Disclaimer

The following report 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, post market 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_wp087, Report 1

Request ID: cder_mpl1r_wp087

Request Description: The goal of this request was to examine the distribution of time between patients' first new central precocious puberty (CPP) diagnosis and Lupron Depot-Ped utilization in the Sentinel Distributed Database (SDD). This is report 1 of 2. Report 2 contains counts of individuals with well child visits in the SDD.

Sentinel Modular Program Tool Used: Cohort Identification and Descriptive Analysis tool, version 5.2.1

Data Source: Data from January 1, 2000 to October 31, 2017 from 17 Data Partners contributing to the SDD were included in this report. This request was distributed to Data Partners on March 29, 2018. Please see Appendix A for a list of the latest dates of available data for each Data Partner.

Study Design: This request used a retrospective cohort study. Results of the analysis were stratified by sex, sex and age group, and sex and year.

Event of Interest: The event of interest was members' first qualifying CPP diagnosis that occurred between January 1, 2000 and October 31, 2017 and was defined using International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-9-CM and ICD-10-CM) diagnosis codes. Three separate diagnosis criteria with varying levels of specificity were used to define CPP diagnosis; each of the three separate diagnosis criteria required only one of the listed diagnosis codes to qualify. Members could meet more than one diagnosis criterion. Please see Appendix B for specific diagnosis codes used to define CPP in this report.

Outcome of Interest: The outcome of interest was evidence of Lupron Depot-Ped utilization and was defined using National Drug Codes (NDCs), and Healthcare Common Procedure Coding System (HCPCS) codes. Please see Appendix C for a list of brand and generic drug names of medical products and Appendix D for specific procedure codes used to define Lupron Depot-Ped in this report.

Cohort Eligibility Criteria: Members included in the cohort were required to be continuously enrolled in plans with medical and drug coverage for at least 183 days prior to their index diagnosis, during which gaps in coverage of up to 45 days were allowed. The index diagnosis was defined as no evidence of a CPP diagnosis in any care setting in the previous 183 days. Members with evidence of Lupron Depot-Ped utilization during the same period were excluded. Members of the following age groups on the day of index diagnosis were included in the cohort: 0-4, 5-6, 7-8, 9-10, 11-12, and 13-18 years.

Follow-Up Time: Follow-up began on the day of the first CPP diagnosis and continued until the first occurrence of any of the following: 1) disenrollment; 2) the end date of the data provided by each Data Partner (see Appendix A); 3) death; 4) occurrence of the outcome.

Please see Appendix E for the specifications of parameters used in the analyses for this request.

Limitations: Algorithms to define events and outcomes may not have been validated. Measures in this request are subject to misclassification.

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.

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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. This is equivalent to the "RxAmt" value in the Sentinel Common Data Model.

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.

Code Days - indicates the number of times a condition occurs in a member's enrollment history during the lookback period. Multiple codes identified on the same day will only count once (i.e., count code days and not code instances).

Cohort Definition (drug/exposure) - indicates how the cohort will be defined: (1) 01: Cohort includes only the first valid treatment episode during the query period; (2) 02: Cohort includes all valid treatment episodes during the query period; (3) 03: 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.

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

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.

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) 0: Counts all occurrences of an HOI during an exposure episode; (1) 1: de-duplicates occurrences of the same HOI code and code type on the same day; (2) 2: de-duplicates occurrences of the same HOI group on the same day (e.g., de-duplicates at the group level).

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.

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

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

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.

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.

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 observation of the incident query code during follow-up requires truncation of valid treatment episodes. A value of Y indicates that the treatment episodes should be truncated at the first occurrence of an incident query code. A value of N indicates that the treatment episodes should not be truncated at the occurrence of the incident query code.

Users - number of members with exposure during the query period. Member must have no evidence of exposure(s) of interest (defined by incidence criteria) in the prior washout period. A user may only be counted once in a query period.

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.

