Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	April 4, 2011
To:	Lisa L. Mathis M.D., Associate Director Pediatric and Maternal Health Staff (PMHS) Office of New Drugs (OND) and M. Dianne Murphy, M.D., Director Office of Pediatric Therapeutics (OPT), OC and Susan Walker, M.D., F.A.A.D., Director, Division of Dermatology and Dental Products (DDDP), OND
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From:	Namita Kothary, Pharm.D., Safety Evaluator, DPV I
Subject:	Update on malignancies in children
Drug Name(s):	Elidel (pimecrolimus) Cream Protopic (tacrolimus) Ointment
Application Type/Number:	NDA 21-302 NDA 50-777
Applicant/sponsor:	Novartis Astellas
OSE RCM #:	2011-320

1 INTRODUCTION

In preparation for an upcoming Pediatric Advisory Committee (PAC) on May 16, 2011, the Office of Pediatric Therapeutics (OPT) requested that the Division of Pharmacovigilance I (DPV I) provide updated case counts for malignancies reported with the use of topical calcineurin inhibitors (TCI) pimecrolimus (PIM) and topical tacrolimus (tTAC) in children. Cases of pediatric malignancies reported with TCI use have been described in previous post-marketing safety reviews and presented to the PAC on multiple occasions.[1-8] The most recent presentation of pediatric malignancy cases in AERS to the PAC was in March 2010. At this meeting, the PAC requested that the FDA complete a literature review of malignancies reported with TCIs, which will be presented at the upcoming May 16, 2011 PAC. Since we continue to receive new malignancy cases and follow-up information for previously identified cases in AERS, this review provides updated total case counts for the 72 pediatric malignancies reported following TCI use, including a summary of the 15 cases not described in previous post-marketing safety reviews.

Following the approval of tTAC ointment (Protopic, NDA 50-777) on December 8, 2000 and PIM cream (Elidel, NDA 21-302) on December 13, 2001 for the treatment of atopic dermatitis, a Boxed Warning was added in January 2006 to both product labels.[9,10] The Boxed Warning contains information regarding the potential risk for malignancies, recommendations to avoid continuous long-term use, and a limitation on the indication to decrease use in children younger than two years old. Additionally, both products have ongoing pediatric registries to assess the potential risk of malignancies.

2 METHODS AND MATERIALS

Case definition[11-13]

We analyzed cases based on the reported adverse event terms as well as information provided in the case narratives. We used the following inclusion and exclusion criteria to develop the pediatric malignancy case series.

Inclusion criteria

- We included cases that reported an age of 0-16 years or cases that indicated the adverse event occurred in a "child," "infant," "pediatric patient," etc.
- We included cases that reported a malignancy or cancer.
- We also included cases that reported an uncontrolled growth of cells that results in lack of differentiation, local tissue invasion, or metastasis.
- We also included "brain tumors" and other tumors affecting the central nervous system as cancers because they can be life-threatening or fatal, and have the potential to affect normal tissue and function, regardless of whether or not they invade local tissue or metastasize.

Exclusion criteria

- We excluded cases in which the adverse events occurred in adults or cases that did not indicate the adverse event occurred in a "child," "infant," "pediatric patient," etc.
- We excluded cases that reported benign, non-malignant, or unspecified "tumors" or "neoplasms" that did not have the potential to affect surrounding normal tissue and function.
- We excluded cases that reported pre-malignant conditions.
- We excluded cases that did not report a definitive diagnosis of malignancy.

