Disclaimer

The following report(s) provides findings from an FDA-initiated query using Sentinel. While Sentinel queries may be undertaken to assess potential medical product safety risks, they may also be initiated for various other reasons. Some examples include determining a rate or count of an identified health outcome of interest, examining medical product use, exploring the feasibility of future, more detailed analyses within Sentinel, and seeking to better understand Sentinel capabilities.

Data obtained through Sentinel are intended to complement other types of evidence such as preclinical studies, clinical trials, postmarket studies, and adverse event reports, all of which are used by FDA to inform regulatory decisions regarding medical product safety. The information contained in this report is provided as part of FDA's commitment to place knowledge acquired from Sentinel in the public domain as soon as possible. Any public health actions taken by FDA regarding products involved in Sentinel queries will continue to be communicated through existing channels.

FDA wants to emphasize that the fact that FDA has initiated a query involving a medical product and is reporting findings related to that query does not mean that FDA is suggesting health care practitioners should change their prescribing practices for the medical product or that patients taking the medical product should stop using it. Patients who have questions about the use of an identified medical product should contact their health care practitioners.

The following report contains a description of the request, request specifications, and results from the modular program run(s).

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Overview for Request: cder_mpl1r_wp101

Request ID: cder_mpl1r_wp101_nsdp_v01

Request Description: This report contains estimates of incident pulmonary arterial hypertension (PAH), interstitial lung disease (ILD), and macrophage activation syndrome (MAS) among an adult cohort with Adult-Onset Still's Disease (AOSD) and a pediatric cohort with Systemic Juvenile Idiopathic Arthritis (SJIA) in the Sentinel Distributed Database (SDD). This is report 1 of 2. Report 2 contains estimates of interleukin-1 (IL-1) and interleukin-6 (IL-6) inhibitor use and occurrence of PAH, ILD, and MAS among an adult cohort with AOSD and a pediatric cohort with SJIA in the SDD.

Sentinel Modular Program Tool Used: Cohort Identification and Descriptive Analysis (CIDA) tool, version 5.4.4

Data Source: Data from October 1, 2015 to March 31, 2018 from 15 Data Partners contributing to the SDD were included in this report. See Appendix A for a list of dates of available data for each Data Partner. This request was distributed to Data Partners on August 15, 2018.

Study Design: The purpose of this request was to estimate the proportion of incident PAH, ILD, and MAS diagnoses among:

1) the overall adult population
2) a cohort of adult members diagnosed with AOSD
3) the overall pediatric population
4) a cohort of pediatric members diagnosed with SJIA

Cohort Eligibility Criteria: Those included in the cohorts were required to be continuously enrolled in plans with medical and drug coverage for at least 183 days prior to their first qualifying diagnosis event, during which gaps in coverage of up to 45 days were allowed. The adult cohorts included members who were 17 to less than 65 years of age. The pediatric cohorts included members who were six months to less than 17 years of age. Eligible members in any of the four cohorts could not have evidence of PAH or ILD events in their entire available enrollment history prior to their first qualifying event. See Appendix B for a list of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM codes used as exclusion criteria in defining first qualifying diagnosis events.

Events of Interest: In all four identified cohorts, the main events of interest were incident PAH, ILD, and MAS. In the overall adult population cohort, incident AOSD was also evaluated, and in the cohort of adult members diagnosed with AOSD, subsequent diagnoses of AOSD after the first cohort-defining event were included as events of interest. In the overall pediatric population cohort, incident SJIA was also evaluated, and in the cohort of pediatric members diagnosed with SJIA, subsequent diagnoses of SJIA after the first cohort-defining event were included as events of interest. Please see Appendix C for International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes used to define first qualifying events.

Among members with incident PAH and ILD events, recorded history of MAS was identified throughout their entire available prior enrollment history. See Appendix D for ICD-9-CM and ICD-10-CM codes used to assess prior diagnoses of MAS.

Please see Appendices E (adult population) and F (pediatric population) for the specifications of parameters used in the analyses for this request.

Limitations: Algorithms used to define exposures, outcomes, and inclusion criteria are imperfect; thus, it is possible that there may be misclassification. Therefore, data should be interpreted with this limitation in mind.

Notes: Please contact the Sentinel Operations Center Query Fulfillment Team (qf@sentinelsystem.org) for questions and to provide comments/suggestions for future enhancements to this document.

Sentinel

Table of Contents

Glossary of Terms for Analyses Using
Cohort Identification and Descriptive Analysis (CIDA) Tool*

Amount Supplied - number of units (pills, tablets, vials) dispensed. Net amount per NDC per dispensing.

Blackout Period - number of days at the beginning of a treatment episode that events are to be ignored. If an event occurs during the blackout period, the episode is excluded.

