Scientific Workshop on Erythropoietic Protoporphyria (EPP)

October 24, 2016

U.S. FOOD & DRUG ADMINISTRATION

Welcome

Sara Eggers, PhD
Office of Strategic Programs
Center for Drug Evaluation and Research
Food and Drug Administration

October 24, 2016

Agenda

- Overview of EPP and Current Treatment Approaches
- Patient Perspectives on EPP and Current Treatments
- Open Public Comment

LUNCH

- Overview of FDA Regulatory Process
- Scientific Discussion on Clinical Trial Design for EPP
- Open Public Comment
- Closing Remarks

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Opening Remarks

Kendall Marcus, MD
Director, Division of Dermatology and Dental Products (DDDP)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

October 24, 2016

Epidemiology and Natural History of Erythropoietic Protoporphyria

Henry W. Lim, MD
Chairman and C.S. Livingood Chair
Department of Dermatology
Henry Ford Hospital, Detroit, MI

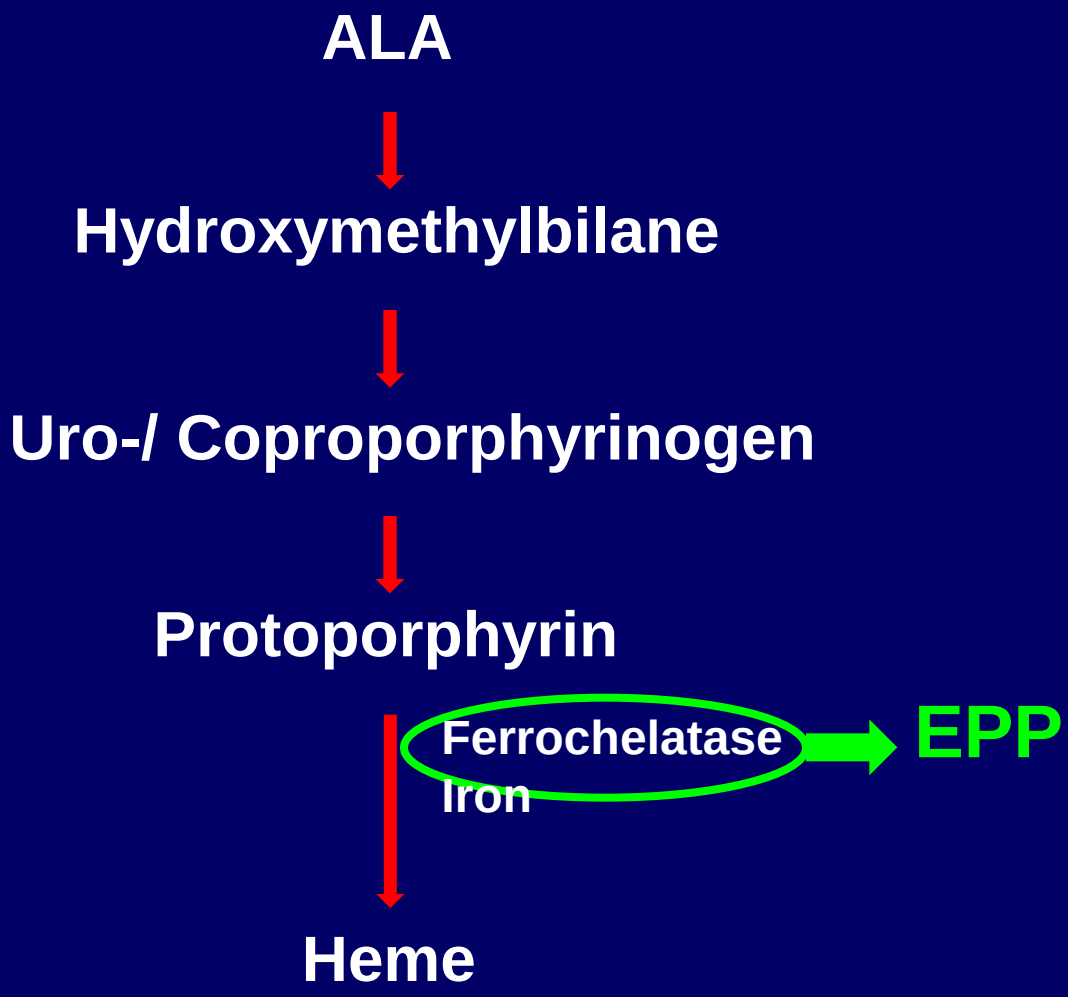
Disclosure

- *Consultant :*
  - Pierre Fabre
- *Investigator:*
  - Clinuvel
  - Estée Lauder
  - Ferndale

Erythropoietic Protoporphyria

- Onset in childhood
- Burning, stinging sensation
- Erythema, edema, urticarial lesions
- Rare: late onset with myelodysplasia

Heme Biosynthetic Pathway



X-linked Dominant Protoporphyria (XLDPP)

(Schulenburg-Brand, D, … Badminton, MN. Dermatol Clinics 2014; 32:369. Cardiff, Wales)

- **Similar to EPP: burning, stinging, edema upon exposure to sunlight**

Prevalence of EPP (per 100,000)

(Horner, ME, et al. Int J Dermatol. 2013 Dec;52:1464; Gouya L, et al. Am J Hum Genet 2006 Jan; 78:2.)

Country	Per 100,000
Japan	4.00
Slovenia	1.75
United Kingdom	0.77
North Ireland	1.27
Netherlands	1.33
South Africa	
General population	0.06
European immigrant	0.70

EPP in the UK

(Holme SA,… Badminton, MN. Br J Dermatol 10/2006; 155:574. Cardiff)

- 389 living subjects identified
- 223 (114 f, 109 m) investigated
- Median age: 34 yrs (5-87 yrs)
- Median total erythrocyte porphyrin:
  - Males: 25.3 micromole/l
  - Females: 19.3 micromole/l

EPP in the UK

(Holme SA,… Badminton, MN. Br J Dermatol 10/2006; 155:574. Cardiff)

- Mean age of onset: 1 yr; mean age of diagnosis: 12 yrs
- Median time to:
  - Onset of symptoms after sun: 20 min
  - Onset of signs (edema, erythema): 6 hr
  - Resolution of signs: 3 days

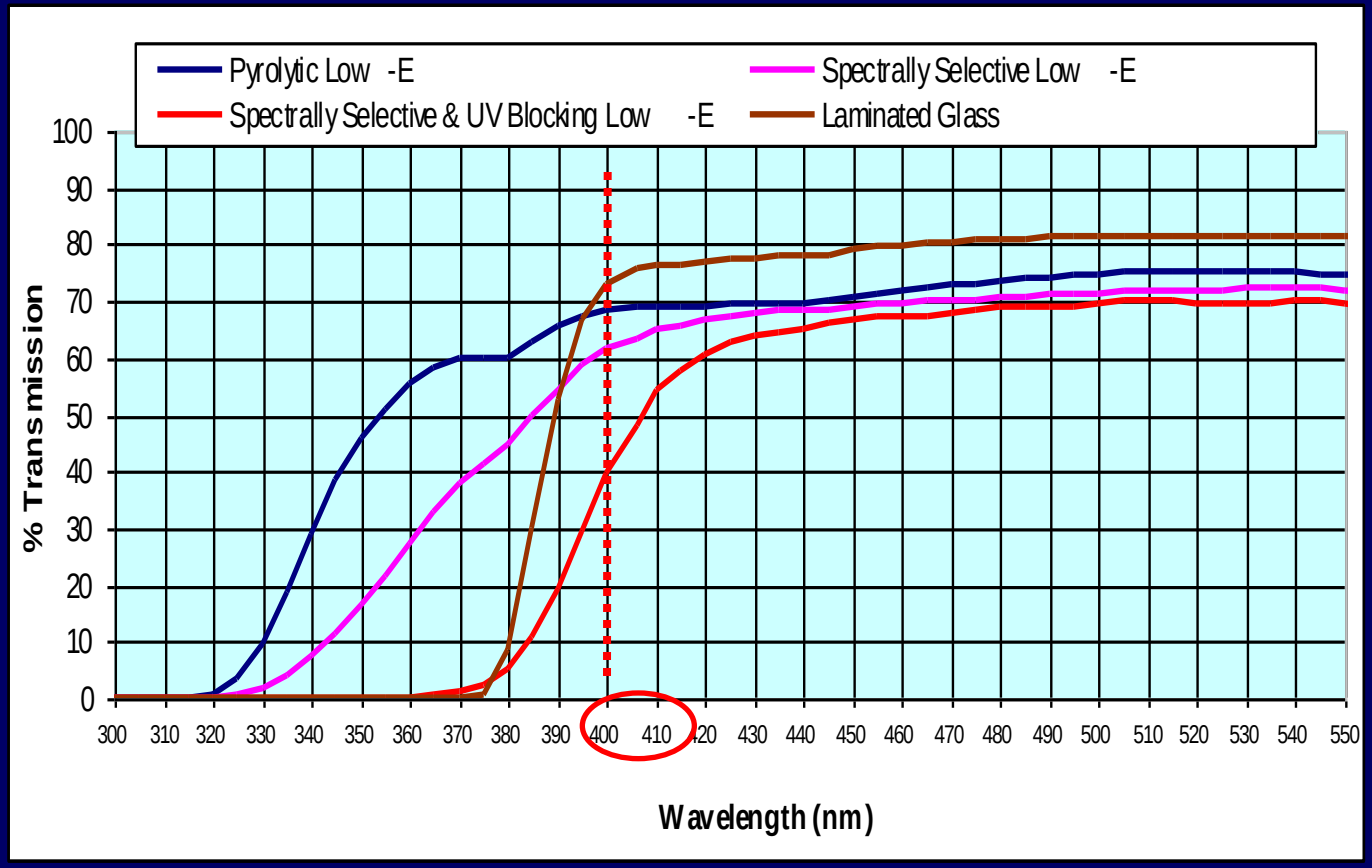
EPP in the UK

(Holme SA,… Badminton, MN. Br J Dermatol 10/2006; 155:574. Cardiff)