*all terms may not be used in this report

**incident treatment episodes must be incident to both the exposure and the event

Table 1a. Summary of Central Precocious Puberty (CPP) Diagnosis and Subsequent Lupron Depot-Ped Use in the Sentinel Distributed Database (SDD) between January 1, 2000 and October 31, 2017, by Sex

	Incident CPP Diagnoses	Eligible Members	Incident CPP Diagnosis per 1,000 Eligible Members	Members with Lupron Depot-Ped Use following Incident CPP Diagnosis	Years at Risk since Incident CPP Diagnosis	Incidence Rate of Lupron Depot-Ped Use per 1,000 Years at Risk
Diagnosis Criterion 1*						
Female	93,240	17,299,977	5.39	3,201	274,985.4	11.64
Male	29,140	18,060,613	1.61	937	80,133.4	11.69
Diagnosis Criterion 2*						
Female	81,467	17,300,984	4.71	2,904	266,672.3	10.89
Male	25,626	18,060,917	1.42	870	77,684.4	11.20
Diagnosis Criterion 3*						
Female	93,364	17,299,923	5.40	3,203	275,076.9	11.64
Male	29,187	18,060,599	1.62	940	80,165.1	11.73

*Each of the three separate diagnosis criteria required only one of the diagnosis codes listed in Appendix B to qualify. Diagnosis criterion 2 was the most narrow definition of CPP and diagnosis criterion 3 was the most broad definition of CPP. Members could contribute to more than one diagnosis criterion; therefore, aggregation across diagnosis criteria is not advised.

Table 1b. Summary of Time between Central Precocious Puberty (CPP) Diagnosis and Lupron Depot-Ped Use in the Sentinel Distributed Database (SDD) between January 1, 2000 and October 31, 2017, by Sex

	Minimum (Days)	Quartile 1 (Days)	Median (Days)	Quartile 3 (Days)	Maximum (Days)	Mean (Days)
Diagnosis Criterion 1*						
Female	1	44	117	320	3,615	255.5
Male	1	29	73	212	5,290	191.9
Diagnosis Criterion 2*						
Female	1	45	122	351	3,615	269.8
Male	1	29	75	223	5,290	199.0
Diagnosis Criterion 3*						
Female	1	44	117	320	3,615	255.4
Male	1	28	73	211	5,290	191.3

*Each of the three separate diagnosis criteria required only one of the diagnosis codes listed in Appendix B to qualify. Diagnosis criterion 2 was the most narrow definition of CPP and diagnosis criterion 3 was the most broad definition of CPP. Members could contribute to more than one diagnosis criterion; therefore, aggregation across diagnosis criteria is not advised.

Table 2a. Summary of Central Precocious Puberty (CPP) Diagnosis and Subsequent Lupron Depot-Ped Use in the Sentinel Distributed Database (SDD) between January 1, 2000 and October 31, 2017, by Sex and Age Group

	Incident CPP Diagnoses	Eligible Members	Incident CPP Diagnosis per 1,000 Eligible Members	Members with Lupron Depot-Ped Use following Incident CPP Diagnosis	Years at Risk since Incident CPP Diagnosis	Incidence Rate of Lupron Depot-Ped Use per 1,000 Years at Risk
Diagnosis Criterion 1*						
Female						
0-4 years	15,986	5,872,930	2.72	309	50,619.6	6.10
5-6 years	15,403	4,089,613	3.77	712	45,967.3	15.49
7-8 years	34,757	4,195,668	8.28	1,523	99,769.3	15.27
9-10 years	19,149	4,271,701	4.48	509	55,400.7	9.19
11-12 years	4,854	4,345,261	1.12	100	14,079.6	7.10
13-18 years	3,091	7,971,096	0.39	48	9,148.9	5.25
Male						
0-4 years	1,361	6,174,636	0.22	38	4,112.5	9.24
5-6 years	1,820	4,292,454	0.42	75	5,211.0	14.39
7-8 years	5,942	4,405,197	1.35	228	16,837.5	13.54
9-10 years	6,095	4,499,584	1.35	363	16,215.6	22.39
11-12 years	6,460	4,563,036	1.42	151	17,283.9	8.74
13-18 years	7,462	8,287,108	0.90	82	20,472.9	4.01