AERS search strategy

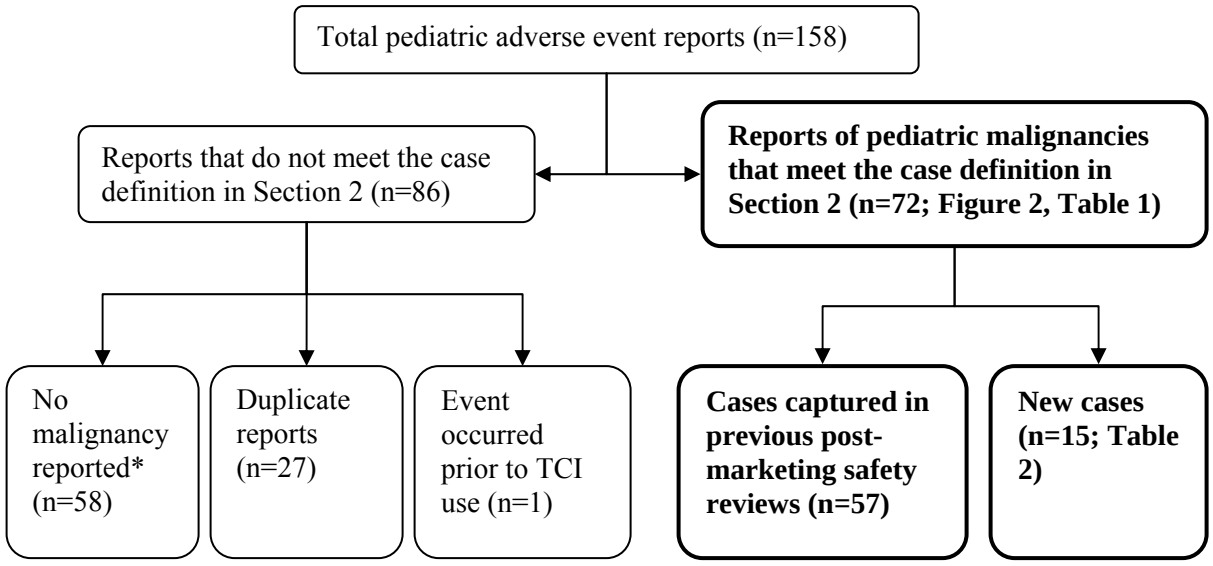
In addition to summarizing new pediatric malignancy cases, the purpose of this review is to provide cumulative totals for pediatric malignancies reported with TCI use. Since we continue to receive follow-up information in AERS that may change the classification of malignancy cases captured in previous post-marketing safety reviews, we did not limit the time period (i.e. we retrieved cases from market approval to March 4, 2011). Additionally, we did not limit the search by age because we wanted to retrieve cases that did not report a specific age from 0-16 years, but did report the adverse event occurring in a child or pediatric patient (i.e. the AERS data field for age contains a null value). Therefore, we searched AERS on March 4, 2011 using the following criteria:

- Time period: from market approval to March 4, 2011
- PIM drug terms: pimecrolimus and Elidel (including associated trade, active ingredient, and verbatim names), NDA 21302
- tTAC drug terms: Protopic (including associated trade and verbatim names), NDA 50777 *(Note: tacrolimus was not searched as an active ingredient since there are two other dosage forms available, including oral and injectable tacrolimus)*
- MedDRA adverse event search terms: Neoplasms benign, malignant, and unspecified-including cysts and polyps (SOC)

3 RESULTS

The AERS search retrieved 503 adverse event reports under the Neoplasms benign, malignant, and unspecified- including cysts and polyps (SOC) for all ages. We excluded 345 reports because the report indicated the adverse event occurred in an adult (309) or we were unable to determine the age based on the information provided (36). The remaining 158 reports were for children 0-16 years old or pediatric patients (age unspecified, but reported as "child" or "pediatric"). Figure 1 describes the disposition of the 158 pediatric reports based on the case definition in Section 2, and takes into account both the new malignancy cases and follow-up information received for cases captured in previous post-marketing safety reviews.

Figure 1. Results of the AERS search for malignancy cases reported with TCI use in children, initially received by the FDA from market approval to March 4, 2011