- **Others:**
  - **Priming: 85%**
  - **Absence of protection by glass: 92%**

Penetration of UV and Visible Light

- **Transmission through window glass: visible light > UVA1 > UVA2 > UVB**



UVB UVA2 UVA1 Visible light

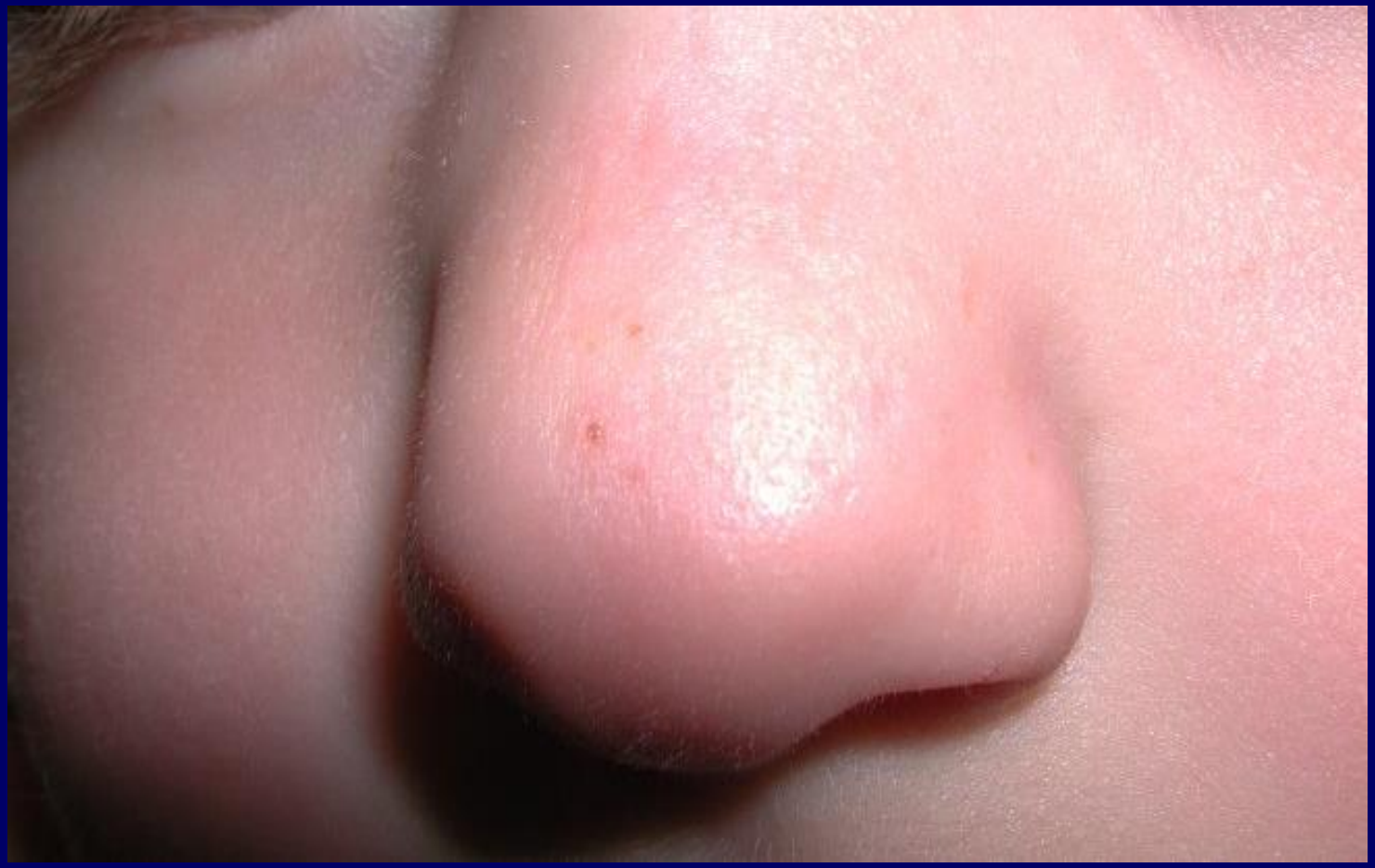
(Tuchinda, C. JAAD 5/06; 54:845)

EPP in the UK

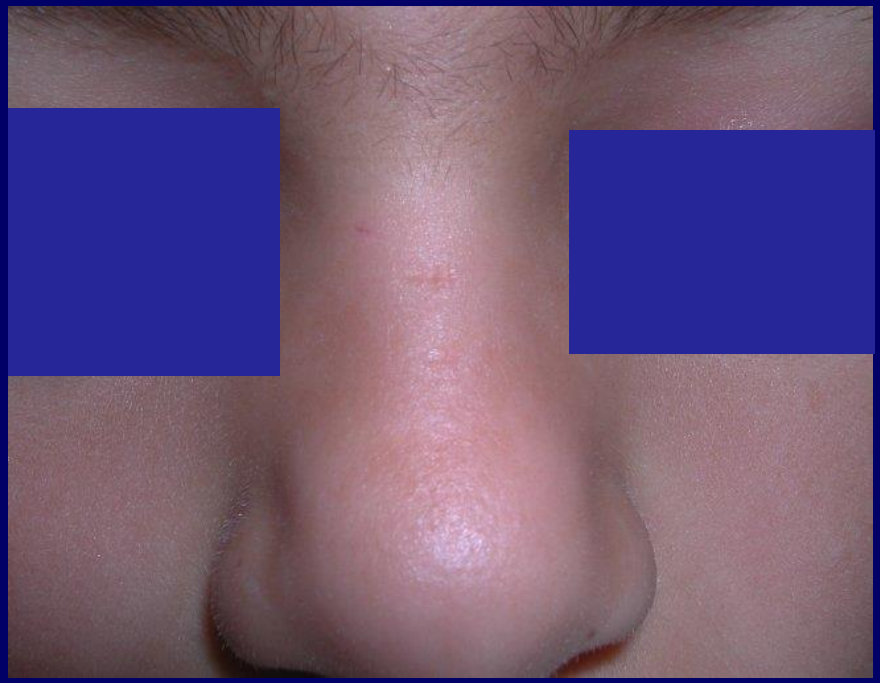
(Holme SA,… Badminton, MN. Br J Dermatol 10/2006; 155:574. Cardiff)

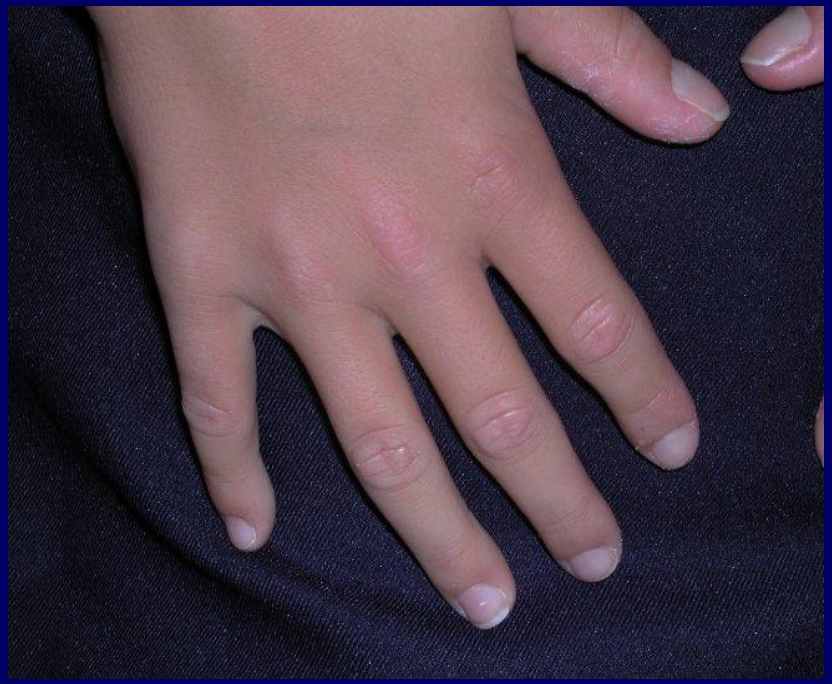
- **Others:**
  - **Priming: 85%**
  - **Absence of protection by glass: 92%**
  - **Exacerbation by wind: 68%**
  - **No fam history of photosens: 58%**
  - **Chronic skin lesions: 79%**

