

# **Elidel® (pimecrolimus) Cream 1% Safety Update Feb, 2005**

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## Overview

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- ◆ **No clinical evidence for increased risk of malignancies**
- ◆ **No evidence for systemic immunosuppression**
  - **Pharmacokinetics**
  - **Immunocompetence in children**
  - **Infections rates in children**
- ◆ **Ongoing safety monitoring programs**
- ◆ **Conclusions**

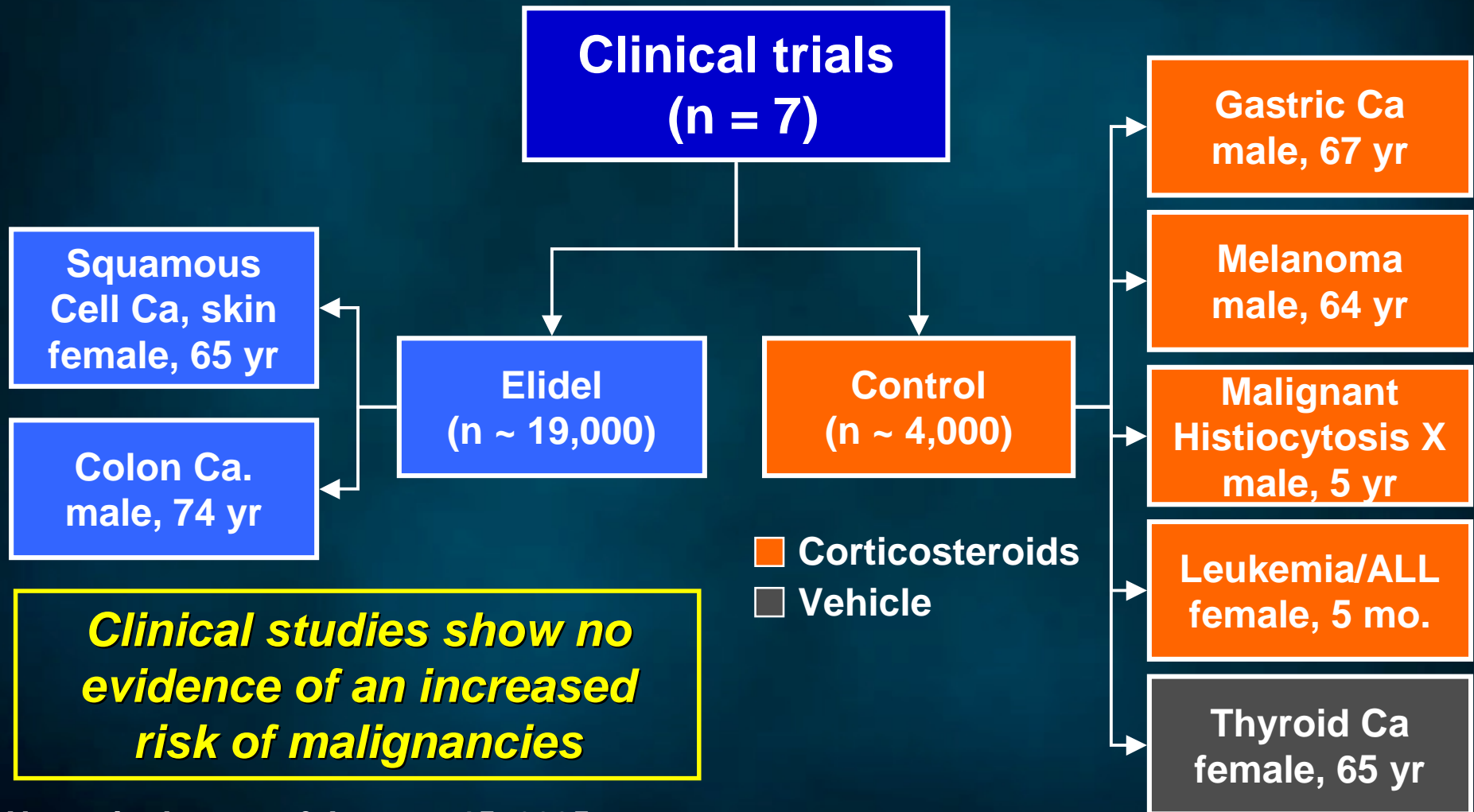
**Is there clinical evidence of increased risk of malignancies?**