Care Setting - type of medical encounter or facility where the exposure, event, or condition code was recorded. Possible care settings include: Inpatient Hospital Stay (IP), Non-Acute Institutional Stay (IS), Emergency Department (ED), Ambulatory Visit (AV), and Other Ambulatory Visit (OA). For laboratory results, possible care settings include: Emergency department (E), Home (H), Inpatient (I), Outpatient (O), or Unknown or Missing (U). Along with the Principal Diagnosis Indicator, forms the Care Setting/PDX parameter.

- **Ambulatory Visit (AV) -** includes visits at outpatient clinics, same-day surgeries, urgent care visits, and other same-day ambulatory hospital encounters, but excludes emergency department encounters.
- **Emergency Department (ED) -** includes ED encounters that become inpatient stays (in which case inpatient stays would be a separate encounter). Excludes urgent care visits.
- **Inpatient Hospital Stay (IP) -** includes all inpatient stays, same-day hospital discharges, hospital transfers, and acute hospital care where the discharge is after the admission date.
- **Non-Acute Institutional Stay (IS) -** includes hospice, skilled nursing facility (SNF), rehab center, nursing home, residential, overnight non-hospital dialysis and other non-hospital stays.
- **Other Ambulatory Visit (OA) -** includes other non overnight AV encounters such as hospice visits, home health visits, skilled nursing facility visits, other non-hospital visits, as well as telemedicine, telephone and email consultations.

Cohort Definition (drug/exposure) - indicates how the cohort will be defined: (1): Cohort includes only the first valid treatment episode during the query period; (2): Cohort includes all valid treatment episodes during the query period; (3): Cohort includes all valid treatment episodes during the query period until an event occurs.

Days Supplied - number of days supplied for all dispensings in qualifying treatment episodes.

Eligible Members - number of members eligible for an incident treatment episode (defined by the drug/exposure and event washout periods) with drug and medical coverage during the query period.

Enrollment Gap - number of days allowed between two consecutive enrollment periods without breaking a "continuously enrolled" sequence.

Episodes - treatment episodes; length of episode is determined by days supplied in one dispensing or consecutive dispensings bridged by the episode gap.

Episode Gap - number of days allowed between two (or more) consecutive exposures (dispensings/procedures) to be considered the same treatment episode.

Event Deduplication - specifies how events are counted by the MP algorithm: (0): Counts all occurrences of an HOI during an exposure episode; (1): de-duplicates occurrences of the same HOI code and code type on the same day; (2): de-duplicates occurrences of the same HOI group on the same day (e.g., de-duplicates at the group level).

Exposure Episode Length - number of days after exposure initiation that is considered "exposed time."

Exposure Extension Period - number of days post treatment period in which the outcomes/events are counted for a treatment episode. Extensions days are added after any episode gaps have been bridged.

Lookback Period - number of days wherein a member is required to have evidence of pre-existing condition (diagnosis/procedure/drug dispensing).

Maximum Episode Duration - truncates exposure episodes after a requester-specified number of exposed days. Applied after any gaps are bridged and extension days added to the length of the exposure episode.

Member-Years - sum of all days of enrollment with medical and drug coverage in the query period preceded by an exposure washout period all divided by 365.25.

Minimum Days Supplied - specifies a minimum number of days in length of the days supplied for the episode to be considered.

Minimum Episode Duration - specifies a minimum number of days in length of the episode for it to be considered. Applied after any gaps are bridged and extension days added to the length of the exposure episode.

Monitoring Period - used to define time periods of interest for both sequential analysis and simple cohort characterization requests.

Principal Diagnosis (PDX) - diagnosis or condition established to be chiefly responsible for admission of the patient to the hospital. 'P' = principal diagnosis, 'S' = secondary diagnosis, 'X' = unspecified diagnosis, '.' = blank. Along with the Care Setting values, forms the Caresetting/PDX parameter.

Query Period - period in which the modular program looks for exposures and outcomes of interest.

Treatment Episode Truncation Indicator - indicates whether the exposure episode will be truncated at the occurrence of a requester-specified code.

Washout Period (drug/exposure) - number of days a user is required to have no evidence of prior exposure (drug dispensing/procedure) and continuous drug and medical coverage prior to an incident treatment episode.

Washout Period (event/outcome) - number of days a user is required to have no evidence of a prior event (procedure/diagnosis) and continuous drug and medical coverage prior to an incident treatment episode.

Years at Risk - number of days supplied plus any episode gaps and exposure extension periods all divided by 365.25.

