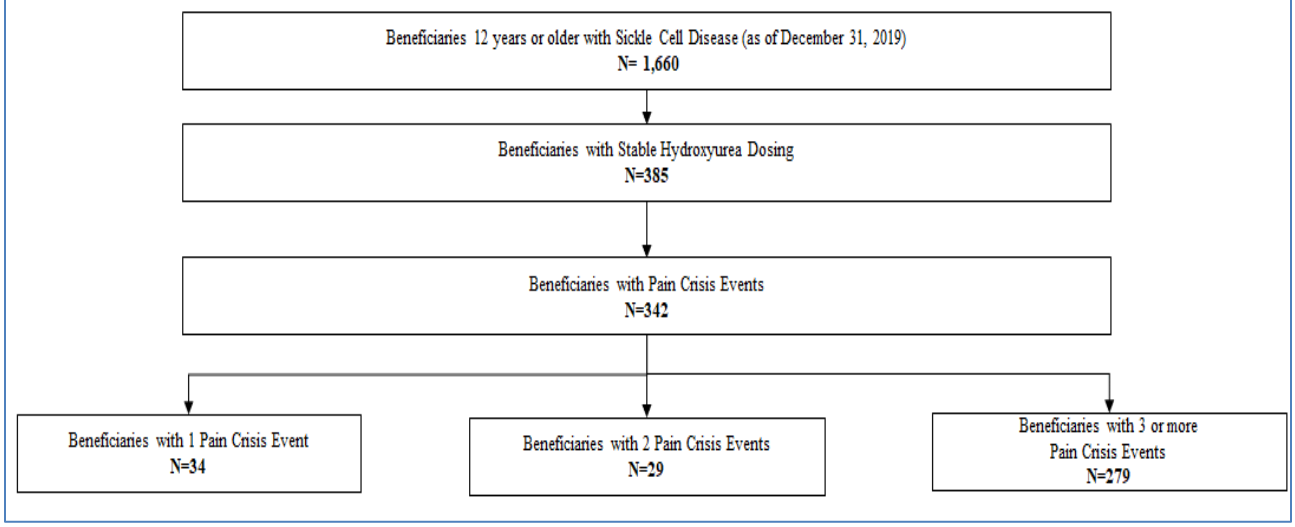
- Only 6 additional potential beneficiaries were added when those receiving chronic transfusions were included in the forecasting.

TABLE 5: Description of Pain Crisis Events in Beneficiaries ≥ 12 Years on Stable Hydroxyurea Doses
(January 2018 - December 2019)

Plan	Beneficiaries on Hydroxyurea N= 446	Beneficiaries on Stable Hydroxyurea Dose* N = 385	Beneficiaries with Pain Crisis by Number of Pain Crises in Previous Year*** (N= 342) 1	2	3	Total
FFS	105	91	10	11	56	77
UHC	143	123	10	8	91	109
MAG	197	170	14	10	131	155
MOL	1	1	0	0	1	1
Total	446	385	34	29	279	342

Notes: FFS - Fee-for-Service; UHC - UnitedHealthcare; MAG - Magnolia; MOL - Molina
*Stable Hydroxyurea dosing was identified as beneficiaries on the same dose of hydroxyurea for 90 days or more, allowing for compliance gaps of up to 60 days.
***Pain crisis identified using ICD-10 codes as used in Stettler, N., McKiernan, C. M., Melin, C. Q., Adejoro, O. O., & Walczak, N. B. (2015). Proportion of adults with sickle cell anemia and pain crises receiving hydroxyurea. JAMA - Journal of the American Medical Association, 313(16), 1671–1672. https://doi.org/10.1001/jama.2015.3075

FIGURE 4: Sample Attrition for Beneficiaries ≥ 12 years with Stable Hydroxyurea Doses Having Pain Crisis Events
(January 2018 - December 2019)



CONCLUSIONS

Although sickle cell disease affects a relatively small proportion of the population, the impact on the health-related quality of life for those living with sickle cell disease can be substantial. Historically, treatment options have been limited. Two new agents recently received FDA approval and more are expected to be approved in the near future. Balancing clinical and cost effectiveness in determining the most appropriate place in therapy for these new agents is essential. Modeling prior authorization requirements after the criteria utilized in clinical trials used to gain FDA approval is a logical place to begin.

RECOMMENDATIONS

1. MS-DUR recommends that DOM create manual prior authorization criteria for Oxbryta® and Adakveo® for review/approval of appropriate use of these products.

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