## **Elidel<sup>®</sup>—The Clinical Experience**

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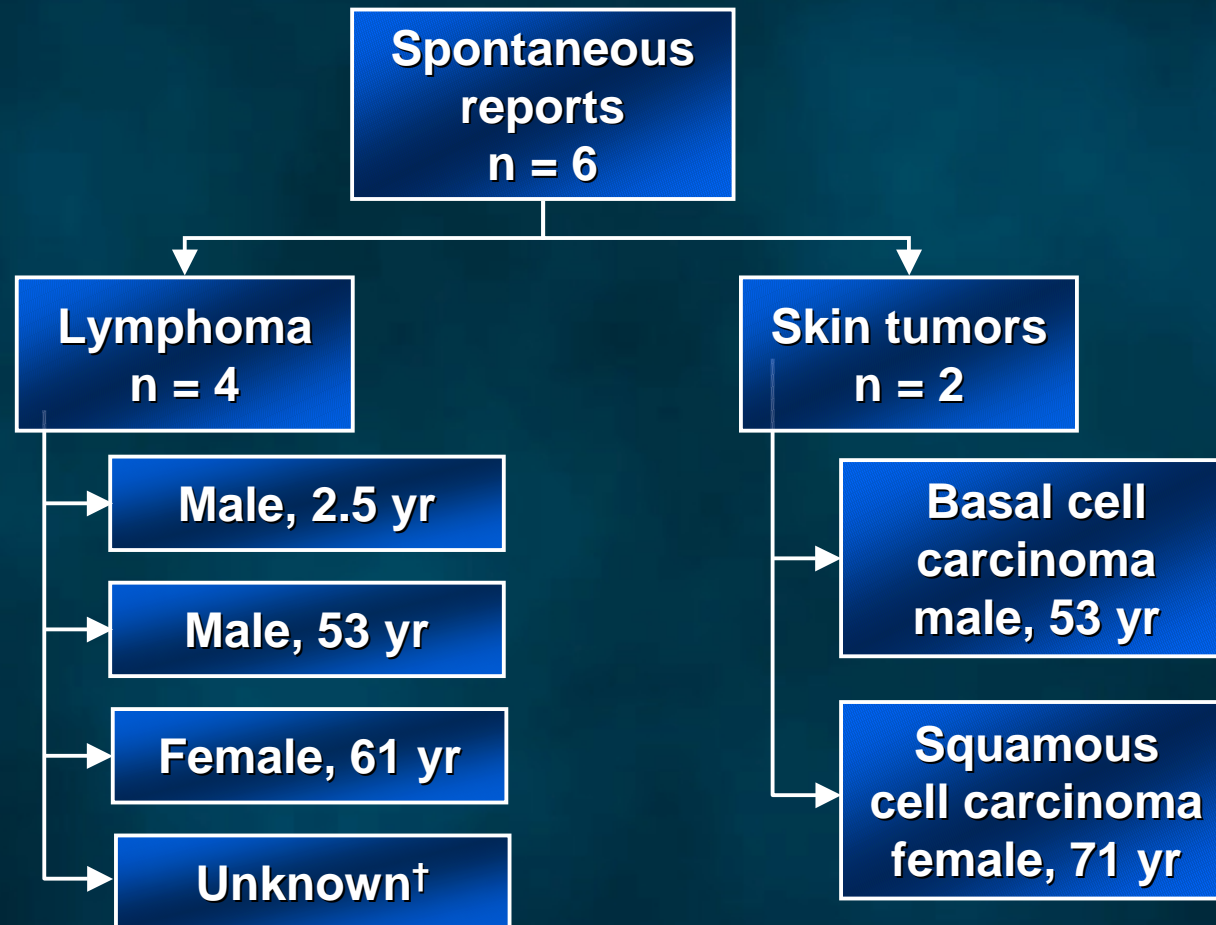
- ◆ **In clinical studies > 19,000 patients since 1996**
  - ~ 3,000 infants (3 - 24 mo)
  - > 7,000 children (2 - 17 yr)
- ◆ **In clinical practice > 5 million patients since Dec 2001**
  - ~ 2.7 million patients < 10 years of age
  - Average Elidel usage
    - Intermittently, 45 days/year
    - ~ 1.6 grams/day

# Reports of Malignancies—Clinical Trials



Novartis data as of January 15, 2005.

# Reports of Malignancies—Spontaneous Reporting



† Unconfirmed, poorly documented case, non-US.  
Novartis data as of January 15, 2005.