*not all terms may be used in this report

Table 1. Summary of Incident Events in the Sentinel Distributed Database (SDD) between October 1, 2015 and March 31, 2018 among Adults Aged 17 to 64 years, with No Prior Evidence of PAH or ILD

Incident Event	Patients	Eligible Members[1]	Number of Patients per 10,000 Eligible Members	Eligible Member-Years[1]
Adult-Onset Still's Disease (AOSD)	1,137	45,467,526	0.25	54,838,651.5
Pulmonary Arterial Hypertension (PAH)	73,089	45,467,526	16.07	54,838,651.5
And a recorded history of MAS [2]	23 (0.03%)	--	--	--
Interstitial Lung Disease (ILD)	67,250	45,467,526	14.79	54,838,651.5
And a recorded history of MAS [3]	45 (0.07%)	--	--	--
Macrophage Activation Syndrome (MAS)	2,484	45,467,526	0.55	54,836,625.0

[1]Eligible Members and Member- Years are reflective of the number of patients that met all cohort entry criteria on at least one day during the query period.
[2]Recorded history of MAS is assessed prior to first qualifying PAH diagnosis.
[3]Recorded history of MAS is assessed prior to first qualifying ILD diagnosis.

Table 2. Summary of Incident Events in the Sentinel Distributed Database (SDD) between October 1, 2015 and March 31, 2018 among Adults Aged 17 to 64 years, with prior Adult-Onset Still's Disease (AOSD) Diagnosis and No Prior Evidence of PAH or ILD

Incident Event	Patients	Eligible Members[1]	Number of Patients per 10,000 Eligible Members	Eligible Member Years[1]
Pulmonary Arterial Hypertension (PAH)	16	1,262	126.78	1,190.2
And a recorded history of MAS [2]	2 (12.5%)	--	--	--
Interstitial Lung Disease (ILD)	7	1,262	55.47	1,194.9
And a recorded history of MAS [3]	2 (28.57%)	--	--	--
Macrophage Activation Syndrome (MAS)	28	1,262	221.87	1,180.0
Subsequent AOSD diagnosis	726	1,262	5,752.77	526.7

[1]Eligible Members and Member-Years are reflective of the number of patients that met all cohort entry criteria on at least one day during the query period.

[2]Recorded history of MAS is assessed prior to first qualifying PAH diagnosis.

[3]Recorded history of MAS is assessed prior to first qualifying ILD diagnosis.

Table 3. Summary of Incident Events in the Sentinel Distributed Database (SDD) between October 1, 2015 and March 31, 2018 among Children Aged 6 months to 16 years, with No Prior Evidence of PAH or ILD

Incident Event	Patients	Eligible Members[1]	Number of Patients per 10,000 Eligible Members	Eligible Member Years[1]
Systemic Juvenile Idiopathic Arthritis (SJIA)	820	12,349,473	0.66	14,693,501.3
Pulmonary Arterial Hypertension (PAH)	1,087	12,349,473	0.88	14,693,501.3
And a recorded history of MAS [2]	1 (0.09%)	--	--	--
Interstitial Lung Disease (ILD)	3,006	12,349,473	2.43	14,693,501.3
And a recorded history of MAS [3]	4 (0.13%)	--	--	--
Macrophage Activation Syndrome (MAS)	1,331	12,349,473	1.08	14,692,331.3

[1]Eligible Members and Member-Years are reflective of the number of patients that met all cohort entry criteria on at least one day during the query period.

[2]Recorded history of MAS is assessed prior to first qualifying PAH diagnosis.

[3]Recorded history of MAS is assessed prior to first qualifying ILD diagnosis.

Table 4. Summary of Incident Events in the Sentinel Distributed Database (SDD) between October 1, 2015 and March 31, 2018 among Children Aged 6 months to 16 years, with prior Systemic Juvenile Idiopathic Arthritis (SJIA) Diagnosis and No Prior Evidence of PAH or ILD

Incident Event	Patients	Eligible Members[1]	Number of Patients per 10,000 Eligible Members	Eligible Member Years[1]
Pulmonary Arterial Hypertension (PAH)	1	897	11.15	858.5
And a recorded history of MAS [2]	0 (0.00%)	--	--	--
Interstitial Lung Disease (ILD)	5	897	55.74	856.9
And a recorded history of MAS [3]	1 (20.00%)	--	--	--
Macrophage Activation Syndrome (MAS)	29	897	323.30	832.0
Subsequent SJIA diagnosis	498	897	5,551.84	387.1

[1]Eligible Members and Member-Years are reflective of the number of patients that met all cohort entry criteria on at least one day during the query period.
[2]Recorded history of MAS is assessed prior to first qualifying PAH diagnosis.
[3]Recorded history of MAS is assessed prior to first qualifying ILD diagnosis.