EPP

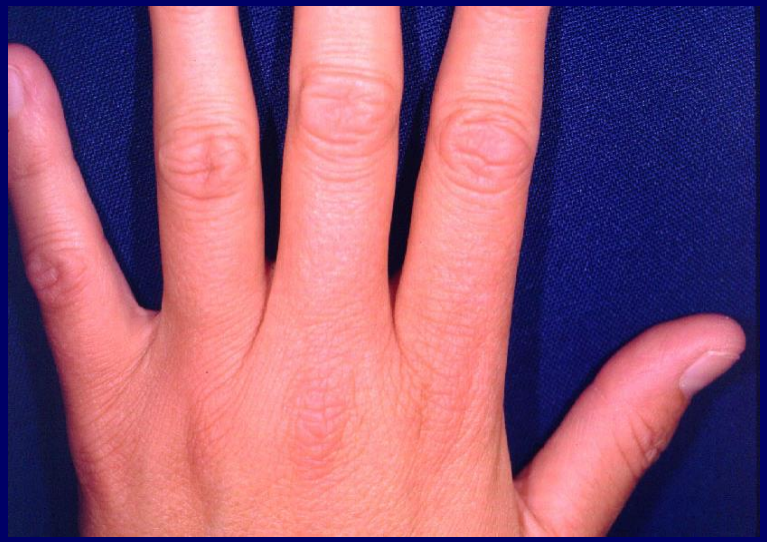


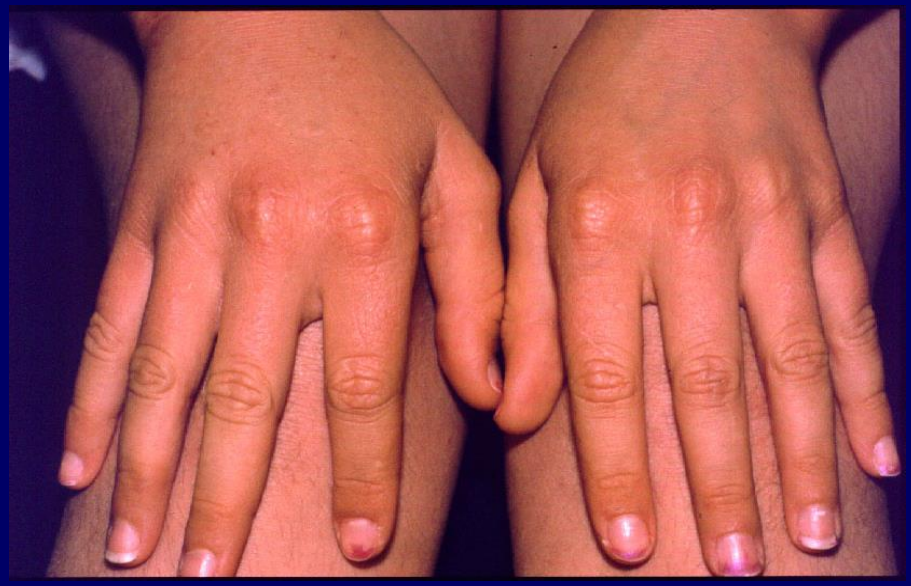
EPP



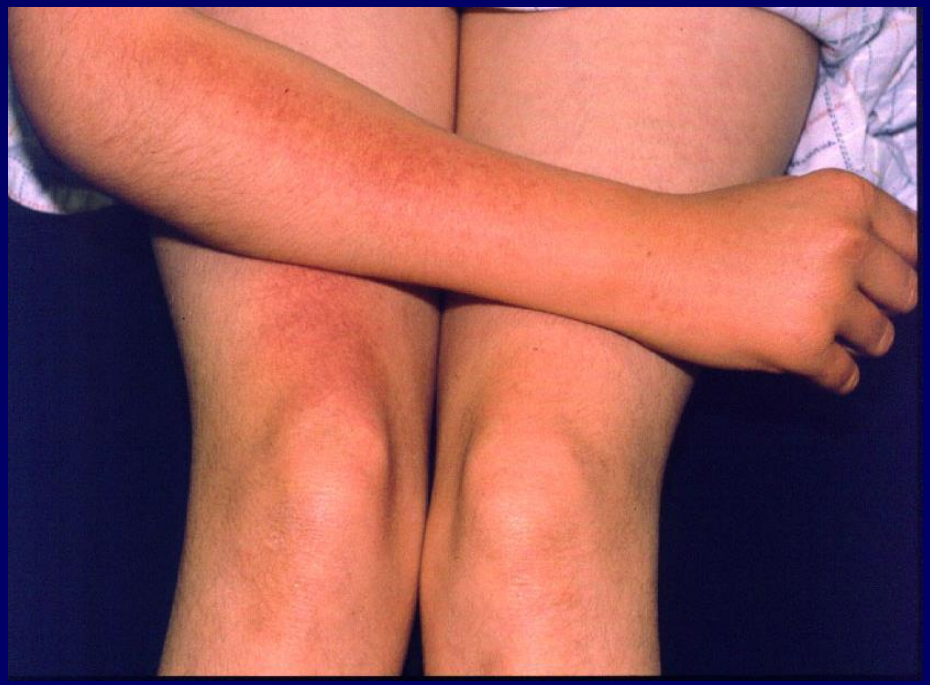


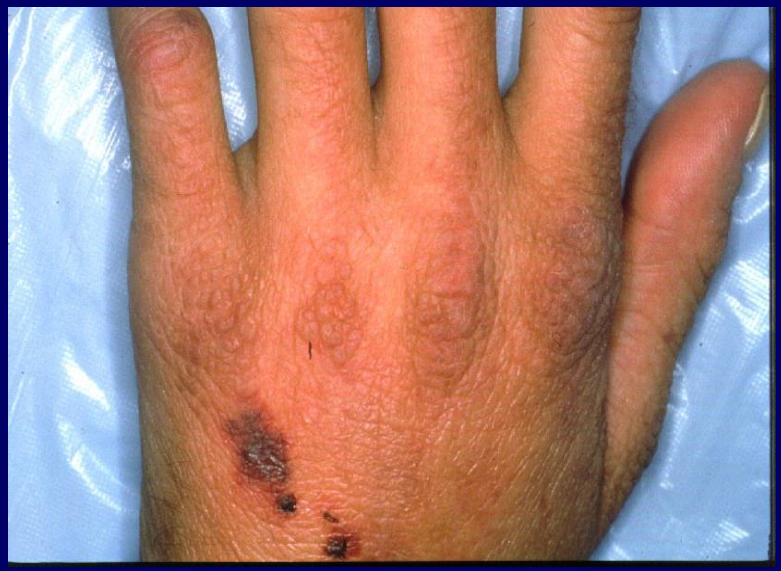
EPP

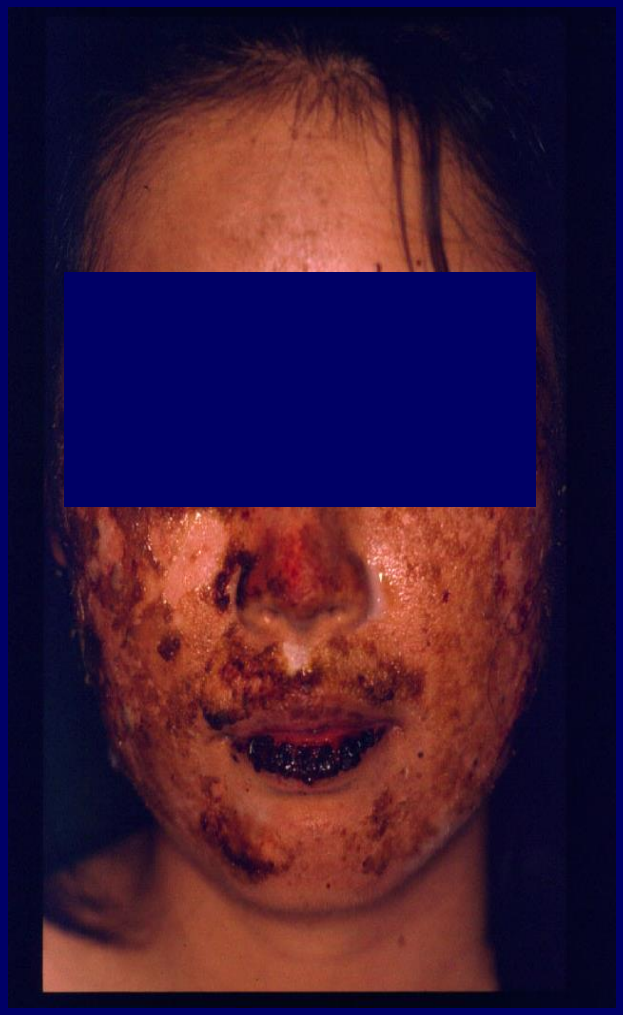




EPP







EPP

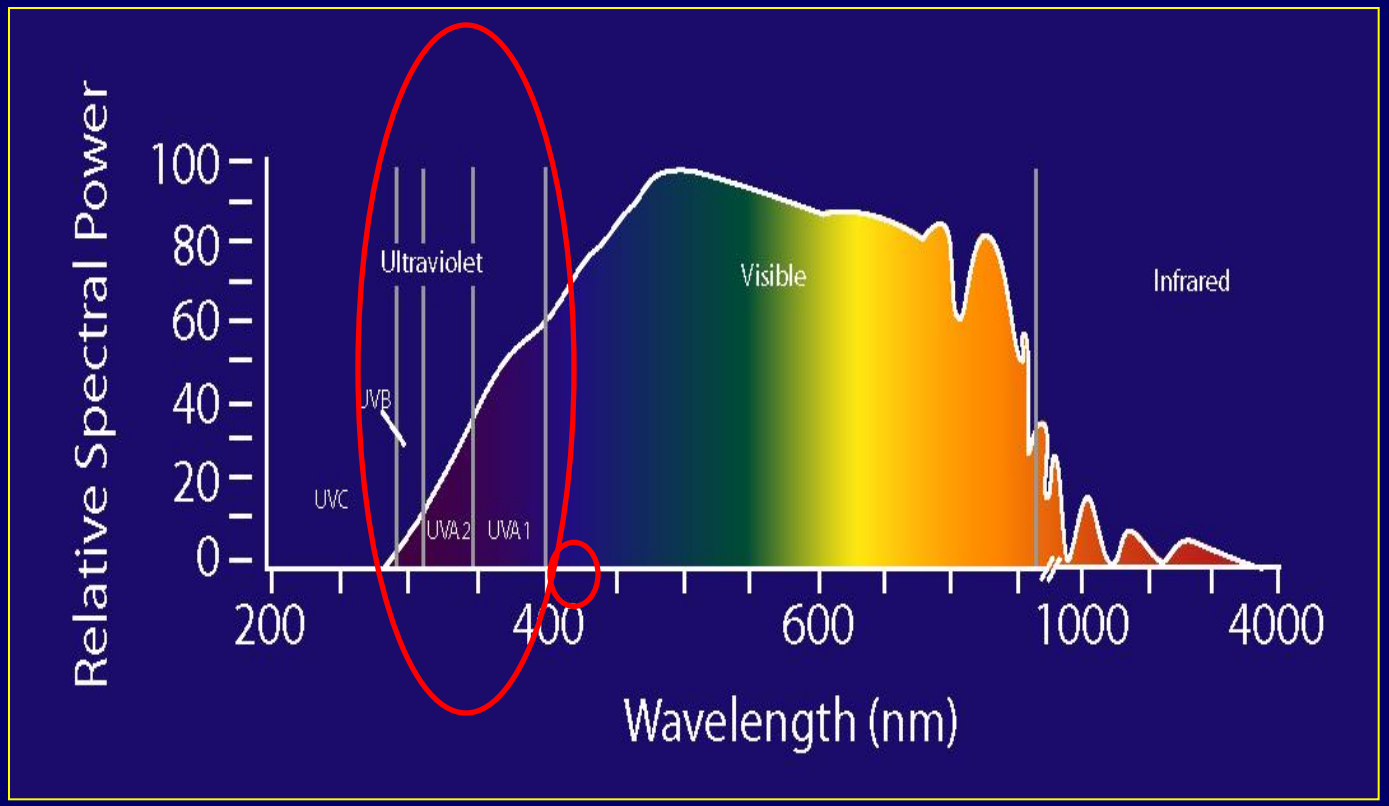
Courtesy of R. Kamide, MD.
Tokyo

EPP in the UK

(Holme SA,… Badminton, MN. Br J Dermatol 10/2006; 155:574. Cardiff)

- Symptoms changed little with age
- Symptoms improved during pregnancy: 47%
- 28% were taking beta-carotene and a further 56% had taken it
- Most patients used protective clothing and a sunscreen

Ground Level
Spectrum of Sunlight



EPP in the UK

(Holme SA,… Badminton, MN. Br J Dermatol 10/2006; 155:574. Cardiff)

- **Liver failure: 1%**
- **Gallstone disease: 8%**
- **QoL: markedly impaired, with scores similar to those in severe dermatological disease**
- **Total erythrocyte porphyrin, age at onset, time to onset of symptoms: *none* is a useful predictor of impaired QoL**