Table 2a. Summary of Central Precocious Puberty (CPP) Diagnosis and Subsequent Lupron Depot-Ped Use in the Sentinel Distributed Database (SDD) between January 1, 2000 and October 31, 2017, by Sex and Age Group

	Incident CPP Diagnoses	Eligible Members	Incident CPP Diagnosis per 1,000 Eligible Members	Members with Lupron Depot-Ped Use following Incident CPP Diagnosis	Years at Risk since Incident CPP Diagnosis	Incidence Rate of Lupron Depot-Ped Use per 1,000 Years at Risk
Diagnosis Criterion 2*						
Female						
0-4 years	13,925	5,873,166	2.37	299	49,118.7	6.09
5-6 years	13,426	4,090,006	3.28	641	44,589.8	14.38
7-8 years	30,130	4,197,043	7.18	1,375	96,484.2	14.25
9-10 years	16,767	4,273,726	3.92	449	53,763.9	8.35
11-12 years	4,339	4,346,000	1.00	94	13,717.5	6.85
13-18 years	2,880	7,971,307	0.36	46	8,998.0	5.11
Male						
0-4 years	1,247	6,174,667	0.20	35	4,042.2	8.66
5-6 years	1,617	4,292,498	0.38	69	5,067.0	13.62
7-8 years	5,180	4,405,379	1.18	216	16,291.3	13.26
9-10 years	5,252	4,500,006	1.17	332	15,643.5	21.22
11-12 years	5,618	4,563,420	1.23	139	16,683.2	8.33
13-18 years	6,712	8,287,520	0.81	79	19,957.2	3.96

Table 2a. Summary of Central Precocious Puberty (CPP) Diagnosis and Subsequent Lupron Depot-Ped Use in the Sentinel Distributed Database (SDD) between January 1, 2000 and October 31, 2017, by Sex and Age Group

	Incident CPP Diagnoses	Eligible Members	Incident CPP Diagnosis per 1,000 Eligible Members	Members with Lupron Depot-Ped Use following Incident CPP Diagnosis	Years at Risk since Incident CPP Diagnosis	Incidence Rate of Lupron Depot-Ped Use per 1,000 Years at Risk
Diagnosis Criterion 3*						
Female						
0-4 years	15,992	5,872,928	2.72	309	50,623.5	6.10
5-6 years	15,408	4,089,606	3.77	711	45,971.7	15.47
7-8 years	34,778	4,195,647	8.29	1,524	99,781.4	15.27
9-10 years	19,162	4,271,649	4.49	510	55,413.7	9.20
11-12 years	4,865	4,345,242	1.12	101	14,087.5	7.17
13-18 years	3,159	7,971,085	0.40	48	9,199.1	5.22
Male						
0-4 years	1,364	6,174,636	0.22	38	4,115.3	9.23
5-6 years	1,822	4,292,451	0.42	75	5,211.2	14.39
7-8 years	5,947	4,405,196	1.35	228	16,840.6	13.54
9-10 years	6,099	4,499,577	1.36	363	16,218.3	22.38
11-12 years	6,466	4,563,022	1.42	153	17,287.6	8.85
13-18 years	7,489	8,287,098	0.90	83	20,492.0	4.05

*Each of the three separate diagnosis criteria required only one of the diagnosis codes listed in Appendix B to qualify. Diagnosis criterion 2 was the most narrow definition of CPP and diagnosis criterion 3 was the most broad definition of CPP. Members could contribute to more than one diagnosis criterion; therefore, aggregation across diagnosis criteria is not advised.

Table 3a. Summary of Central Precocious Puberty (CPP) Diagnosis and Subsequent Lupron Depot-Ped Use in the Sentinel Distributed Database (SDD) between January 1, 2000 and October 31, 2017, by Sex and Year