Appendix A. Dates of Available Data for Each Data Partner (DP) as of Request End Date (March 31, 2018)

Data Partner ID	Start Date[1]	End Date[1]
DP01	01/01/2000	03/31/2018
DP02	01/01/2005	09/30/2017
DP03	01/01/2008	06/30/2017
DP04	01/01/2008	11/30/2017
DP05	01/01/2000	06/30/2017
DP06	01/01/2006	12/31/2017
DP07	01/01/2000	08/31/2017
DP08	01/01/2000	10/31/2017
DP09	06/01/2007	10/31/2017
DP10	01/01/2000	12/31/2017
DP11	01/01/2004	01/31/2018
DP12	01/01/2000	01/31/2017
DP13	01/01/2000	12/31/2016
DP14	01/01/2000	03/31/2016
DP15	01/01/2012	06/30/2017

[1]Start Date and End Date are first calculated by individual table (enrollment, dispensing, etc). End Date is defined as the greatest year-month with a record count that is within 80% of the previous year-month. After Start Date and End Dates are calculated by individual tables, the overall End Date is the minimum of all the table End Dates.

Appendix B. List of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Diagnosis Codes Used as Exclusion Criteria in Defining First Qualifying Diagnosis Events

Code	Description	Code Type
	Pulmonary Arterial Hypertension	
416.0	Primary pulmonary hypertension	ICD-9-CM
416.2	Chronic pulmonary embolism	ICD-9-CM
416.8	Other chronic pulmonary heart diseases	ICD-9-CM
416.9	Unspecified chronic pulmonary heart disease	ICD-9-CM
I27.0	Primary pulmonary hypertension	ICD-10-CM
I27.2	Other secondary pulmonary hypertension	ICD-10-CM
I27.20	Pulmonary hypertension, unspecified	ICD-10-CM
I27.21	Secondary pulmonary arterial hypertension	ICD-10-CM
I27.22	Pulmonary hypertension due to left heart disease	ICD-10-CM
I27.23	Pulmonary hypertension due to lung diseases and hypoxia	ICD-10-CM
I27.24	Chronic thromboembolic pulmonary hypertension	ICD-10-CM
I27.29	Other secondary pulmonary hypertension	ICD-10-CM
I27.8	Other specified pulmonary heart diseases	ICD-10-CM
I27.81	Cor pulmonale (chronic)	ICD-10-CM
I27.82	Chronic pulmonary embolism	ICD-10-CM
I27.83	Eisenmenger's syndrome	ICD-10-CM
I27.89	Other specified pulmonary heart diseases	ICD-10-CM
I27.9	Pulmonary heart disease, unspecified	ICD-10-CM
	Interstitial Lung Disease	
515	Postinflammatory pulmonary fibrosis	ICD-9-CM
516.0	Pulmonary alveolar proteinosis	ICD-9-CM
516.1	Idiopathic pulmonary hemosiderosis	ICD-9-CM
516.2	Pulmonary alveolar microlithiasis	ICD-9-CM
516.30	Idiopathic interstitial pneumonia, not otherwise specified	ICD-9-CM
516.31	Idiopathic pulmonary fibrosis	ICD-9-CM
516.32	Idiopathic non-specific interstitial pneumonitis	ICD-9-CM
516.33	Acute interstitial pneumonitis	ICD-9-CM
516.34	Respiratory bronchiolitis interstitial lung disease	ICD-9-CM
516.35	Idiopathic lymphoid interstitial pneumonia	ICD-9-CM
516.36	Cryptogenic organizing pneumonia	ICD-9-CM
516.37	Desquamative interstitial pneumonia	ICD-9-CM
516.4	Lymphangioleiomyomatosis	ICD-9-CM
516.5	Adult pulmonary Langerhans cell histiocytosis	ICD-9-CM
516.61	Neuroendocrine cell hyperplasia of infancy	ICD-9-CM
516.62	Pulmonary interstitial glycogenosis	ICD-9-CM
516.63	Surfactant mutations of the lung	ICD-9-CM
516.64	Alveolar capillary dysplasia with vein misalignment	ICD-9-CM
516.69	Other interstitial lung diseases of childhood	ICD-9-CM
516.8	Other specified alveolar and parietoalveolar pneumonopathies	ICD-9-CM
516.9	Unspecified alveolar and parietoalveolar pneumonopathy	ICD-9-CM
J84	Other interstitial pulmonary diseases	ICD-10-CM
J84.0	Alveolar and parieto-alveolar conditions	ICD-10-CM

Appendix B. List of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Diagnosis Codes Used as Exclusion Criteria in Defining First Qualifying Diagnosis Events