EPP in the UK

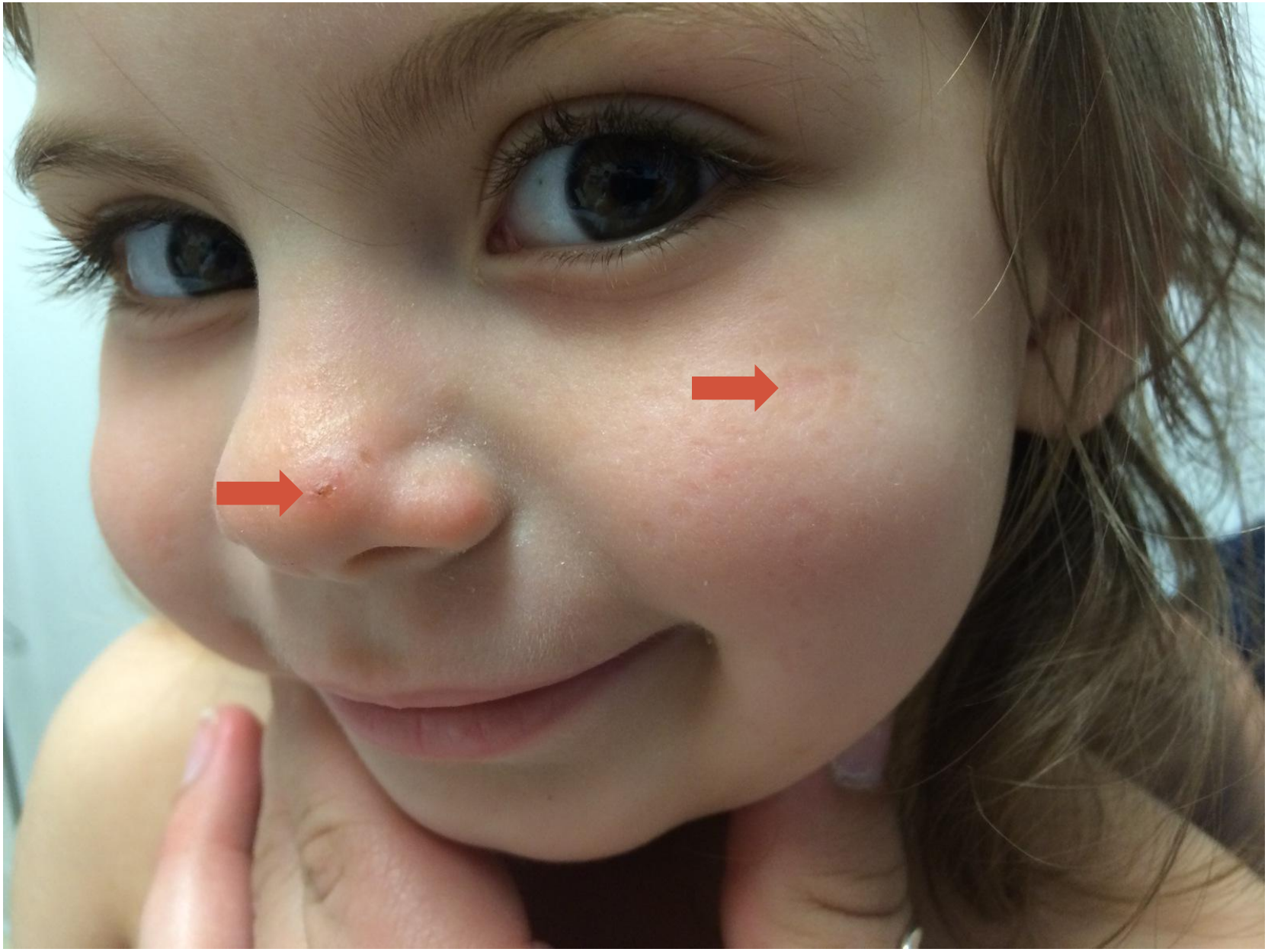
(Holme SA,… Badminton, MN. Br J Dermatol 10/2006; 155:574. Cardiff)

- **EPP is a persistent, severely painful, socially disabling disease with a marked impact on QoL.**

Erythro Protoporphytia

October 24, 2016

Joyce Teng, MD PhD
Director of Pediatric Dermatology
Clinical Associate Professor of Dermatology & Pediatrics
Stanford University School of Medicine



Management of EPP

- **Screening**
  - Assess erythrocyte protoporphyrin levels,
  - CBC (microcytic hypochromic anemia)
  - Fe profile,
  - liver panel,
  - consult medical genetics
- Abdominal US, LFTs if cholethiasis suspected

- **Therapeutic Challenges:**
  - No FDA approved treatment, or specific treatment for acute photosensitivity
  - May not respond to narcotic analgesics

Management of EPP

- Fe, vitamin D supplementation
- Hepatitis A/B immunization
- **Monitor:**
  - Laboratory studies: Vitamin D 25-OH
  - Every 6-12 mo: LFTs
  - Erythrocyte protoporphyrin levels, CBC, Fe

Diagnostic Tests

Enhanced urinary excretion of coproporphyrins can predict liver complications

- Detection of increased free erythrocyte protoporphyrin

Deficient Enzyme	Enzyme Activity	Erythro - cytes	Urine	Stool	Other
Ferro-chelatase	~10%-30% of normal	Free proto-porphyrin: increased	Proto-porphyrins: not increased	Proto-porphyrin: normal or increased	Plasma porphyrins: increased

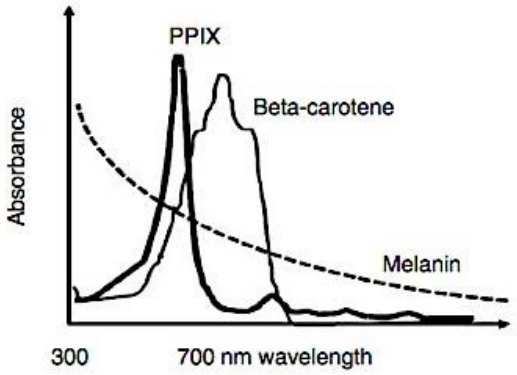
- Elevated erythrocyte protoporphyrin (10–100 x): Mostly free not Zn-complexed
- Genetic mutation analysis

Supportive Treatments

- **Identifying precipitating factor(s)**
  - Bone marrow reticulocytes source of protoporphyrin
  - UV light causes release of free protoporphyrin
  - DDx: PMLE, solar urticaria, Rx-induced photosensitivity

- **Analgesia**
  - Opiates
  - Anxiolytics i.e. Chlorpromazine, benzodiazepine.
  - Address the danger of additions especially those use treatment chronically.
- Other
  - Electrolyte imbalance
  - Nutritional monitoring

Potential Therapies



- **Beta-carotene** 30-100 mg daily (Lumitene)
  - Quenches the formation of free radicals
  - Clinical effect of beta carotene is achieved concomitantly with carotenodermia, which develops over 3–6 weeks.
  - Treatment has to be started early enough.

Limitations

- Most studies being **not blinded, controlled or randomized**
- Minimal efficacy. Corbett MF, Herxheimer A, et al. The long term treatment with beta-carotene in erythropoietic protoporphyria: a controlled trial. Br J Dermatol 1977;97:655-62
- High discontinuation rate.
  - (UK) Holme SA, et al. Br J Dermatol 2006;155:574-81.
  - (Sweden) Wahlin S, et al. J Intern Med 2010 online.

Potential Therapies

Other natural products studied.

- [N-acetyl-]cysteine, cysteine, vitamin C, dihydroxy-acetone and lawsone, canthaxanthin
- No efficacy showed in meta analysis.

Physical Protection

- Tinted windows (Scotch tint)
- Protective clothing and sunscreens against long-wave ultraviolet (UV) radiation (broad spectrum coverage) with high protection factors (>30)
- Protective (yellow glass) filter over operating room lights

- Minder et al. Afamelanotide, an agonistic analog of α-melanocyte-stimulating hormone, in dermal phototoxicity of erythropoietic protoporphyria. Expert Opinion on Investigational Drug. Vol 19, 2010.
- Wahlin S, et al. Protection from phototoxic injury during surgery and endoscopy in erythropoietic protoporphyria. Liver Transpl 2008;14:1340-6

Potential Therapies (cont)

- **Phototherapy**-decrease penetration of light?
  - i) induction of melanin pigment in the epidermis
  - ii) increase in epidermal thickness also called ‘skin hardening’.

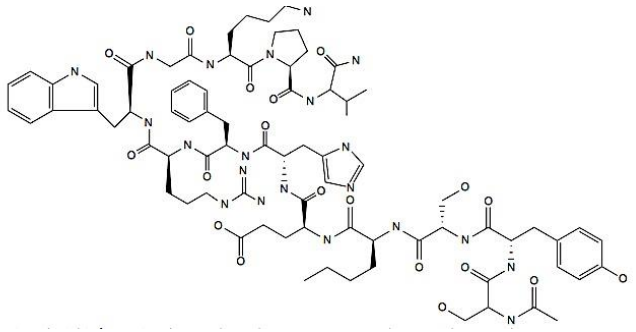
- **Limitations**
  - Only case studies available

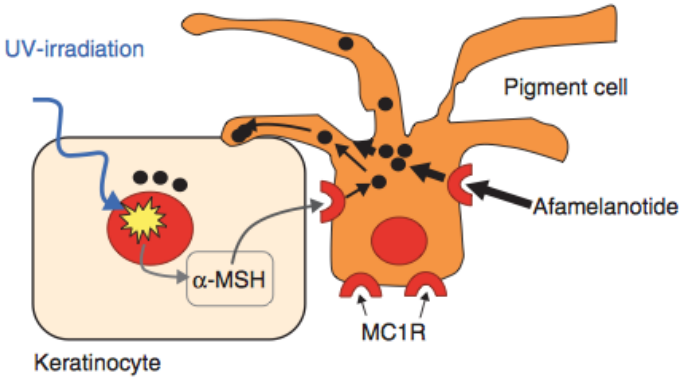
Collins P, et al. Br J Dermatol 1995;132:956-63
García-Martín P et al. Photodermatol Photoimmunol Photomed. 2012 Oct;28(5):261-3.

Potential Therapies (cont)

Afamelanotide
(Melanotan I; Scenesse®)

- slow-releasing α-MSH analog Nle^4-D-Phe^7-α-MSH (melanocortin peptide hormone)
- Bind MC1R-MC5R
- Increases melanin, thus increasing pigmentation
- Approved May 2010 in Italy, then in Europe in 2014 for EPP
- Phase 2 trials completed in US, phase 3 trials underway (completed in Europe)





Biolcati G, et al. Br J Dermatol 2015;172(6):1601—12
Minder EI, et al. Expert Rev Clin Pharmacol 2010
Minder EI, et al. Expert Rev Clin Pharmacol 2015;8(1):43—53

Afamelanotide for Erythropoietic Protoporphyria. N Engl J Med. 2015 Jul 2;373(1):48-59.