## Non-Hodgkin Lymphomas—Spontaneous Reports

Sex/ age	Lymphoma histology (localization)	Treatment duration and regimen	Extent of Elidel® use	Independent expert assessment of causality
Female 61 yr	Histiocytic lymphoma (neck)	A few weeks, “continuously”	~ 5% TBSA	Unlikely
Male 53 yr	Subcutaneous panniculitis like T-cell lymphoma (trunk, limbs)	~ 6 months intermittent use	~ 60% TBSA	Unlikely
Male 2.5 yr	Lymphoblastic lymphoma (T cell) (mediastinum)	~ 6 months intermittent use	~ 20% TBSA	Unlikely

TBSA = Total body surface area.

Novartis data as of January 15, 2005.



## No Evidence of Increased Incidence of NHL in Any Age Group

	< 5	5 - 9	10 - 14	15 - 19	Total children	Adults	Total (US)
Person-years of exposure	278,842	118,196	65,224	33,431	495,694	237,030	732,724
Expected no of cases (SEER), general population	1.8	1.0	0.7	0.5	4.0	42.1	46.1
Reported cases	1	0	0	0	1	2	3

SEER = Surveillance, epidemiology, and end result.

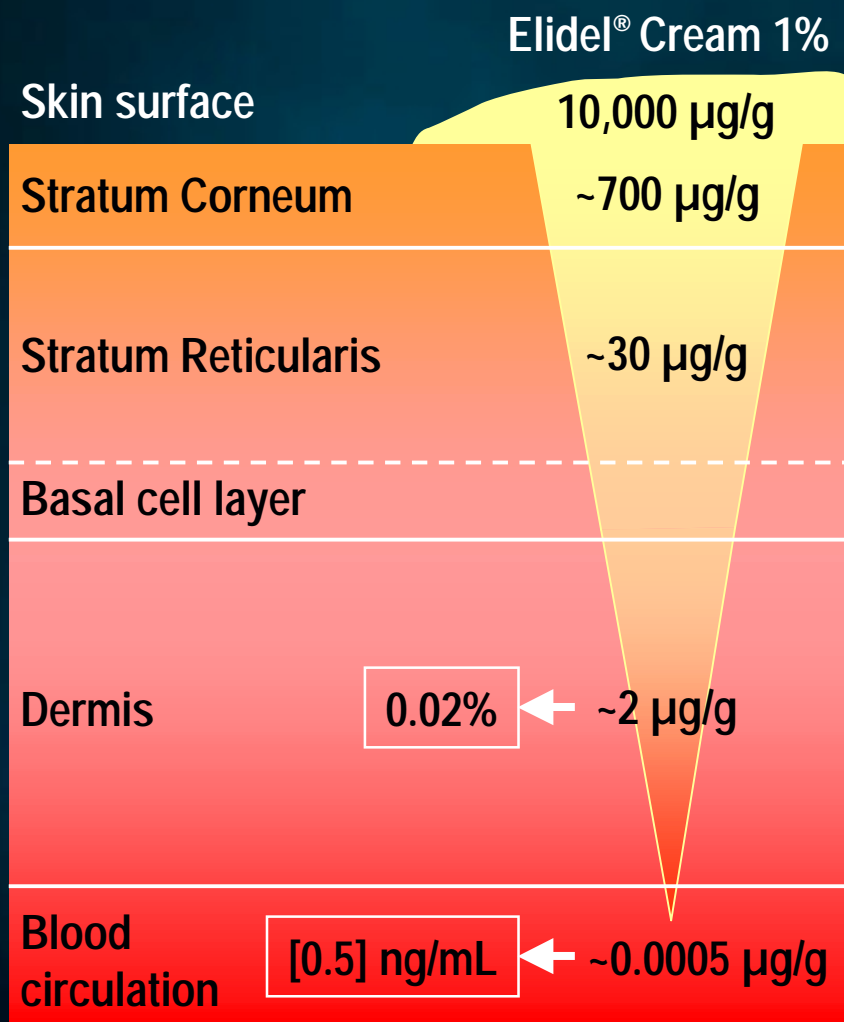


## **No Evidence of Immunosuppression**

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- ◆ **Pharmacokinetics**
- ◆ **Objective measures of the immune response**
  - **Vaccination responses (B-cell dependent)**
  - **Delayed hypersensitivity (T-cell dependent)**
- ◆ **Infection rates**