Code	Description	Code Type
J84.01	Alveolar proteinosis	ICD-10-CM
J84.02	Pulmonary alveolar microlithiasis	ICD-10-CM
J84.03	Idiopathic pulmonary hemosiderosis	ICD-10-CM
J84.09	Other alveolar and parieto-alveolar conditions	ICD-10-CM
J84.1	Other interstitial pulmonary diseases with fibrosis	ICD-10-CM
J84.10	Pulmonary fibrosis, unspecified	ICD-10-CM
J84.11	Idiopathic interstitial pneumonia	ICD-10-CM
J84.111	Idiopathic interstitial pneumonia, not otherwise specified	ICD-10-CM
J84.112	Idiopathic pulmonary fibrosis	ICD-10-CM
J84.113	Idiopathic non-specific interstitial pneumonitis	ICD-10-CM
J84.114	Acute interstitial pneumonitis	ICD-10-CM
J84.115	Respiratory bronchiolitis interstitial lung disease	ICD-10-CM
J84.116	Cryptogenic organizing pneumonia	ICD-10-CM
J84.117	Desquamative interstitial pneumonia	ICD-10-CM
J84.17	Other interstitial pulmonary diseases with fibrosis in diseases classified elsewhere	ICD-10-CM
J84.2	Lymphoid interstitial pneumonia	ICD-10-CM
J84.8	Other specified interstitial pulmonary diseases	ICD-10-CM
J84.81	Lymphangioleiomyomatosis	ICD-10-CM
J84.82	Adult pulmonary Langerhans cell histiocytosis	ICD-10-CM
J84.83	Surfactant mutations of the lung	ICD-10-CM
J84.84	Other interstitial lung diseases of childhood	ICD-10-CM
J84.841	Neuroendocrine cell hyperplasia of infancy	ICD-10-CM
J84.842	Pulmonary interstitial glycogenosis	ICD-10-CM
J84.843	Alveolar capillary dysplasia with vein misalignment	ICD-10-CM
J84.848	Other interstitial lung diseases of childhood	ICD-10-CM
J84.89	Other specified interstitial pulmonary diseases	ICD-10-CM
J84.9	Interstitial pulmonary disease, unspecified	ICD-10-CM

Appendix C. List of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Diagnosis Codes Used to Define First Qualifying Events in this Request

Code	Description	Code Type
	Pulmonary Arterial Hypertension	
I27.0	Primary pulmonary hypertension	ICD-10-CM
I27.2	Other secondary pulmonary hypertension	ICD-10-CM
I27.20	Pulmonary hypertension, unspecified	ICD-10-CM
I27.21	Secondary pulmonary arterial hypertension	ICD-10-CM
I27.22	Pulmonary hypertension due to left heart disease	ICD-10-CM
I27.23	Pulmonary hypertension due to lung diseases and hypoxia	ICD-10-CM
I27.24	Chronic thromboembolic pulmonary hypertension	ICD-10-CM
I27.29	Other secondary pulmonary hypertension	ICD-10-CM
I27.8	Other specified pulmonary heart diseases	ICD-10-CM
I27.81	Cor pulmonale (chronic)	ICD-10-CM
I27.82	Chronic pulmonary embolism	ICD-10-CM
I27.83	Eisenmenger's syndrome	ICD-10-CM
I27.89	Other specified pulmonary heart diseases	ICD-10-CM
I27.9	Pulmonary heart disease, unspecified	ICD-10-CM
	Interstitial Lung Disease	
J84	Other interstitial pulmonary diseases	ICD-10-CM
J84.0	Alveolar and parieto-alveolar conditions	ICD-10-CM
J84.01	Alveolar proteinosis	ICD-10-CM
J84.02	Pulmonary alveolar microlithiasis	ICD-10-CM
J84.03	Idiopathic pulmonary hemosiderosis	ICD-10-CM
J84.09	Other alveolar and parieto-alveolar conditions	ICD-10-CM
J84.1	Other interstitial pulmonary diseases with fibrosis	ICD-10-CM
J84.10	Pulmonary fibrosis, unspecified	ICD-10-CM
J84.11	Idiopathic interstitial pneumonia	ICD-10-CM
J84.111	Idiopathic interstitial pneumonia, not otherwise specified	ICD-10-CM
J84.112	Idiopathic pulmonary fibrosis	ICD-10-CM
J84.113	Idiopathic non-specific interstitial pneumonitis	ICD-10-CM
J84.114	Acute interstitial pneumonitis	ICD-10-CM
J84.115	Respiratory bronchiolitis interstitial lung disease	ICD-10-CM
J84.116	Cryptogenic organizing pneumonia	ICD-10-CM
J84.117	Desquamative interstitial pneumonia	ICD-10-CM
J84.17	Other interstitial pulmonary diseases with fibrosis in diseases classified elsewhere	ICD-10-CM
J84.2	Lymphoid interstitial pneumonia	ICD-10-CM
J84.8	Other specified interstitial pulmonary diseases	ICD-10-CM
J84.81	Lymphangioleiomyomatosis	ICD-10-CM
J84.82	Adult pulmonary Langerhans cell histiocytosis	ICD-10-CM
J84.83	Surfactant mutations of the lung	ICD-10-CM
J84.84	Other interstitial lung diseases of childhood	ICD-10-CM
J84.841	Neuroendocrine cell hyperplasia of infancy	ICD-10-CM
J84.842	Pulmonary interstitial glycogenosis	ICD-10-CM
J84.843	Alveolar capillary dysplasia with vein misalignment	ICD-10-CM
J84.848	Other interstitial lung diseases of childhood	ICD-10-CM
J84.89	Other specified interstitial pulmonary diseases	ICD-10-CM