	Incident CPP Diagnoses	Eligible Members	Incident CPP Diagnosis per 1,000 Eligible Members	Members with Lupron Depot-Ped Use following Incident CPP Diagnosis	Years at Risk since Incident CPP Diagnosis	Incidence Rate of Lupron Depot-Ped Use per 1,000 Years at Risk
Diagnosis Criterion 1*						
Female						
2000	629	967,076	0.65	20	4,661.4	4.29
2001	1,151	1,065,971	1.08	25	8,385.4	2.98
2002	1,190	1,076,201	1.11	35	8,098.3	4.32
2003	1,238	1,067,671	1.16	32	8,680.5	3.69
2004	1,268	1,115,086	1.14	55	8,388.0	6.56
2005	1,278	1,146,648	1.11	61	7,850.1	7.77
2006	2,623	2,558,543	1.03	115	13,499.0	8.52
2007	3,699	2,974,988	1.24	177	16,797.7	10.54
2008	6,708	5,570,985	1.20	253	25,581.3	9.89
2009	9,070	5,732,997	1.58	327	31,226.6	10.47
2010	8,880	5,386,356	1.65	308	29,424.7	10.47
2011	8,695	5,085,801	1.71	289	26,866.6	10.76
2012	8,602	5,006,727	1.72	302	24,550.1	12.30
2013	9,125	5,191,293	1.76	301	22,060.0	13.64
2014	9,459	5,226,376	1.81	314	19,059.4	16.47
2015	9,194	5,174,852	1.78	314	13,399.3	23.43
2016	7,420	5,179,822	1.43	221	5,730.2	38.57
2017	3,011	3,847,779	0.78	52	726.7	71.56

Table 3a. Summary of Central Precocious Puberty (CPP) Diagnosis and Subsequent Lupron Depot-Ped Use in the Sentinel Distributed Database (SDD) between January 1, 2000 and October 31, 2017, by Sex and Year

	Incident CPP Diagnoses	Eligible Members	Incident CPP Diagnosis per 1,000 Eligible Members	Members with Lupron Depot-Ped Use following Incident CPP Diagnosis	Years at Risk since Incident CPP Diagnosis	Incidence Rate of Lupron Depot-Ped Use per 1,000 Years at Risk
Diagnosis Criterion 1*						
Male						
2000	124	1,008,501	0.12	*****	*****	7.56
2001	215	1,109,055	0.19	*****	*****	5.93
2002	237	1,120,980	0.21	*****	*****	1.91
2003	221	1,112,916	0.20	*****	*****	2.10
2004	257	1,163,789	0.22	12	1,748.6	6.86
2005	265	1,199,540	0.22	14	1,623.1	8.63
2006	607	2,679,486	0.23	36	2,980.1	12.08
2007	977	3,115,918	0.31	43	4,513.3	9.53
2008	2,069	5,835,567	0.35	78	7,371.9	10.58
2009	2,958	6,005,759	0.49	111	9,825.6	11.30
2010	2,908	5,644,706	0.52	110	9,468.7	11.62
2011	3,000	5,330,918	0.56	99	8,948.4	11.06
2012	2,921	5,249,731	0.56	91	8,051.9	11.30
2013	3,113	5,449,424	0.57	79	7,561.4	10.45
2014	3,307	5,489,244	0.60	107	6,627.5	16.14
2015	2,869	5,438,712	0.53	72	4,228.7	17.03
2016	2,141	5,446,456	0.39	49	1,650.1	29.70
2017	951	4,050,998	0.23	15	225.5	66.52

Table 3a. Summary of Central Precocious Puberty (CPP) Diagnosis and Subsequent Lupron Depot-Ped Use in the Sentinel Distributed Database (SDD) between January 1, 2000 and October 31, 2017, by Sex and Year