- Two multicenter, randomized, double-blind, placebo-controlled trials
- **Patients**
  - Above 18 yo
  - No hepatic abnormality
  - European Union (74 patients);United States (94 patients) were randomly assigned, in a 1:1 ratio
- **Drug Delivery**
- Placebo poly(D,L-lactide-co-glycolide) only; or with16 mg of afamelanotide.
- Implant inserted on days 0, 60, and 120 (6 mo US trial); in EU trial, as well as days 180 and 240 (9 mo)
- Implants placed into the subcutaneous fat above the iliac crest with a 14-gauge catheter needle and then pushed into the fat tissue with a 16-gauge stylet

Outcome Measurements

Clinical End Points

- *Primary:* duration of direct exposure to sunlight without pain10 am-3 pm (EU trial) or 10 am - 6 p.m. (US trial).
  - The intensity and duration of pain and exposure to sunlight and shade were recorded daily
  - Pain was scored on an 11-point Likert pain-intensity scale
- Phototoxic reactions = >4 pain score occurring in light-exposed skin for one or more consecutive days
- QOL & Photoprovocation Test

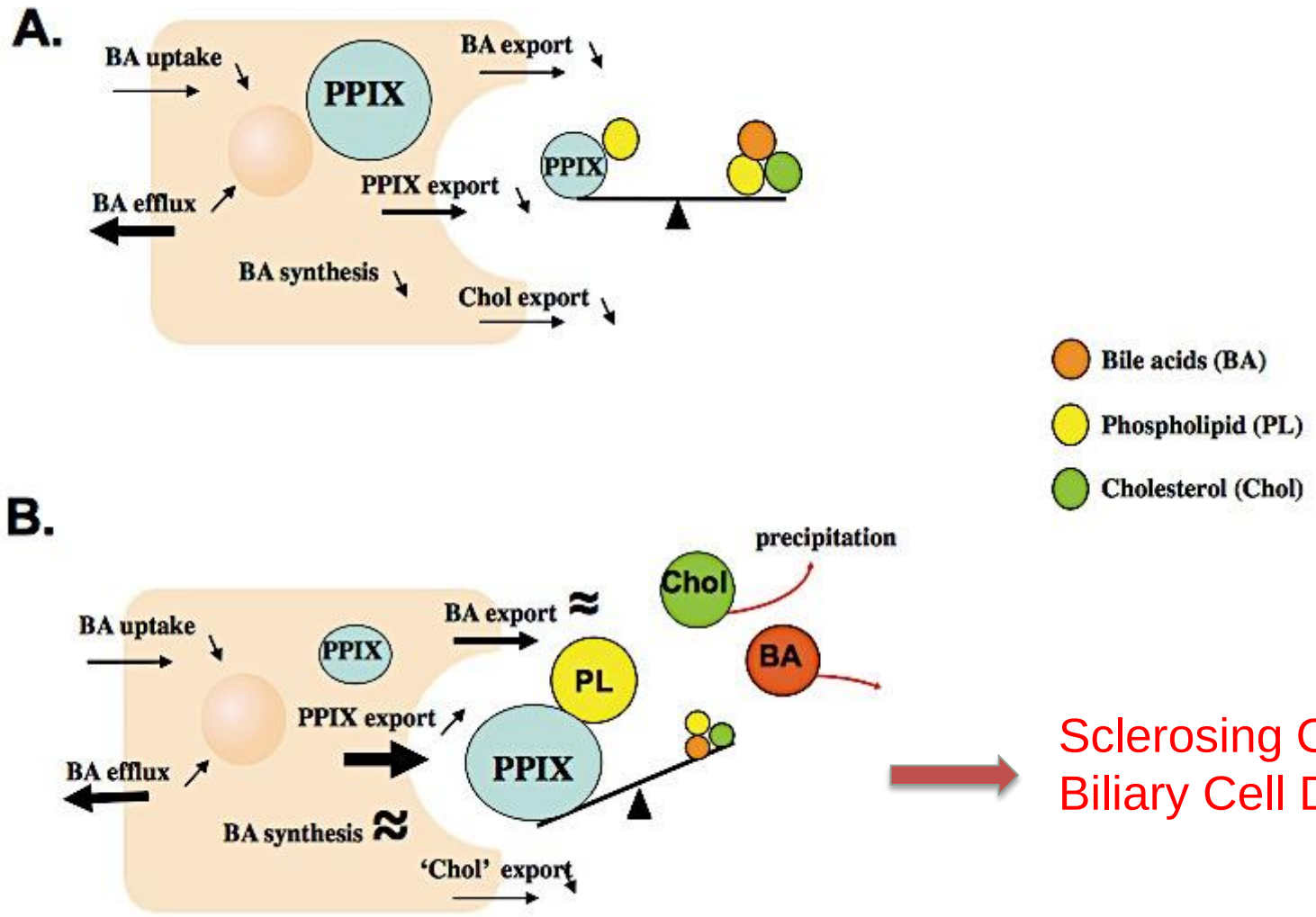
Results

	US Trial		EU Trial	
	Tx	**Placebo**	**Tx**	**Placebo**
PFT in Sun	69.4	40.8	6	0.8
Phototoxic Rx	46	43	77	146
Photo-p Test (J/cm2) (Hand/lower back)				
30d p (2^{nd} dose)	208/227	56/2.4		
60d p(2^{nd} dose)	162/82	82/12		
QOL score				
Δ60/120/180d	44/50/51	23/30/37		

Limitation of Alfamelanotide

- Invasive method of drug delivery
- **Does not** provide visceral organ protection
- Lack of safety data in children
- Current clinical trial and long term study did not provide laboratory studies data to investigate systemic disease burden

What is the long term implication on disease surveillance and management as a result of skin disease improvement and behavior changes?



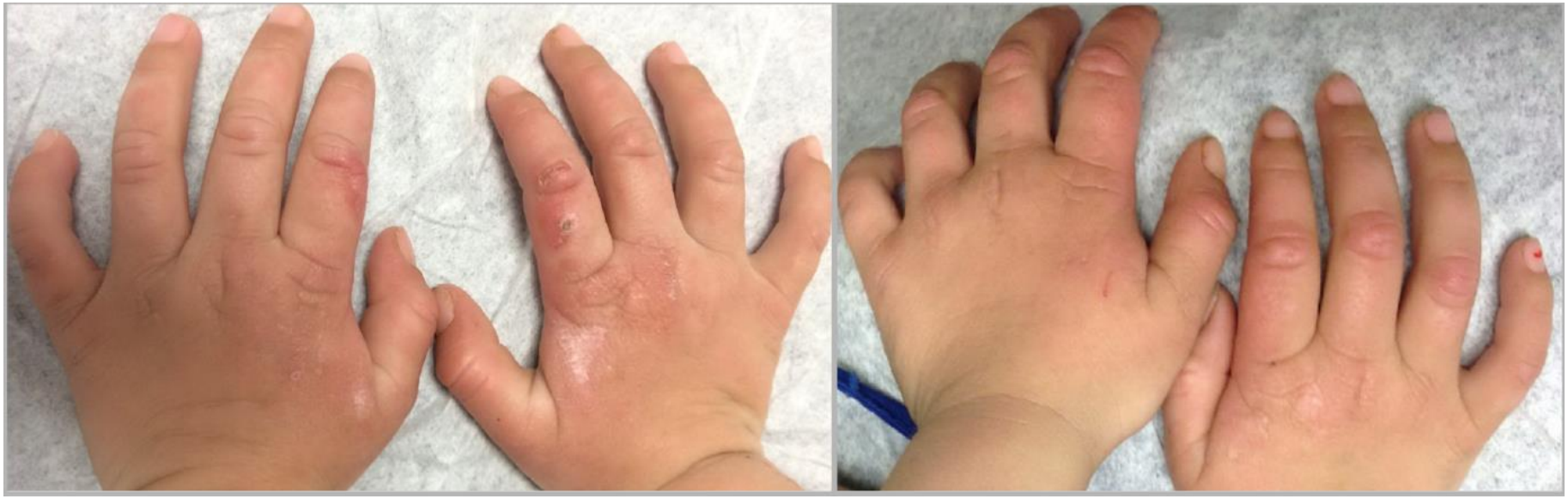
Sclerosing Cholangitis
Biliary Cell Death

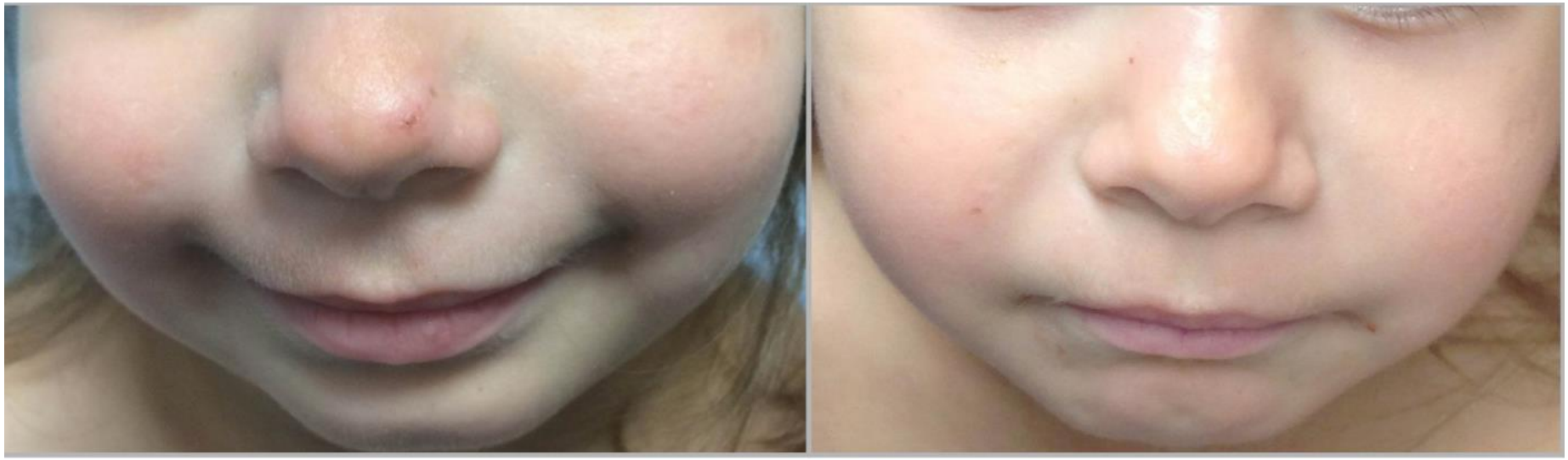
Lyoumi S et al. Gastroenterology 2011;141(4):1509—19.