Appendix C. List of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Diagnosis Codes Used to Define First Qualifying Events in this Request

Code	Description	Code Type
J84.9	Interstitial pulmonary disease, unspecified	ICD-10-CM
	Macrophage Activation Syndrome	
D76.1	Hemophagocytic lymphohistiocytosis	ICD-10-CM
D76.2	Hemophagocytic syndrome, infection-associated	ICD-10-CM
D76.3	Other histiocytosis syndromes	ICD-10-CM
	Adult-Onset Still's Disease	
M06.1	Adult-onset Still's disease	ICD-10-CM
	Systemic Juvenile Idiopathic Arthritis	
M08.2	Juvenile rheumatoid arthritis with systemic onset	ICD-10-CM
M08.20	Juvenile rheumatoid arthritis with systemic onset, unspecified site	ICD-10-CM
M08.21	Juvenile rheumatoid arthritis with systemic onset, shoulder	ICD-10-CM
M08.211	Juvenile rheumatoid arthritis with systemic onset, right shoulder	ICD-10-CM
M08.212	Juvenile rheumatoid arthritis with systemic onset, left shoulder	ICD-10-CM
M08.219	Juvenile rheumatoid arthritis with systemic onset, unspecified shoulder	ICD-10-CM
M08.22	Juvenile rheumatoid arthritis with systemic onset, elbow	ICD-10-CM
M08.221	Juvenile rheumatoid arthritis with systemic onset, right elbow	ICD-10-CM
M08.222	Juvenile rheumatoid arthritis with systemic onset, left elbow	ICD-10-CM
M08.229	Juvenile rheumatoid arthritis with systemic onset, unspecified elbow	ICD-10-CM
M08.23	Juvenile rheumatoid arthritis with systemic onset, wrist	ICD-10-CM
M08.231	Juvenile rheumatoid arthritis with systemic onset, right wrist	ICD-10-CM
M08.232	Juvenile rheumatoid arthritis with systemic onset, left wrist	ICD-10-CM
M08.239	Juvenile rheumatoid arthritis with systemic onset, unspecified wrist	ICD-10-CM
M08.24	Juvenile rheumatoid arthritis with systemic onset, hand	ICD-10-CM
M08.241	Juvenile rheumatoid arthritis with systemic onset, right hand	ICD-10-CM
M08.242	Juvenile rheumatoid arthritis with systemic onset, left hand	ICD-10-CM
M08.249	Juvenile rheumatoid arthritis with systemic onset, unspecified hand	ICD-10-CM
M08.25	Juvenile rheumatoid arthritis with systemic onset, hip	ICD-10-CM
M08.251	Juvenile rheumatoid arthritis with systemic onset, right hip	ICD-10-CM
M08.252	Juvenile rheumatoid arthritis with systemic onset, left hip	ICD-10-CM
M08.259	Juvenile rheumatoid arthritis with systemic onset, unspecified hip	ICD-10-CM
M08.26	Juvenile rheumatoid arthritis with systemic onset, knee	ICD-10-CM
M08.261	Juvenile rheumatoid arthritis with systemic onset, right knee	ICD-10-CM
M08.262	Juvenile rheumatoid arthritis with systemic onset, left knee	ICD-10-CM
M08.269	Juvenile rheumatoid arthritis with systemic onset, unspecified knee	ICD-10-CM
M08.27	Juvenile rheumatoid arthritis with systemic onset, ankle and foot	ICD-10-CM
M08.271	Juvenile rheumatoid arthritis with systemic onset, right ankle and foot	ICD-10-CM
M08.272	Juvenile rheumatoid arthritis with systemic onset, left ankle and foot	ICD-10-CM
M08.279	Juvenile rheumatoid arthritis with systemic onset, unspecified ankle and foot	ICD-10-CM
M08.28	Juvenile rheumatoid arthritis with systemic onset, vertebrae	ICD-10-CM
M08.29	Juvenile rheumatoid arthritis with systemic onset, multiple sites	ICD-10-CM

Appendix D. List of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Diagnosis Codes Used to Define Prior History of Macrophage Activation Syndrome in this Request

Code	Description	Code Type
	Macrophage Activation Syndrome	
288.4	Hemophagocytic syndromes	ICD-9-CM
D76.1	Hemophagocytic lymphohistiocytosis	ICD-10-CM
D76.2	Hemophagocytic syndrome, infection-associated	ICD-10-CM
D76.3	Other histiocytosis syndromes	ICD-10-CM

Appendix E. Specifications Defining Parameters for the Adult Population Used in this Request

This request used the Cohort Identification and Descriptive Analysis (CIDA) tool version 5.4.4 to calculate the proportion of pulmonary arterial hypertension, interstitial lung disease, and macrophage activation syndrome diagnoses among an adult population with adult onset still's disease after exposure to interleukin inhibitors in the Sentinel Distributed Database (SDD).