	Incident CPP Diagnoses	Eligible Members	Incident CPP Diagnosis per 1,000 Eligible Members	Members with Lupron Depot-Ped Use following Incident CPP Diagnosis	Years at Risk since Incident CPP Diagnosis	Incidence Rate of Lupron Depot-Ped Use per 1,000 Years at Risk
Diagnosis Criterion 2*						
Female						
2000	629	967,076	0.65	20	4,661.4	4.29
2001	1,151	1,065,971	1.08	25	8,385.4	2.98
2002	1,190	1,076,201	1.11	35	8,098.3	4.32
2003	1,238	1,067,671	1.16	32	8,680.5	3.69
2004	1,268	1,115,086	1.14	55	8,388.0	6.56
2005	1,278	1,146,648	1.11	61	7,850.1	7.77
2006	2,623	2,558,543	1.03	115	13,499.0	8.52
2007	3,699	2,974,988	1.24	177	16,797.7	10.54
2008	6,708	5,570,985	1.20	253	25,581.3	9.89
2009	9,070	5,732,997	1.58	327	31,226.6	10.47
2010	8,880	5,386,356	1.65	308	29,424.7	10.47
2011	8,695	5,085,801	1.71	289	26,866.6	10.76
2012	8,602	5,006,727	1.72	302	24,550.1	12.30
2013	9,125	5,191,293	1.76	301	22,060.0	13.64
2014	9,459	5,226,376	1.81	314	19,059.4	16.47
2015	7,470	5,175,040	1.44	242	11,344.0	21.33
2016	254	5,182,423	0.05	30	172.2	174.22
2017	128	3,854,903	0.03	18	26.9	669.14

Table 3a. Summary of Central Precocious Puberty (CPP) Diagnosis and Subsequent Lupron Depot-Ped Use in the Sentinel Distributed Database (SDD) between January 1, 2000 and October 31, 2017, by Sex and Year

	Incident CPP Diagnoses	Eligible Members	Incident CPP Diagnosis per 1,000 Eligible Members	Members with Lupron Depot-Ped Use following Incident CPP Diagnosis	Years at Risk since Incident CPP Diagnosis	Incidence Rate of Lupron Depot-Ped Use per 1,000 Years at Risk
Diagnosis Criterion 2*						
Male						
2000	124	1,008,501	0.12	*****	*****	7.56
2001	215	1,109,055	0.19	*****	*****	5.93
2002	237	1,120,980	0.21	*****	*****	1.91
2003	221	1,112,916	0.20	*****	*****	2.10
2004	257	1,163,789	0.22	12	1,748.6	6.86
2005	265	1,199,540	0.22	14	1,623.1	8.63
2006	607	2,679,486	0.23	36	2,980.1	12.08
2007	977	3,115,918	0.31	43	4,513.3	9.53
2008	2,069	5,835,567	0.35	78	7,371.9	10.58
2009	2,958	6,005,759	0.49	111	9,825.6	11.30
2010	2,908	5,644,706	0.52	110	9,468.7	11.62
2011	3,000	5,330,918	0.56	99	8,948.4	11.06
2012	2,921	5,249,731	0.56	91	8,051.9	11.30
2013	3,113	5,449,424	0.57	79	7,561.4	10.45
2014	3,307	5,489,244	0.60	107	6,627.5	16.14
2015	2,332	5,438,775	0.43	57	3,595.8	15.85
2016	85	5,447,296	0.02	*****	*****	129.39
2017	30	4,053,182	0.01	*****	*****	925.93

Table 3a. Summary of Central Precocious Puberty (CPP) Diagnosis and Subsequent Lupron Depot-Ped Use in the Sentinel Distributed Database (SDD) between January 1, 2000 and October 31, 2017, by Sex and Year

	Incident CPP Diagnoses	Eligible Members	Incident CPP Diagnosis per 1,000 Eligible Members	Members with Lupron Depot-Ped Use following Incident CPP Diagnosis	Years at Risk since Incident CPP Diagnosis	Incidence Rate of Lupron Depot-Ped Use per 1,000 Years at Risk
Diagnosis Criterion 3*						
Female						
2000	629	967,076	0.65	20	4,661.4	4.29
2001	1,151	1,065,971	1.08	25	8,385.4	2.98
2002	1,190	1,076,201	1.11	35	8,098.3	4.32
2003	1,238	1,067,671	1.16	32	8,680.5	3.69
2004	1,268	1,115,086	1.14	55	8,388.0	6.56
2005	1,278	1,146,648	1.11	61	7,850.1	7.77
2006	2,623	2,558,543	1.03	115	13,499.0	8.52
2007	3,699	2,974,988	1.24	177	16,797.7	10.54
2008	6,708	5,570,985	1.20	253	25,581.3	9.89
2009	9,070	5,732,997	1.58	327	31,226.6	10.47
2010	8,880	5,386,356	1.65	308	29,424.7	10.47
2011	8,695	5,085,801	1.71	289	26,866.6	10.76
2012	8,602	5,006,727	1.72	302	24,550.1	12.30
2013	9,125	5,191,293	1.76	301	22,060.0	13.64
2014	9,459	5,226,376	1.81	314	19,059.4	16.47
2015	9,222	5,174,848	1.78	314	13,428.8	23.38
2016	7,487	5,179,742	1.45	222	5,784.7	38.38
2017	3,040	3,847,658	0.79	53	734.2	72.19