Novel Treatment Using Cimetidine for Erythropoietic Protoporphyria in Children. Tu et al. JAMA Derm 2016

- Case studies of 3 pediatric patients x 3 years.
- Treatment: Cimetidine 30-40 mg/kg po divided BID
- **Results:**
- Rapid improvement in pain and photosensitivity < 4 weeks
- Normalized LFT in two of the patients.
- **No** adverse effects reported
  - i.e. diarrhea, rashes, dizziness, fatigue, constipation, and muscle pain

- 19 publications on using cimetidine for **PCT and AIP**
- ***Cimetidine*** *reduces erythrocyte protoporphyrin in erythropoietic protoporphyria.* Yamamoto S, Hirano Y, Horie Y. Am J Gastroenterol. 1993 Sep;88(9):1465-6





Cimetidine Treatment for EPP

Possible MOA

- Known inhibitor of CYP-450, a heme-containing enzyme
- Inhibits δ-aminolevulinic acid synthase, 1st enzyme in the heme biosynthetic pathway

Justification for additional study

- Has also been used successfully for other subtypes of congenital porphyria with cutaneous photosensitivity
- Positive global feedbacks from patients
- Rapid onset and LFT improvement in case study
- None invasive treatment
- Long term safety profile as an over the counter medication (FDA appr 1979)
- Frequently used in the pediatric population
- No other therapeutic options currently for patients at risks for liver disease especially children

Effect of **cimetidine** on **delta-aminolevulinic acid synthase** and microsomal heme oxygenase in rat liver.
Marcus DL, et al. Biochem Pharmacol. 1984 Jul 1;33(13):2005-8.

Cimetidine Treatment for EPP

Possible Future Direction

- Randomized trials about safety efficacy
- Special focus on its potential hepatoprotective effects
- Optimal dosing & frequency
  - *Male vs. female*

- Additional study about the mechanism of action
  - *Personalized approach to different subtypes of EPP*
  - *Platform for additional drug discovery*

Potential Therapies (cont)

- Bone Marrow Transplant has been recommended for patients with liver failure or those post transplant

- Rand EB, et al. Sequential liver and bone marrow transplantation for treatment of erythropoietic protoporphyria. Pediatrics 2006
- Wahlin S, et al. Curative bone marrow transplantation in erythropoietic protoporphyria after reversal of severe cholestasis. J Hepatol 2007;46:174-9

Erythropoietic Protoporphyria

- 3rd most common porphyria; most common in children
- Pseudo dominant; AD, AR, X-linked
- 1:5,000-140,000, equally common in males and females
- **Genetic:**
  - Biallelic or compound heterozygous *FECH* mutations
    - *FECH IVS3-48C* allele (65% in China)
  - X-linked GOF*ALAS2* mutations (OMIM 300752)
    - 2% in UK and France; 10% in US
    - 40% Zn-PPIX
  - Late-onset phenotype 2/2 MDS somatic mutations
- Ferrochelatase deficiency (<35% normal activity)

Other Resources

More information:

- www.porphyriafoundation.com
- www.rarediseasesnetwork.org/porphyrias/index.htm
- www.porphyria-europe.org/

Overview of Discussion Format

Sara Eggers, PhD
Office of Strategic Programs
Center for Drug Evaluation and Research
Food and Drug Administration

October 24, 2016

Discussion Format

- **We will first hear from a panel of patients**
  - The purpose is to set a good foundation for our discussion
  - They reflect a range of experiences with organ transplantation

- **We will then broaden the dialogue to include patients and caregivers in the audience**
  - The purpose is to build on the experiences shared by the panel
  - We will ask questions and invite you to raise your hand to respond
  - Please state your name before answering

Discussion Format, continued

- **You'll have a chance to answer "polling" questions**
  - Their purpose is to aid our discussion
  - In-person participants, use the "clickers" to respond
  - Web participants, answer the questions through the webcast
  - Patients or parents of patients only, please

- **Web participants can add comments through the webcast**
  - Although they may not all be read or summarized today, your comments will be incorporated into our summary report
  - We'll occasionally go to the phones to give you another opportunity to contribute

Discussion Ground Rules

- We encourage patients to contribute to the dialogue– caregivers and advocates are welcome too
- FDA is here to listen
- Discussion will focus on symptoms and treatment experiences
  - Open Public Comment Period is available to comment on other topics
- The views expressed today are personal opinions
- Respect for one another is paramount
- Let us know how the meeting went today; evaluation forms are available at the registration table

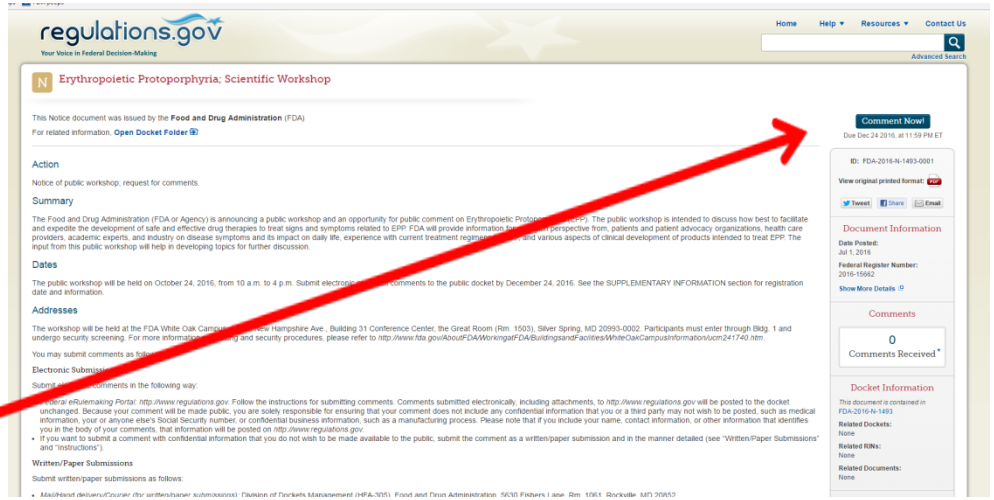
Send us your comments!

- **You can send us comments through the "public docket"**
  - The docket will be open until December 24, 2016
  - Share your experience, or expand upon something discussed today
  - Comments will be incorporated into our summary report
  - Anyone is welcome to comment

Visit:
https://www.regulations.gov/document?D=FDA-2016-N-1493-0001

Or Search "Erythropoietic Protoporphyria" on
www.regulations.gov

And **Click Comment Now!**



Where do you live?

A. Within Washington, DC metropolitan area (including the Virginia and Maryland suburbs)
B. Outside of the Washington, D.C. metropolitan area

Have you ever been diagnosed as having EPP, or do you have a child who has been diagnosed with EPP?

A. Yes
B. No

What is your age?

A. Younger than 18
B. 18 – 29
C. 30 – 49
D. 50 – 69
E. 70 or greater

Do you identify as:

A. Male
B. Female
C. Other

At what age did you first notice symptoms related to EPP?

A. Younger than 5
B. 5 – 12
C. 13 – 17
D. 18 – 29
E. 30 – 49
F. 50 – 69
G. 70 or greater

At what age were you diagnosed with EPP?

A. Younger than 5
B. 5 – 12
C. 13 – 17
D. 18 – 29
E. 30 – 49
F. 50 – 69
G. 70 or greater

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Patient Perspectives on Symptoms and Current Approaches to Treatments

Sara Eggers, PhD
Facilitator

October 24, 2016

Panel Participants

- Monica Fleegel
- Madelyn Havard
- Victor Mejias
- Meghan Rohn
- Kerry Wiles

Discussion Questions

- Which symptoms have the most significant impact on your daily life?
  - Activities you cannot do at all or as fully as you would like
  - Changes in symptoms and impacts over time
- What are you currently doing to manage your EPP?
  - How well do your treatments control your condition?
- What would you look for in an ideal treatment?
  - What would you consider to be a meaningful improvement in your condition that a treatment could provide?

Of all the symptoms you have experienced because of EPP, which have the most significant impact on your daily life? *Please choose up to three symptoms.*

A. Skin redness or inflammation
B. Itching
C. Burning or stinging
D. Pain or soreness (other than burning or stinging)
E. Blistering or ulcers
F. Swelling
G. Skin thickening or scarring
H. Lightening or darkening of the skin (pigmentation changes)
I. Other impacts not mentioned

Which aspects of daily life are impacted the most by EPP? *Please choose up to three impacts.*

A. Maintaining physical health

B. Ability to participate or perform at work or school

C. Ability to participate fully in extracurricular activities (such as sports, hobbies, etc.)

D. Ability to concentrate or focus

E. Ability to fall asleep or stay asleep

F. Intimacy or relationships

G. Emotional well-being (such as anxiety, self-esteem or stigma)

H. Other impacts not mentioned

What are you currently doing to treat your condition or its symptoms? *Check all that apply.*

A. Topical treatments (such as sunscreen)
B. Protective clothing or masks
C. Lifestyle changes (such as sun or light avoidance)
D. Cimetidine (or Tagamet)
E. Colestipol (or Colestid)
F. Dietary or herbal supplements (such as beta-carotene)
G. Phototherapy (such as light box or tanning booth)
H. Complementary or alternative therapies
I. Other therapies not mentioned

When considering a new treatment for EPP, which of the following benefits would you consider to be most meaningful? Please choose up to three.

A. Increased tolerance of sunlight

B. Reduced skin redness and inflammation

C. Reduced itching, burning or stinging

D. Reduced pain or soreness (other than burning or stinging)

E. Reduced blistering or ulcers

F. Reduced swelling

G. Reduced skin thickening or scarring

H. Reduced lightening or darkening of the skin (i.e., pigmentation changes)

I. Reduced risk of liver damage

Of the following factors, which two would you rank as most important to your decisions about treatments to help reduce or control the symptoms of EPP?