# Pharmacokinetics—Topical



**Pediatric PK studies, moderate to severe AD, up to 92% TBSA (75 pts/366 samples)**

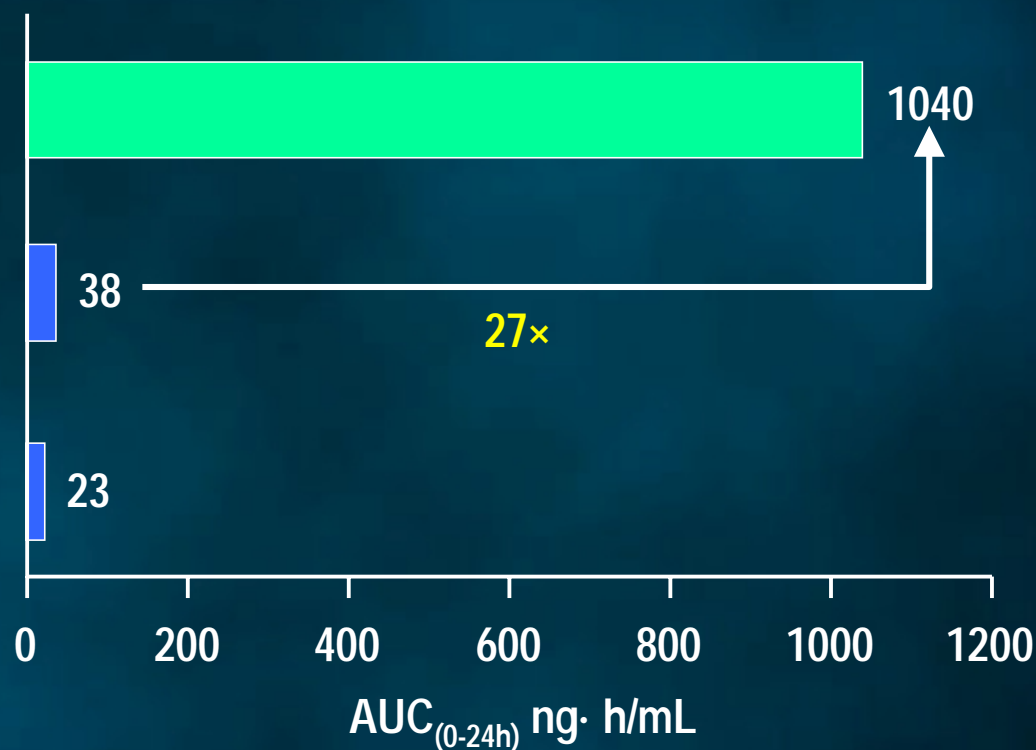
- 68% of samples < [0.5] ng/mL
- 99% of samples < [2.0] ng/mL
- 10 patients with measurable AUCs 11 - 38 ng-h/mL

# Toxicology Study—Dermal

NOAEL 104-week **mouse dermal carcinogenicity** (pimecrolimus in ethanol)