Table 3a. Summary of Central Precocious Puberty (CPP) Diagnosis and Subsequent Lupron Depot-Ped Use in the Sentinel Distributed Database (SDD) between January 1, 2000 and October 31, 2017, by Sex and Year

	Incident CPP Diagnoses	Eligible Members	Incident CPP Diagnosis per 1,000 Eligible Members	Members with Lupron Depot-Ped Use following Incident CPP Diagnosis	Years at Risk since Incident CPP Diagnosis	Incidence Rate of Lupron Depot-Ped Use per 1,000 Years at Risk
Diagnosis Criterion 3*						
Male						
2000	124	1,008,501	0.12	*****	*****	7.56
2001	215	1,109,055	0.19	*****	*****	5.93
2002	237	1,120,980	0.21	*****	*****	1.91
2003	221	1,112,916	0.20	*****	*****	2.10
2004	257	1,163,789	0.22	12	1,748.6	6.86
2005	265	1,199,540	0.22	14	1,623.1	8.63
2006	607	2,679,486	0.23	36	2,980.1	12.08
2007	977	3,115,918	0.31	43	4,513.3	9.53
2008	2,069	5,835,567	0.35	78	7,371.9	10.58
2009	2,958	6,005,759	0.49	111	9,825.6	11.30
2010	2,908	5,644,706	0.52	110	9,468.7	11.62
2011	3,000	5,330,918	0.56	99	8,948.4	11.06
2012	2,921	5,249,731	0.56	91	8,051.9	11.30
2013	3,113	5,449,424	0.57	79	7,561.4	10.45
2014	3,307	5,489,244	0.60	107	6,627.5	16.14
2015	2,876	5,438,711	0.53	72	4,237.5	16.99
2016	2,175	5,446,435	0.40	51	1,672.2	30.50
2017	957	4,050,954	0.24	16	226.2	70.73

*Each of the three separate diagnosis criteria required only one of the diagnosis codes listed in Appendix B to qualify. Diagnosis criterion 2 was the most narrow definition of CPP and diagnosis criterion 3 was the most broad definition of CPP. Members could contribute to more than one diagnosis criterion; therefore, aggregation across diagnosis criteria is not advised.

*****Data are not presented in these cells due to a small sample size or to assure a small cell cannot be recalculated through the cells presented.

Appendix A. Dates of Available Data for Each Data Partner (DP) as of Request Distribution Date (March 29, 2018)

DP ID	DP Start Date[1]	DP End Date[1]
DP01	01/01/2004	10/31/2017
DP02	01/01/2000	08/31/2017
DP03	01/01/2005	08/25/2017
DP04	01/01/2000	07/31/2017
DP05	01/01/2000	07/31/2017
DP06	06/01/2007	07/31/2017
DP07	01/01/2006	07/31/2017
DP08	01/01/2000	07/31/2017
DP09	01/01/2008	06/30/2017
DP10	01/01/2000	06/30/2017
DP11	01/01/2008	03/31/2017
DP12	01/01/2000	12/31/2016
DP13	01/01/2012	06/30/2016
DP14	01/01/2010	12/31/2015
DP15	01/01/2000	10/31/2015
DP16	01/01/2000	05/31/2015
DP17	01/01/2000	10/31/2014

[1]The start and end dates are based on the minimum and maximum dates within each DP. The month with the maximum date must have at least 80% of the number of records in the previous month.