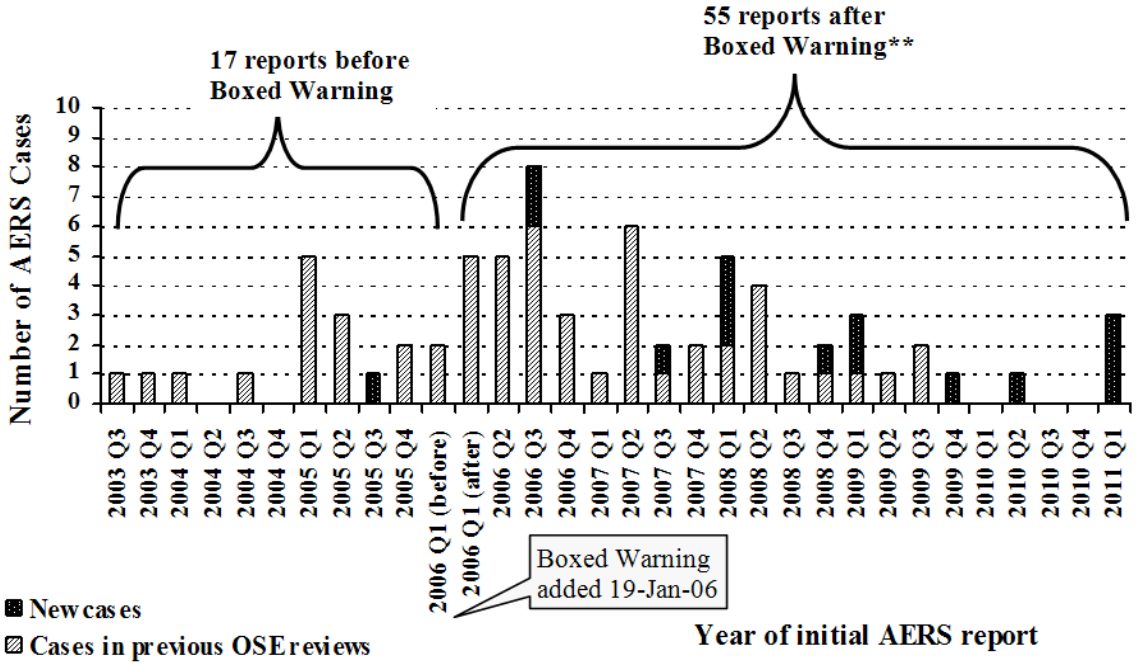
*These include reports of warts/verruca (34), mistakenly checked box for malignancy on form (3), possible unconfirmed lymphoma (3), dysplastic nevus (2), melanocytic nevus (2), benign skin tumor (1), congenital anomaly including cyst + lymphangioma (1), dermatofibroma (1), facial tumor (1), granuloma (1), hemangioma (1), infected epidermal cyst (1), infected epidermal cyst + verruca vulgaris (1), myasthenic syndrome (1), probable spitz nevus (1), skin atheroma (1), thyroglossal cyst (1), "tumor" (1), unspecified lymphoproliferative disorder (1)

Pediatric Malignancies (n=72; 57 captured in previous reviews, 15 new cases)

Based on the case definition in Section 2, we identified 72 unduplicated cases of pediatric malignancies reported with TCI use. Since 57 of the 72 cases are discussed in previous post-marketing safety reviews, these cases will not be discussed in this document. However, these 57 cases are included in the total case counts below (Figure 2 and Table 1). The remaining 15 cases are new cases and are discussed in additional detail (Table 2).

In order to provide the PAC with cumulative up-to-date totals, Figure 2 and Table 1 summarize the total current AERS case counts for pediatric malignancies reported with TCI use. Figure 2 and Table 1 account for both new malignancy cases and follow-up information received for cases captured in previous post-marketing safety reviews.

Figure 2. Pediatric malignancy cases reported with TCI use in AERS meeting the case definition in Section 2. Initially received by the FDA from market approval to March 4, 2011 (n=72)*



* Total case counts reflect the information we have to-date for these cases and may not match previous post-marketing safety reviews.

** Two new cases were identified and captured in the total counts; however, these cases may be reclassified pending additional information. One case of melanoma (2008 Q1) may be a duplicate of ISR 5850928 (captured in a previous OSE review); however, we do not have sufficient information at this time to reconcile the cases. Furthermore, the sponsor is seeking additional information and clarification for the case that reported an unspecified skin cancer (2011 Q1).

Table 1. Summary of pediatric malignancy cases in AERS meeting the case definition in Section 2 reported with TCI use, received by the FDA from market approval to March 4, 2011 (n=72)*