Highest exposure, topical, human **pediatric patients**

Highest exposure, topical, human **adult patients**

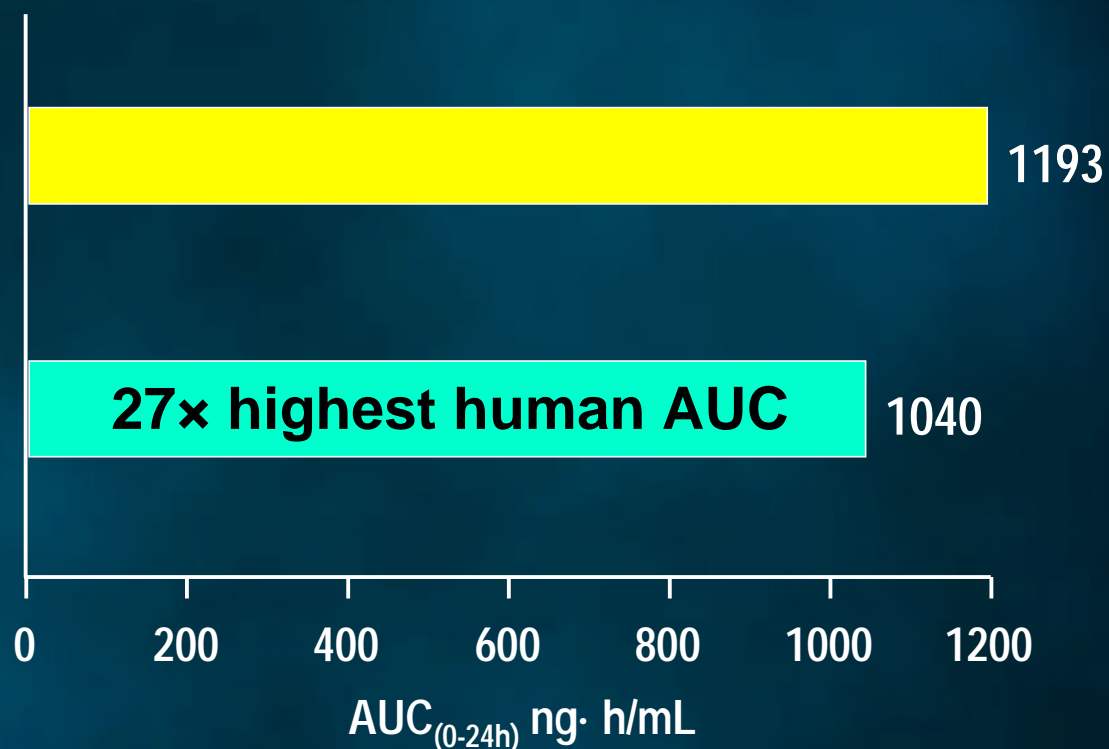


***No malignancies in mice exposed for 104 weeks at 27x the single highest AUC in pediatric patients***

# Beyond Topical Application— Oral Dosing in Monkey Toxicology Study

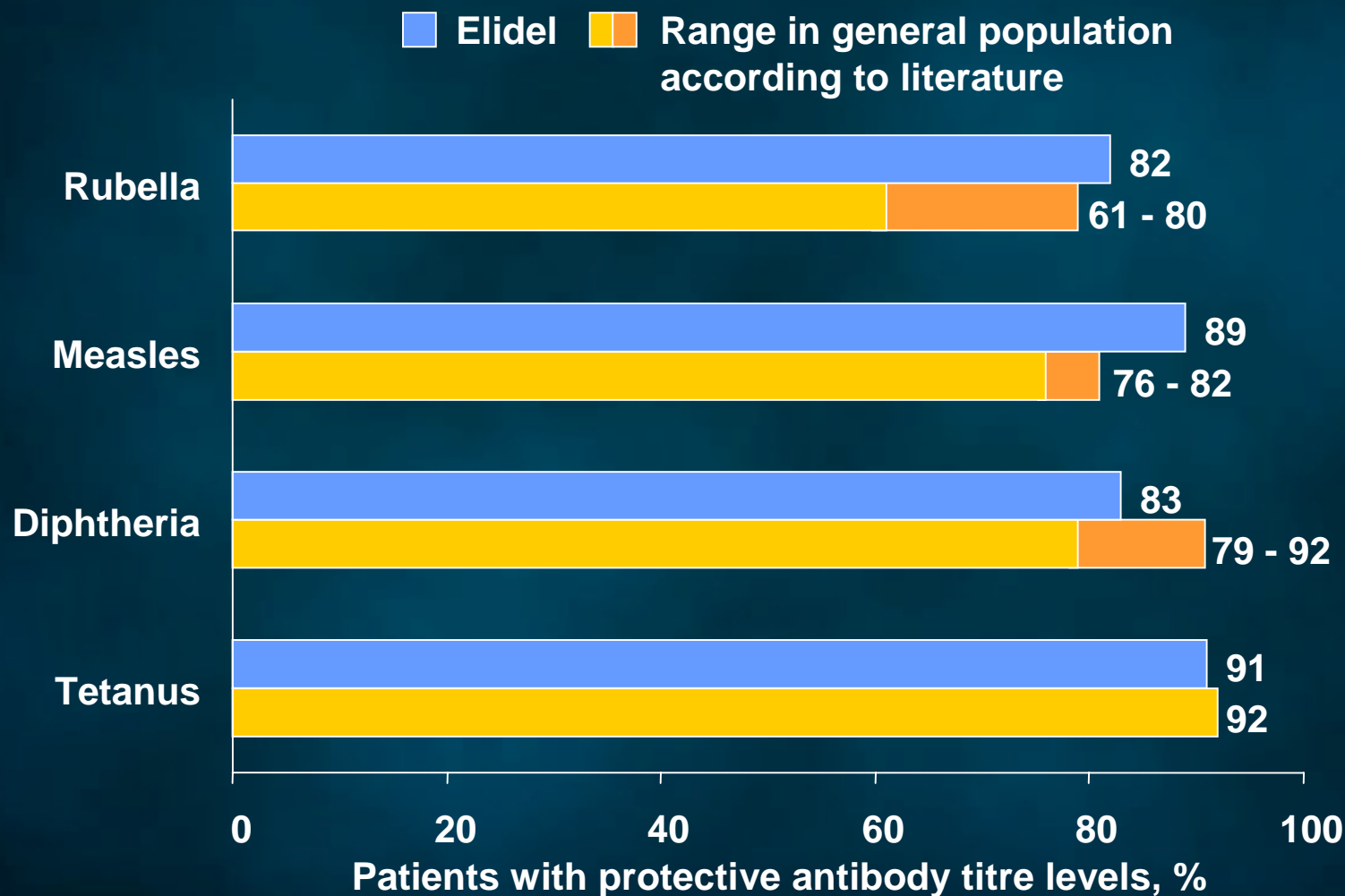
LOAEL 39-week oral  
cynomolgus monkey  
(gavage, oral)