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 to Define Central Precocious Puberty in this Request

Code	Description	Code Type	Code Category
	Diagnosis Criterion 1*		
259.1	Precocious sexual development and puberty, not elsewhere classified	ICD-9-CM	Diagnosis
E30.1	Precocious puberty	ICD-10-CM	Diagnosis
E30.8	Other disorders of puberty	ICD-10-CM	Diagnosis
	Diagnosis Criterion 2*		
259.1	Precocious sexual development and puberty, not elsewhere classified	ICD-9-CM	Diagnosis
E22.8	Other hyperfunction of pituitary gland	ICD-10-CM	Diagnosis
	Diagnosis Criterion 3*		
259.1	Precocious sexual development and puberty, not elsewhere classified	ICD-9-CM	Diagnosis
E30.1	Precocious puberty	ICD-10-CM	Diagnosis
E30.8	Other disorders of puberty	ICD-10-CM	Diagnosis
E22.8	Other hyperfunction of pituitary gland	ICD-10-CM	Diagnosis

*Members were required to have only one of the listed diagnosis codes to fulfill each respective diagnosis criterion

Appendix C. List of Generic and Brand Drug Names of Medical Products Used to Define Lupron Depot-Ped in this Request

Generic Name	Brand Name
LEUPROLIDE ACETATE	Lupron Depot-Ped
LEUPROLIDE ACETATE	Lupron Depot-Ped (3 month)

Appendix D. List of Healthcare Common Procedure Coding System (HCPCS) Procedure Codes Used to Define Lupron Depot-Ped in this Request

Code	Description	Code Type	Code Category
C9430	Leuprolide acetate, per 1 mg, brand name	HCPCS	Procedure
J1950	Injection, leuprolide acetate (for depot suspension), per 3.75 mg	HCPCS	Procedure
J9217	Leuprolide acetate (for depot suspension), 7.5 mg	HCPCS	Procedure
J9218	Leuprolide acetate, per 1 mg	HCPCS	Procedure

Appendix E. Parameter Specifications in this Request

This request used the Cohort Identification and Descriptive Analysis (CIDA) tool, version 5.2.1, to examine the distribution of time between first central precocious puberty (CPP) diagnosis and first Lupron Depot-Ped utilization in the Sentinel Distributed Database (SDD).

Query Period: January 1, 2000 to October 31, 2017
Enrollment Gap: 45 Days
Age Groups: 0-4, 5-6, 7-8, 9-10, 11-12, 13-18 years
Enrollment Requirement: 183 Days
Coverage Requirement: Medical and Drug Coverage
Results Stratified by: Sex, Age by Sex, Year by Sex

	Event							Inclusion Criteria				Outcome		
Scenario	Index Event	Diagnosis Criteria	Care Setting	Washout (Days)	Intention to Treat (Days)	Cohort Definition	Censor at Death	Inclusion	Care Setting	Code Days	Lookback Period	Outcome	Washout (Days)	Blackout Period (Days)
1	CPP Female only	1	Any	183	7,000	Retain first valid diagnosis only	Yes	---	---	---	---	Lupron Depot-Ped	183	0
2	CPP Male only	1	Any	183	7,000	Retain first valid diagnosis only	Yes	---	---	---	---	Lupron Depot-Ped	183	0
3	CPP Female only	2	Any	183	7,000	Retain first valid diagnosis only	Yes	---	---	---	---	Lupron Depot-Ped	183	0
4	CPP Male only	2	Any	183	7,000	Retain first valid diagnosis only	Yes	---	---	---	---	Lupron Depot-Ped	183	0
5	CPP Female only	3	Any	183	7,000	Retain first valid diagnosis only	Yes	---	---	---	---	Lupron Depot-Ped	183	0
6	CPP Male only	3	Any	183	7,000	Retain first valid diagnosis only	Yes	---	---	---	---	Lupron Depot-Ped	183	0

International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-9-CM and ICD-10-CM), International Classification of Diseases, Tenth Revision, Procedure Coding System (ICD-10-PCS), Healthcare Common Procedure Coding System (HCPCS), and Current Procedural Terminology, Fourth Edition (CPT-4) codes are provided by Optum360.

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