	Total cases = new cases + previously captured cases	Cases captured in previous OSE reviews	New cases
Total pediatric malignancies	**72**	**57**	**15**
Lymphomas	**N=25**	**N=21**	**N=4**
B-cell lymphoma	**5**	**4** *(Both-1, PIM-1, tTAC-2)*	**1** *(PIM-1)*
Hodgkin's Disease	**4**	**3** *(PIM-3)*	**1** *(PIM-1)*
Lymphoblastic lymphoma	**4**	**4** *(PIM-3, tTAC-1)*	
Cutaneous T-cell lymphoma (including mycosis fungoides and Sezary syndrome)	**4**	**3** *(tTAC-3)*	**1** *(tTAC-1)*
Non-Hodgkin's lymphoma	**3**	**2** *(PIM-2)*	**1** *(PIM-1)*
Anaplastic large cell lymphoma	**3**	**3** *(PIM-2, tTAC-1)*	
Malignant lymphoma	**1**	**1** *(PIM-1)*	
Cutaneous T-cell and B-cell lymphoma	**1**	**1** *(tTAC-1)*	
Leukemias	**N=25**	**N=19**	**N=6**
Acute lymphocytic leukemia (ALL)	**19**	**14** *(Both-1, PIM-10, tTAC-3)*	**5** *(PIM- 4, tTAC-1)*
Acute myeloid leukemia (AML)	**2**	**2** *(PIM-2)*	
Leukemia	**2**	**1** *(tTAC-1)*	**1** *(PIM-1)*
Chronic myeloid leukemia (CML)	**1**	**1** *(Both-1)*	
T-cell leukemia	**1**	**1** *(tTAC-1)*	
Skin Malignancies	**N=8**	**N=6**	**N=2**
Melanoma**	**5**	**4** *(Both-1, PIM-1, tTAC-2)*	**1** *(Both-1)*
Basal cell carcinoma	**1**	**1** *(Both-1)*	
Cutaneous myoepithelial neoplasm	**1**	**1** *(PIM-1)*	
Skin cancer**	**1**		**1** *(PIM-1)*
Other	**N=14**	**N=11**	**N=3**
Brain tumor	**2**	**2** *(PIM-2)*	
Hepatoblastoma	**2**	**2** *(PIM-1, tTAC-1)*	
Rhabdomyosarcoma	**2**	**1** *(PIM-1)*	**1** *(PIM-1)*
Wilm's tumor	**2**	**2** *(PIM-2)*	
Glioneuronal tumor	**1**	**1** *(tTAC-1)*	
Lung cancer	**1**	**1** *(Both-1)*	
Neuroblastoma	**1**	**1** *(tTAC-1)*	
Angiosarcoma	**1**	**1** *(tTAC-1)*	
Nephroblastoma	**1**		**1** *(tTAC-1)*
Pituitary microadenoma	**1**		**1** *(PIM-1)*

* Total case counts reflect the information we have to-date for these cases and may not match previous post-marketing safety reviews.

** Two new cases were identified and captured in the total counts; however, these cases may be reclassified pending additional information. One case of melanoma may be a duplicate of ISR 5850928 (captured in a previous OSE review); however, we do not have sufficient information at this time to reconcile the cases. Furthermore, the sponsor is seeking additional information and clarification for the case that reported an unspecified skin cancer.

Table 2 summarizes information from the 15 new cases of pediatric malignancies reported with TCI use. Additionally, Appendix A contains line-listing summaries of these 15 cases.

Table 2. Characteristics of new pediatric malignancy cases in AERS reported with the use of TCI, received by the FDA from market approval to March 4, 2011 (n=15)				
Origin	US (11)	Foreign (4)		
Initial report year	2005 (1) 2009 (3)	2006 (2) 2010 (1)	2007 (1) 2011 (3)	2008 (4)
Report type	Expedited (14)	Direct (1)		
Gender	Male (9)	Female (5)	Unknown (1)	
Age at time of event (n=10)*	Mean: 5.6 years	Median: 3.5 years	Range: 11 months - 15 years	
Age at start of therapy	< 2 years (4)	≥ 2 years (3)	Unknown (8)	
Drug	PIM (11)	tTAC (3)	PIM and tTAC (1)	
PIM / tTAC dosing	2x/day (1) Unknown (12)	1x/day (1)	2x/day, then every other day (1)	
Duration of therapy	8 days (1) "Several years" (1)	38 days (1) Unknown (11)	3 months (1)	
Time to event from start of therapy (n=6)	Mean: 1.6 years	Median: 1.3 years	Range: 3 months – 3.9 yrs	
Indications**	Atopic dermatitis (5) Rash + infantile acne (1)		Eczema (2) Unknown (6)	Dermatitis (1)
Malignancy[#]	Leukemias: Lymphomas: Skin malignancies: Other:	ALL (5), Unspecified leukemia (1) Hodgkin's Disease (1), B-cell lymphoma (1), Lymphoma (1), Cutaneous T-cell lymphoma (1) Melanoma (1), Unspecified skin cancer (1) Nephroblastoma (1), Pituitary microadenoma (1), Rhabdomyosarcoma (1)		
Primary Outcome	Life-threatening (3) "Other" Serious / Medically Significant (10)		Hospitalization (1) No serious outcome reported (1)	
Action taken for TCI	Discontinued (2)	Continued (1)	Unknown (12)	
Intervention *(more than one is possible per case)*	Chemotherapy (7) Unspecified (1)	Radiation (1) Unknown (7)	Transfusion (1)	
Event resolution	Improved (3)	Did not improve (1)	Eventual outcome unknown (11)	

* The remaining five cases reported events occurring in a child (2), pediatric patient (2), or minor (1).