A. How the medication is administered (such as topical, oral, injection, etc.)
B. The frequency and length of treatment
C. Your access to treatment (for example, insurance coverage, travel)
D. Whether the medical product showed effectiveness for the specific benefit that is most meaningful to you
E. The common side effects of the treatment (such as nausea or fatigue)
F. The possibility of rare, but serious side effects (such as malignancy)
G. Your previous response to a similar treatment
H. Whether there are other treatment options that you can still try

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An Overview of the FDA Regulatory Process

October 24, 2016

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Overview of Drug Development and the FDA Regulatory Process

Scientific Workshop on Erythropoietic Protoporphyria (EPP)

October 24, 2016

J. Paul Phillips, MS

Division of Dermatology and Dental Products

Outline

- Discovery/Nonclinical development
- Investigational New Drug application
- Clinical development
- New Drug/Biologic application
- Post-approval

Definitions

The Food and Drug Administration (FDA): federal agency responsible for issuing and enforcing regulations that outline the standards for drug development

Investigational New Drug application (IND): enables a sponsor to conduct clinical trials with a drug product for an unapproved use

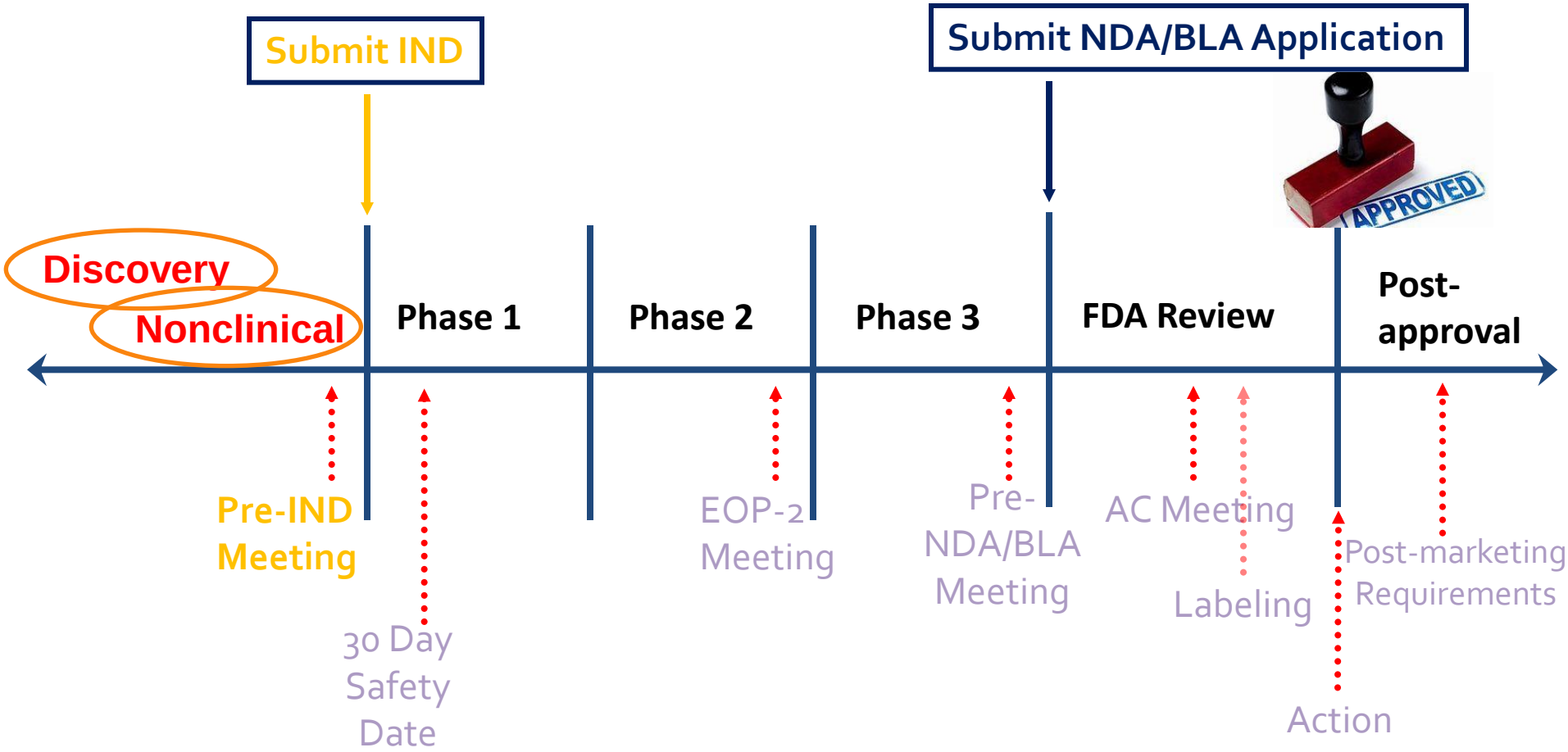
New Drug Application (NDA): contains information about a drug product to support FDA review and if approved allows sales & marketing of the drug product

Biologics License Application (BLA): contains information about a biologic product to support FDA review and if approved allows sales & marketing of the biologic product

Sponsor: any company, physician, or other entity that submits an IND

Applicant: any entity that submits an NDA or BLA

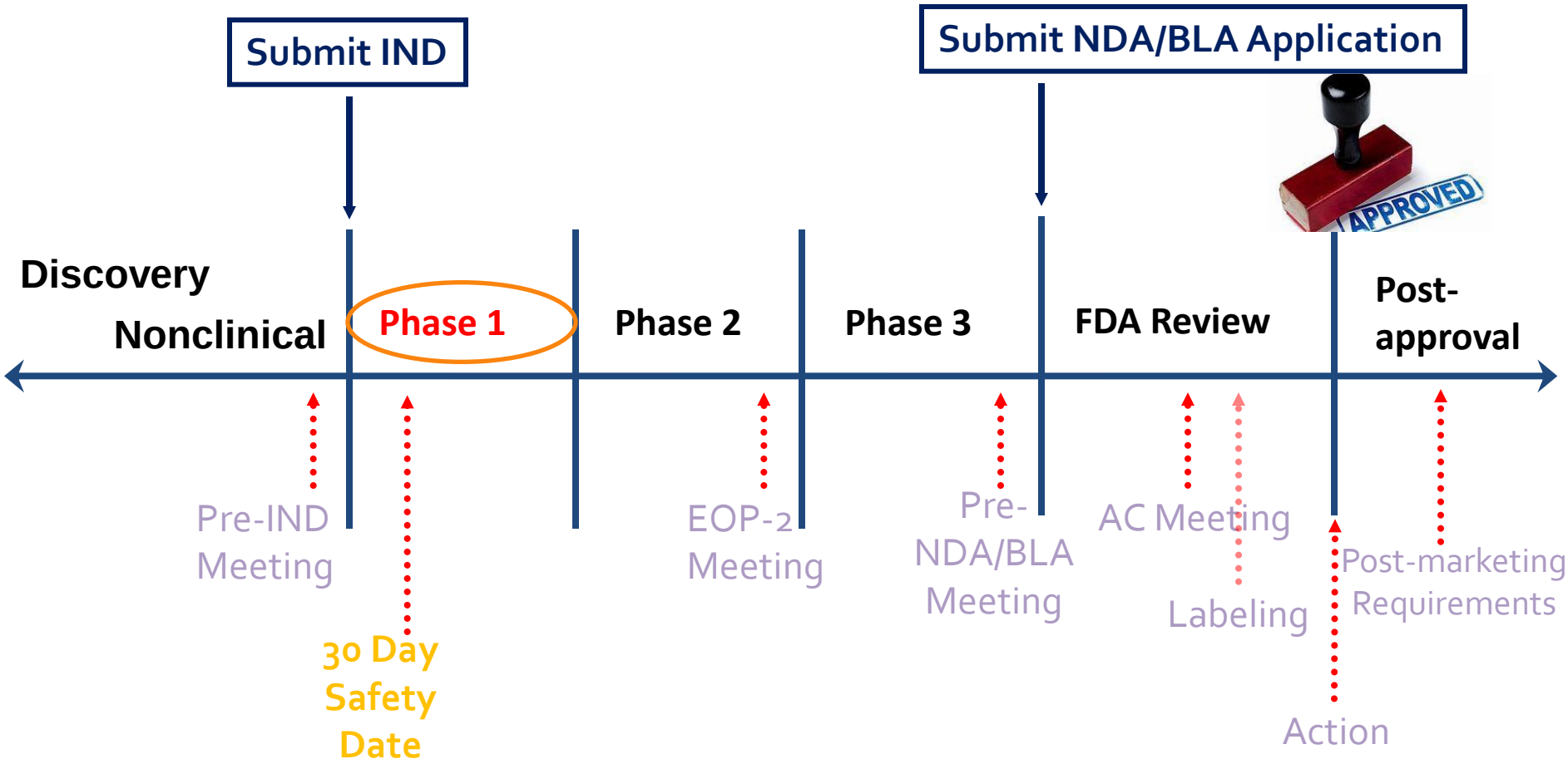
The Drug Development Process



Investigational New Drug Application

- Product quality [21 CFR 312.23(a)(7)]
  - Description of drug substance and drug product
  - Information to assure their identity, quality, purity, and strength
  - Information to support stability for duration of planned clinical studies
- Pharmacology/Toxicology [21 CFR 312.23(a)(8)]
  - Mechanism of action (i.e. what the drug does to the body) if known
  - Results from toxicity tests in a rodent (e.g. rat) and nonrodent (e.g. rabbit)
  - Safety studies to ensure no adverse effect on vital organs (i.e. heart, lungs, brain)
  - Results from tests to ensure the drug does not damage genetic material
- Previous human experience [21 CFR 312.23(a)(9)]
  - Information about the safety and effectiveness (if known) for the intended investigational use