Query period: October 1, 2015 - March 31, 2018
Coverage: Medical and drug coverage
Enrollment required: 183 days
Enrollment gap: 45 days
Age groups: 17 to <65 years

	Event						Inclusion/Exclusion Criteria					Baseline Covariates		
Scenario	Event	Washout period	Incident with respect to:	Cohort definition	Censor enrollment at evidence of	Encounter caresetting	Group	Criteria	Encounter caresetting	Criteria evaluation window relative to index	Code days: number of instances the criteria should be found in baseline period	Covariate	Covariate caresetting	Covariate evaluation window relative to index
ADULT POPULATION														
1	Adult-Onset Still's Disease (AOSD) Diagnosis	--	--	All valid exposure episodes	Death, DP End Date, Query Period End Date	Any	PAH ILD	Exclusion	Any	Beginning of enrollment, -1	1	--	--	--
2	Pulmonary Arterial Hypertension (PAH)	--	--	First valid index date	Death, DP End Date, Query Period End Date	Any	PAH ILD	Exclusion	Any	Beginning of enrollment, -1	1	MAS	Any	Beginning of enrollment, -1
3	Interstitial Lung Disease (ILD)	--	--	First valid index date	Death, DP End Date, Query Period End Date	Any	PAH ILD	Exclusion	Any	Beginning of enrollment, -1	1	MAS	Any	Beginning of enrollment, -1
4	Macrophage Activation Syndrome (MAS)	--	--	First valid index date	Death, DP End Date, Query Period End Date	Any	PAH ILD	Exclusion	Any	Beginning of enrollment, -1	1	--	--	--

Appendix E. Specifications Defining Parameters for the Adult Population Used in this Request

This request used the Cohort Identification and Descriptive Analysis (CIDA) tool version 5.4.4 to calculate the proportion of pulmonary arterial hypertension, interstitial lung disease, and macrophage activation syndrome diagnoses among an adult population with adult onset still's disease after exposure to interleukin inhibitors in the Sentinel Distributed Database (SDD).

Query period: October 1, 2015 - March 31, 2018
Coverage: Medical and drug coverage
Enrollment required: 183 days
Enrollment gap: 45 days
Age groups: 17 to <65 years

	Event						Inclusion/Exclusion Criteria					Baseline Covariates		
Scenario	Event	Washout period	Incident with respect to:	Cohort definition	Censor enrollment at evidence of	Encounter caresetting	Group	Criteria	Encounter caresetting	Criteria evaluation window relative to index	Code days: number of instances the criteria should be found in baseline period	Covariate	Covariate caresetting	Covariate evaluation window relative to index
AOSD ADULT COHORT														
5	Pulmonary Arterial Hypertension (PAH)	--	--	First valid index date	Death, DP End Date, Query Period End Date	Any	AOSD	Inclusion	Any	Beginning of enrollment, -1	1	MAS	Any	Beginning of enrollment, -1
							PAH ILD	Exclusion for the AOSD Inclusion criteria	Any	Beginning of enrollment, -1	1			
6	Interstitial Lung Disease (ILD)	--	--	First valid index date	Death, DP End Date, Query Period End Date	Any	AOSD	Inclusion	Any	Beginning of enrollment, -1	1	MAS	Any	Beginning of enrollment, -1
							PAH ILD	Exclusion for the AOSD Inclusion criteria	Any	Beginning of enrollment, -1	1			
7	Macrophage Activation Syndrome (MAS)	--	--	First valid index date	Death, DP End Date, Query Period End Date	Any	AOSD	Inclusion	Any	Beginning of enrollment, -1	1	--	--	--
							PAH ILD	Exclusion for the AOSD Inclusion criteria	Any	Beginning of enrollment, -1	1			
8	Adult-Onset Still's Disease (AOSD) Second Diagnosis	--	--	First valid index date	Death, DP End Date, Query Period End Date	Any	AOSD	Inclusion	Any	Beginning of enrollment, -1	1	--	--	--
							PAH ILD	Exclusion for the AOSD Inclusion criteria	Any	Beginning of enrollment, -1	1			

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), ICD-10-CM, Healthcare Common Procedure Coding System (HCPCS), and Current Procedural Terminology (CPT) codes are provided by Optum360.

National Drug Codes (NDCs) are checked against First Data Bank's "National Drug Data File (NDDF®) Plus."