NOAEL 104-week mouse  
dermal carcinogenicity  
(pimecrolimus in ethanol)



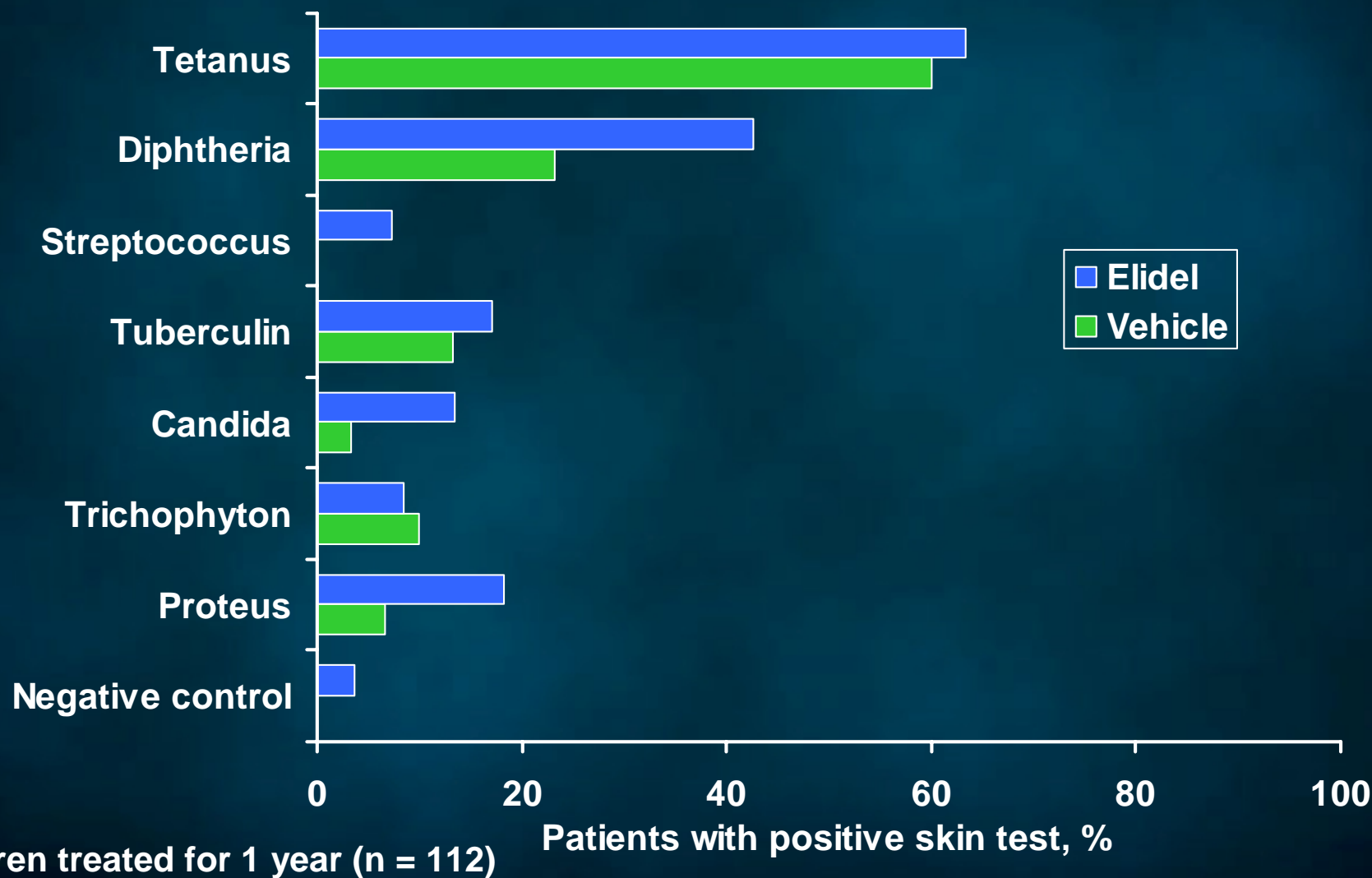
# Vaccination Response (B-cell Mediated)