** PIM and tTAC are only FDA approved for the treatment of atopic dermatitis (may also be called eczema)

[#] Two new cases were identified; however, these cases may be reclassified pending additional information. One case of melanoma may be a duplicate of ISR 5850928 (captured in a previous OSE review); however, we do not have sufficient information at this time to reconcile the cases. Furthermore, the sponsor is seeking additional information and clarification for the case that reported an unspecified skin cancer.

4 DISCUSSION / CONCLUSION

We identified 15 cases of new malignancies; however, only four of these cases were reported to the FDA after the March 2010 PAC meeting. The remaining 11 cases were reported to the FDA prior to the March 2010 PAC and were retrieved in this search because they contained null values in the AERS age field. In general, the majority of the 15 new cases provided limited information (dosing information, duration of therapy, time to event, clinical outcomes, etc.) making it difficult to assess the cases. Five cases reported ALL, which is the most commonly reported pediatric malignancy in the 15 new cases. This is consistent with the previous post-marketing safety reviews in which ALL was the most commonly reported pediatric malignancy. Leukemias are the most common childhood cancer in the US and account for approximately 31% of all cancer cases in children <15 years old; ALL represents 78% of all leukemias in this age group. The incidence of ALL is approximately 39.9 per million US children <15 years old.[14,15] The remaining 10 cases were single reports of the following malignancies: unspecified leukemia, Hodgkin's disease, B-cell lymphoma, lymphoma, cutaneous T-cell lymphoma, melanoma, unspecified skin cancer, nephroblastoma, pituitary microadenoma, and rhabdomyosarcoma. Although we identified two new cases of skin malignancies (melanoma-1, unspecified skin cancer-1); we have insufficient information to classify these cases at the present time. The case of melanoma may be a duplicate of a melanoma case described in a previous post-marketing safety review (ISR 5850928); however, we do not have sufficient information at this time to reconcile the two cases. Furthermore, the sponsor is seeking additional information and clarification for the case that reported an unspecified skin cancer.

Overall, the pediatric malignancies we identified are consistent with those described in previous post-marketing safety reviews. Taking into account the new malignancies identified in this review as well as the malignancies identified in previous post-marketing safety reviews, these cases support the previously identified potential safety signal for malignancies reported with TCI use. However, the precise role these TCIs play is unknown. In general, the information provided in spontaneous post-marketing case reports is not sufficient to determine causality (i.e. information regarding the clinical course, details regarding drug exposure, the role of the underlying diseases, and other contributing factors may be unknown). Additionally, malignancies may be associated with a long latency period making it difficult to attribute the adverse event to a drug, particularly in cases reporting a relatively short time to event onset.

Based on the new pediatric malignancy cases discussed in this review, our conclusions are consistent with the previous OSE post-marketing safety reviews. Therefore, we have no additional recommendations. Please refer to the January 8, 2010 post-marketing safety review for details regarding our previous recommendations.

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6 APPENDICES

Appendix A. Line listing of new pediatric malignancy cases in AERS reported with TCI use, received by the FDA from market approval to March 4, 2011 (n=15)

6.1 APPENDIX A. LINE LISTING OF NEW PEDIATRIC MALIGNANCY CASES IN AERS REPORTED WITH TCI USE, RECEIVED BY THE FDA FROM MARKET APPROVAL TO MARCH 4, 2011 (N=15)