Appendix F. Specifications Defining Parameters for the Pediatric Population Used in this Request

This request used the Cohort Identification and Descriptive Analysis (CIDA) tool version 5.4.4 to calculate the proportion of pulmonary arterial hypertension, interstitial lung disease, and macrophage activation syndrome diagnoses among a pediatric poulation with systemic juvenile idiopathic arthritis after exposure to interleukin inhibitors in the Sentinel Distributed Database (SDD).

Query period: October 1, 2015 - March 31, 2018
Coverage: Medical and drug coverage
Enrollment required: 183 days
Enrollment gap: 45 days
Age groups: 6 months to <17 years

	Event						Inclusion/Exclusion Criteria					Baseline Covariates		
Scenario	Event	Washout period	Incident with respect to:	Cohort definition	Censor enrollment at evidence of	Encounter caresetting	Group	Criteria	Encounter caresetting	Criteria evaluation window relative to index	Code days: number of instances the criteria should be found in baseline period	Covariate	Covariate caresetting	Covariate evaluation window relative to index
PEDIATRIC POPULATION														
1	Systemic Juvenile Idiopathic Arthritis (SJIA) Diagnosis	--	--	All valid exposure episodes	Death, DP End Date, Query Period End Date	Any	PAH ILD	Exclusion	Any	Beginning of enrollment, -1	1	--	--	--
2	Pulmonary Arterial Hypertension (PAH)	--	--	First valid index date	Death, DP End Date, Query Period End Date	Any	PAH ILD	Exclusion	Any	Beginning of enrollment, -1	1	MAS	Any	Beginning of enrollment, -1
3	Interstitial Lung Disease (ILD)	--	--	First valid index date	Death, DP End Date, Query Period End Date	Any	PAH ILD	Exclusion	Any	Beginning of enrollment, -1	1	MAS	Any	Beginning of enrollment, -1
4	Macrophage Activation Syndrome (MAS)	--	--	First valid index date	Death, DP End Date, Query Period End Date	Any	PAH ILD	Exclusion	Any	Beginning of enrollment, -1	1	--	--	--

Appendix F. Specifications Defining Parameters for the Pediatric Population Used in this Request

This request used the Cohort Identification and Descriptive Analysis (CIDA) tool version 5.4.4 to calculate the proportion of pulmonary arterial hypertension, interstitial lung disease, and macrophage activation syndrome diagnoses among a pediatric poulation with systemic juvenile idiopathic arthritis after exposure to interleukin inhibitors in the Sentinel Distributed Database (SDD).

Query period: October 1, 2015 - March 31, 2018
Coverage: Medical and drug coverage
Enrollment required: 183 days
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Age groups: 6 months to <17 years

	Event						Inclusion/Exclusion Criteria					Baseline Covariates		
Scenario	Event	Washout period	Incident with respect to:	Cohort definition	Censor enrollment at evidence of	Encounter caresetting	Group	Criteria	Encounter caresetting	Criteria evaluation window relative to index	Code days: number of instances the criteria should be found in baseline period	Covariate	Covariate caresetting	Covariate evaluation window relative to index
SJIA PEDIATRIC COHORT														
5	Pulmonary Arterial Hypertension (PAH)	--	--	First valid index date	Death, DP End Date, Query Period End Date	Any	SJIA	Inclusion	Any	Beginning of enrollment, -1	1	MAS	Any	Beginning of enrollment, -1
							PAH ILD	Exclusion for the SJIA Inclusion criteria	Any	Beginning of enrollment, -1	1			
6	Interstitial Lung Disease (ILD)	--	--	First valid index date	Death, DP End Date, Query Period End Date	Any	SJIA	Inclusion	Any	Beginning of enrollment, -1	1	MAS	Any	Beginning of enrollment, -1
							PAH ILD	Exclusion for the SJIA Inclusion criteria	Any	Beginning of enrollment, -1	1			
7	Macrophage Activation Syndrome (MAS)	--	--	First valid index date	Death, DP End Date, Query Period End Date	Any	SJIA	Inclusion	Any	Beginning of enrollment, -1	1	--	--	--
							PAH ILD	Exclusion for the SJIA Inclusion criteria	Any	Beginning of enrollment, -1	1			
8	Systemic Juvenile Idiopathic Arthritis (SJIA) Second Diagnosis	--	--	First valid index date	Death, DP End Date, Query Period End Date	Any	SJIA	Inclusion	Any	Beginning of enrollment, -1	1	--	--	--
							PAH ILD	Exclusion for the SJIA Inclusion criteria	Any	Beginning of enrollment, -1	1			

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), ICD-10-CM, Healthcare Common Procedure Coding System (HCPCS), and Current Procedural Terminology (CPT) codes are provided by Optum360. National Drug Codes (NDCs) are checked against First Data Bank's "National Drug Data File (NDDF®) Plus."