## No Effect of Elidel<sup>®</sup> Treatment

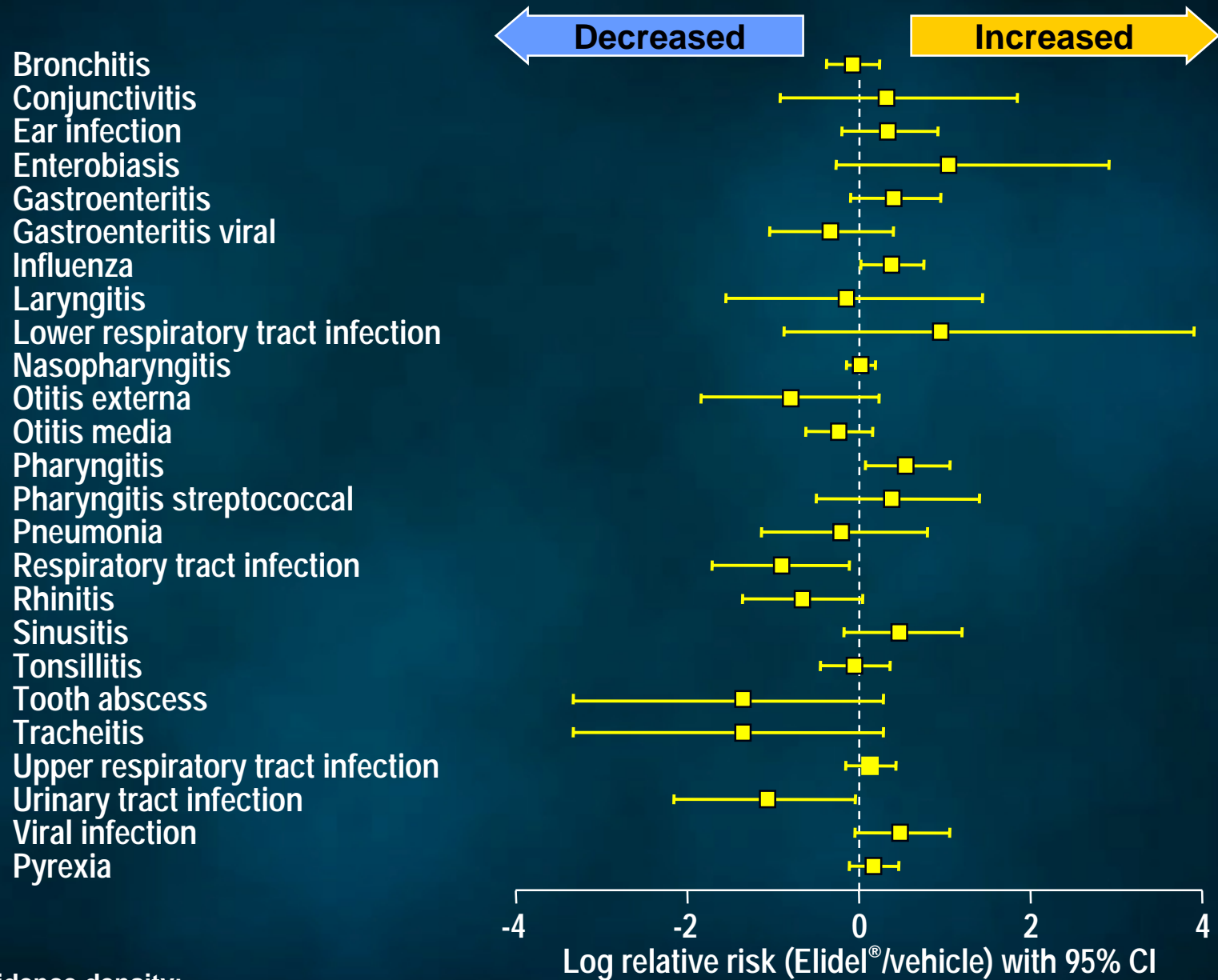


Papp K, et al. *J Am Acad Dermatol.* 2005;52:247-253.