ISR#	Report Source, Type, Initial FDA received date	Age at time of event (years) / Gender (Age <2 at time of Rx?)	Primary Outcomes	TCI: Dosing, Duration of therapy / Application site	Indication	Reported Malignancy (Diagnostic tests)	Time to event from start of therapy	Was the TCI discontinued ? / Did the event improve?	Was medical intervention required?	Comments
1. 5049490	US, D 2006 Q3	1 / M (Yes)	---	PIM: 1x/day for 8 days / ---	Atopic dermatitis	***ALL*** (---)	~1.3 years	Yes / Yes	---	
2. 6707940	Netherlands, E 2010 Q2	Child / M (---)	OT	tTAC: "several years" / ---	---	***ALL*** (---)	---	--- / ---	---	
3. 6760412	US, E 2009 Q1	1 / M (Yes)	OT	PIM: --- / face, chest	Rash, infantile acne	***ALL*** (bone marrow biopsy)	~1.6 years	---/ Yes	Chemo, transfusion	Medical history: herpes zoster IgG positive, family history of colon cancer and cervical cancer
4. 6860217	US, E 2008 Q1	2 / F (---)	OT	PIM: --- / ---	Atopic dermatitis	***ALL*** (peripheral blood smear)	Within 4 months	---/ Yes	Chemo, transfusion	Family history of leukemia
5. 7213160	US, E 2011 Q1	3 / F (---)	HO, LT	PIM: --- / arms, legs, abdomen	Atopic dermatitis	***ALL*** (blood flow cytometry, bone marrow biopsy, chromosomal analysis)	---	No / Yes	Chemo	Family history of colon cancer. *Study CASM981C2311*
6. 5053510	US, E 2006 Q3	Pediatric / M (---)	OT	PIM: --- / ---	---	***Leukemia*** (---)	---	--- / ---	---	
7. 6964115	US, E 2008 Q1	15 / M (No)	HO	PIM: --- / ---	Dermatitis	***Hodgkin's lymphoma, stage IIIA nodular sclerosing*** (CT, lymph node biopsy)	---	---/ Yes	Chemo, radiation	Medical history: exposure to unspecified drug during pregnancy, herpes, varicella
8. 6992464	US, E 2009 Q1	8 / M (No)	OT	PIM: --- / eyelid	Eczema	***B-cell lymphoma / large cell lymphoma and "other lymphomas, unspecified site, extranodal and solid organ sites"*** (excisional biopsy, lymph node biopsy, bone marrow biopsy)	~1.25 years	--- / ---	Chemo	Eczema also treated with mometasone cream.

ISR#	Report Source, Type, Initial FDA received date	Age at time of event (years) / Gender (Age <2 at time of Rx?)	Primary Outcomes	TCI: Dosing, Duration of therapy / Application site	Indication	Reported Malignancy (Diagnostic tests)	Time to event from start of therapy	Was drug discontinued ? / Did event improve?	Was medical intervention required?	Comments
9. 6505255	US, E 2009 Q4	0.9 / F (Yes)	OT	PIM: 3 months / ---	---	***Lymphoma*** (---)	3 months	--- / ---	---	
10. 4823491	US, E 2005 Q3	13 / F (---)	OT	tTAC: --- / ---	---	***Cutaneous T-cell lymphoma*** (biopsy)	---	--- / ---	Unspecified treatment	*Unspecified study*
11. 5615292	US, E 2008 Q1	Minor / M (---)	OT	PIM and tTAC: --- / ---	---	***Melanoma*** (---)	---	--- / ---	---	This case may be a duplicate of ISR 5850928 (captured in previous OSE review); however, the narrative and subsequent follow-up attempts did not provide sufficient information to reconcile the cases.
12. 7248961	NS, E 2011 Q1	8 / M (Yes)	OT	PIM: 2x/day for NS time / ---	Eczema	***Skin cancer, lesions on face and nose*** (---)	---	--- / ---	---	According to sponsor, "the patient's mother specified that this patient did not have skin cancer. This case is under processing and more information has been sought from the treating physician."
13. 7294778	France, E 2011 Q1	4 / M (No)	LT, HO	tTAC 0.03%: 2x/day for 38 days, then every other day / folds of abdomen, back, lower & upper limbs	Atopic dermatitis	***Metastatic nephroblastoma*** (---)	~1.2 years	--- / No	Chemo	Concomitant medications: desloratidine, Xemose cream (emollient). Previously treated with betamethasone, chlorphenamine, and emollients.
14. 5447190	Poland, E 2007 Q3	Pediatric / --- (---)	OT	PIM: --- / ---	---	***Pituitary microadenoma*** (---)	---	--- / ---	---	
15. 5999954	UK, E 2008 Q4	Child / F (---)	LT	PIM: --- / ---	Atopic dermatitis	***Rhabdomyosarcoma, orbital*** (---)	~3.9 yrs	Yes / ---	Chemo	Also used emollients and steroids for eczema.

Chemo= Chemotherapy
CT= Computerized tomography
D= Direct report
E= Expedited (15-day) report
F= Female
HO= Hospitalization
LT= Life-threatening
M= Male
US= United Sates of America
OT= "Other" serious/medically significant
PET= Positron emission tomography
PIM= Pimecrolimus (Elidel)
tTAC= Topical tacrolimus (Protopic)

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/s/

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ANN WARD W MCMAHON
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I concur.