## Delayed Type Hypersensitivity (T-cell Mediated) No Effect of Elidel<sup>®</sup> Treatment



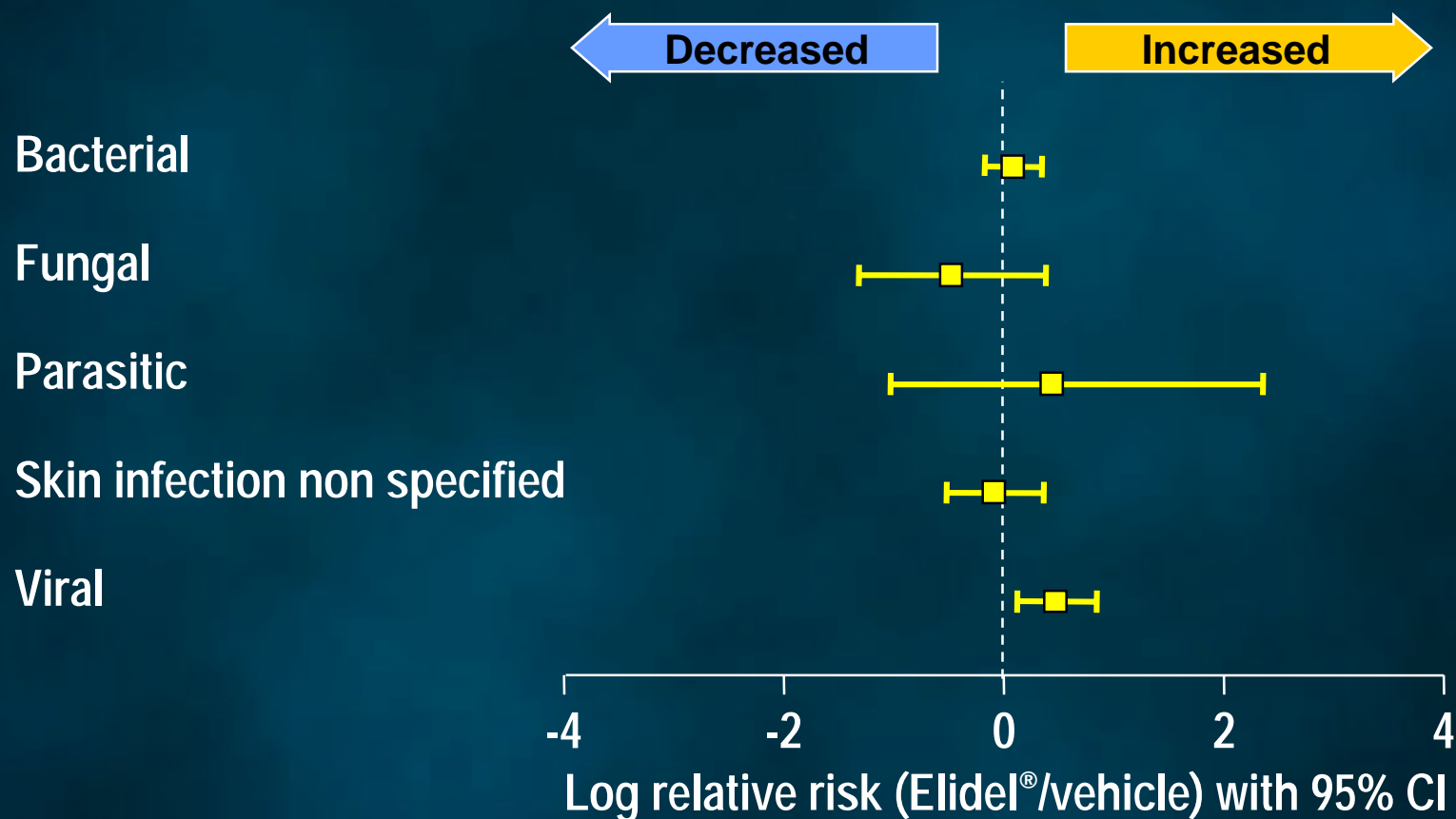
# No Imbalance in Systemic Infections in Children



based on incidence density;  
Elidel (n = 1135), vehicle (n = 707)



# Skin Infections in Children



based on incidence density;  
Elidel (n = 1135), vehicle (n = 707)

## **Extensive Clinical Program Further Monitor Elidel<sup>®</sup> Safety**

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- 1. 6-year safety and efficacy study in infants 3 - 18 mo, started Sep 2003 (n = 1,100)**
- 2. 5-year safety study in infants 3 - < 12 mo, started Apr 2004 (n = 2,400)**
- 3. 10-year, prospective registry to assess risk of malignancies in children 2 - 17 yr, started Nov 2004 (n = 4,000)**
- 4. Controlled safety and efficacy study in HIV-positive patients**
- 5. Case control study to assess the risk of non-melanoma skin cancer in adults**
- 6. Case control study to assess the risk of melanoma skin cancer in adults**

## **Elidel® Cream—Conclusion**

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- ◆ **Clinical data do not show evidence for an increased risk of malignancies**
- ◆ **Systemic immunosuppression is clinically implausible based on**
  - **Pharmacokinetics (minimal blood levels)**
  - **Maintained immunocompetence**
  - **No increased risk of systemic infections**
- ◆ **Extensive clinical program further monitor Elidel safety**