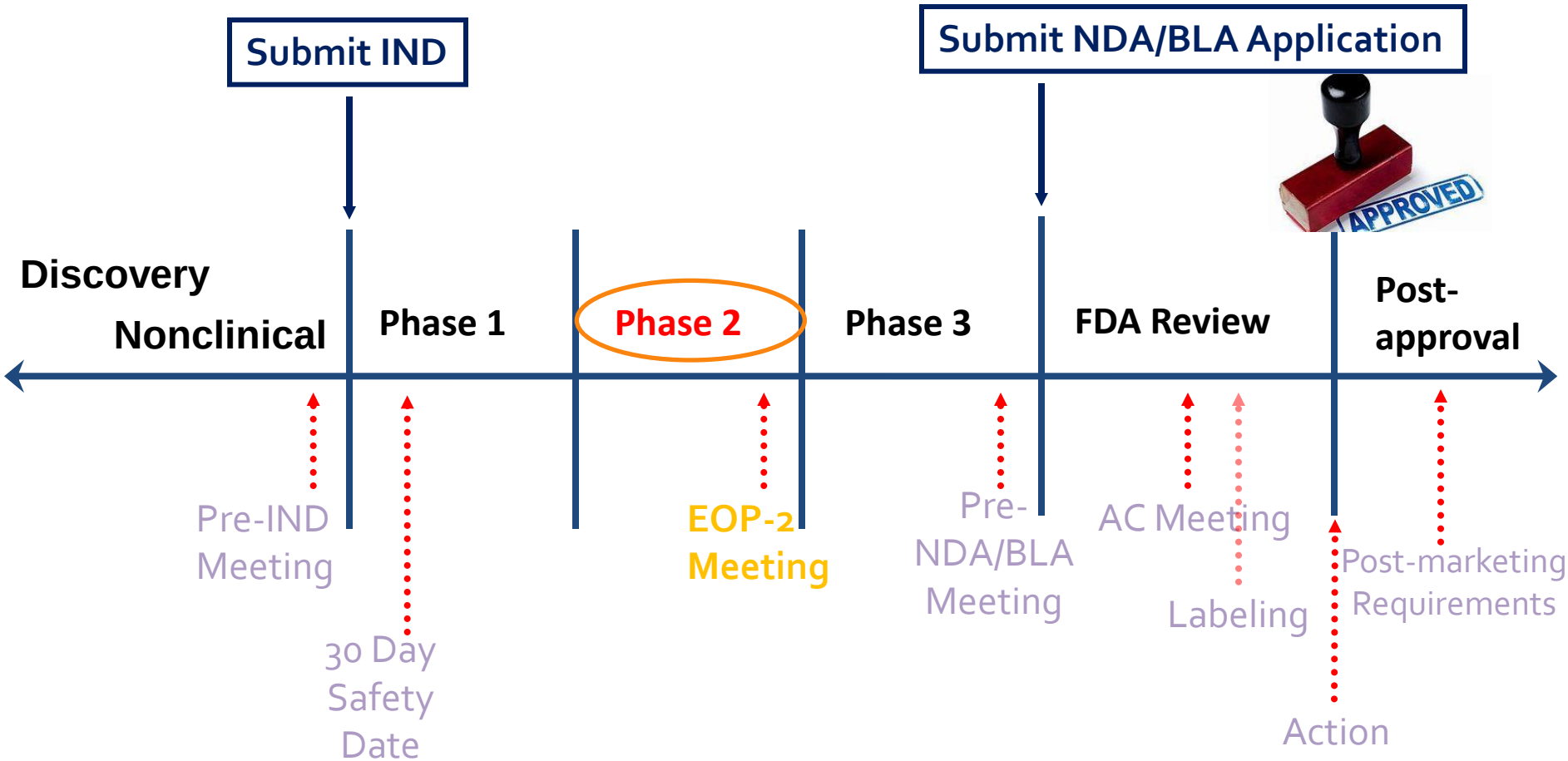
The Drug Development Process



Clinical- Phase 1

- First-in-human
- Healthy volunteers
- Low dose
- Assess safety
- Gather Pharmacokinetic (PK) data
- Food effects
- Good Clinical Practice [ICH E6 guidance]

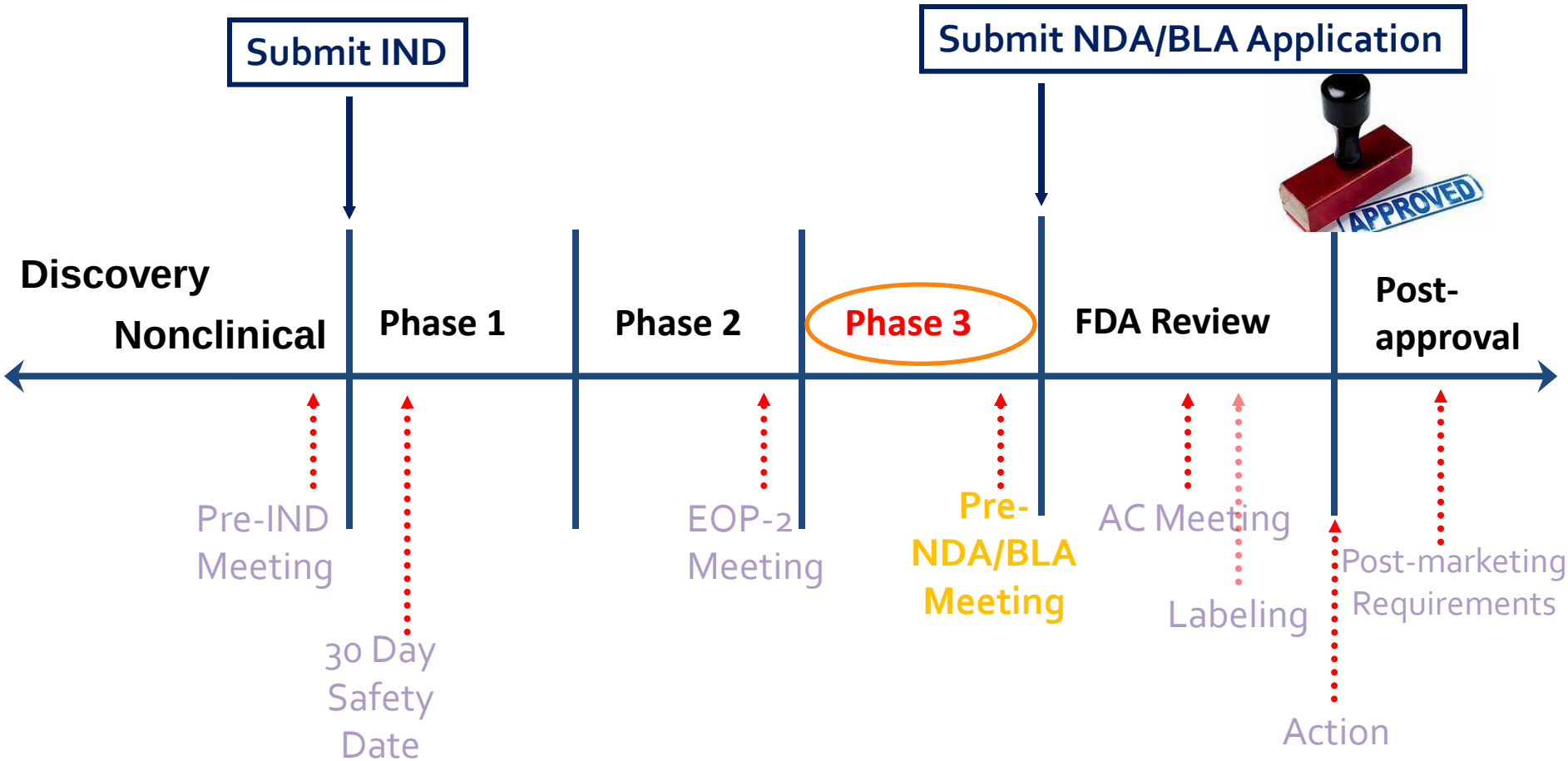
The Drug Development Process



Clinical- Phase 2

- Volunteers with disease of interest
- Dose ranging
- Preliminary efficacy
- Continue to assess safety
- Gather PK data
- Food effects
- Good Clinical Practice [ICH E6]
- End-of-Phase 2 meeting [21 CFR 312.47]

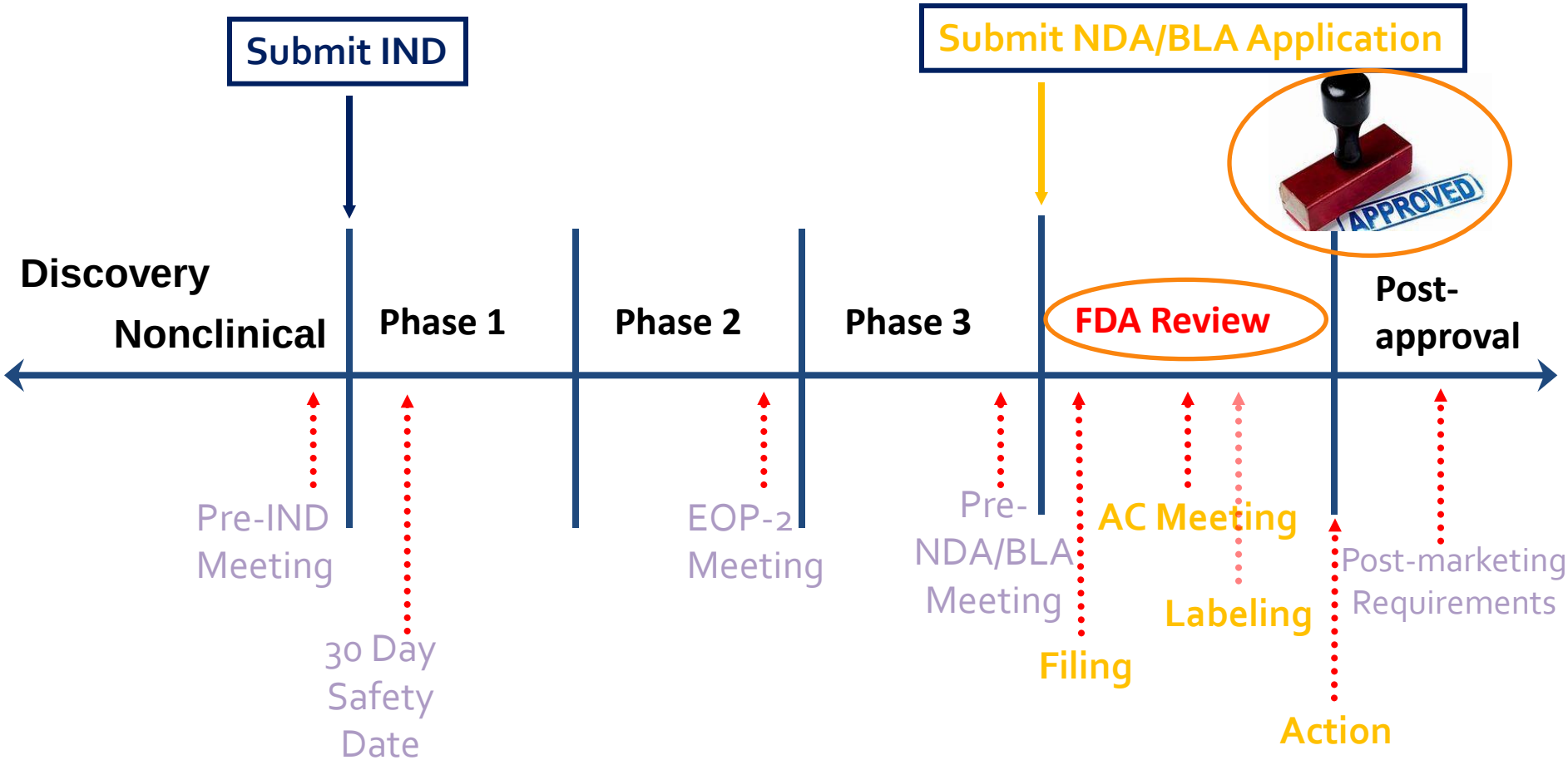
The Drug Development Process



Clinical- Phase 3

- Volunteers with disease of interest
- To-be-marketed drug product formulation and dose(s)
- Confirm efficacy—“substantial evidence” [FD&C § 355]
- “adequate and well-controlled” [21 CFR 314.126(b)] trials
- Continue to assess safety
- Gather PK data
- Food effects
- Good Clinical Practice [ICH E6]
- pre-NDA/BLA meeting [21 CFR 312.47]

The Drug Development Process

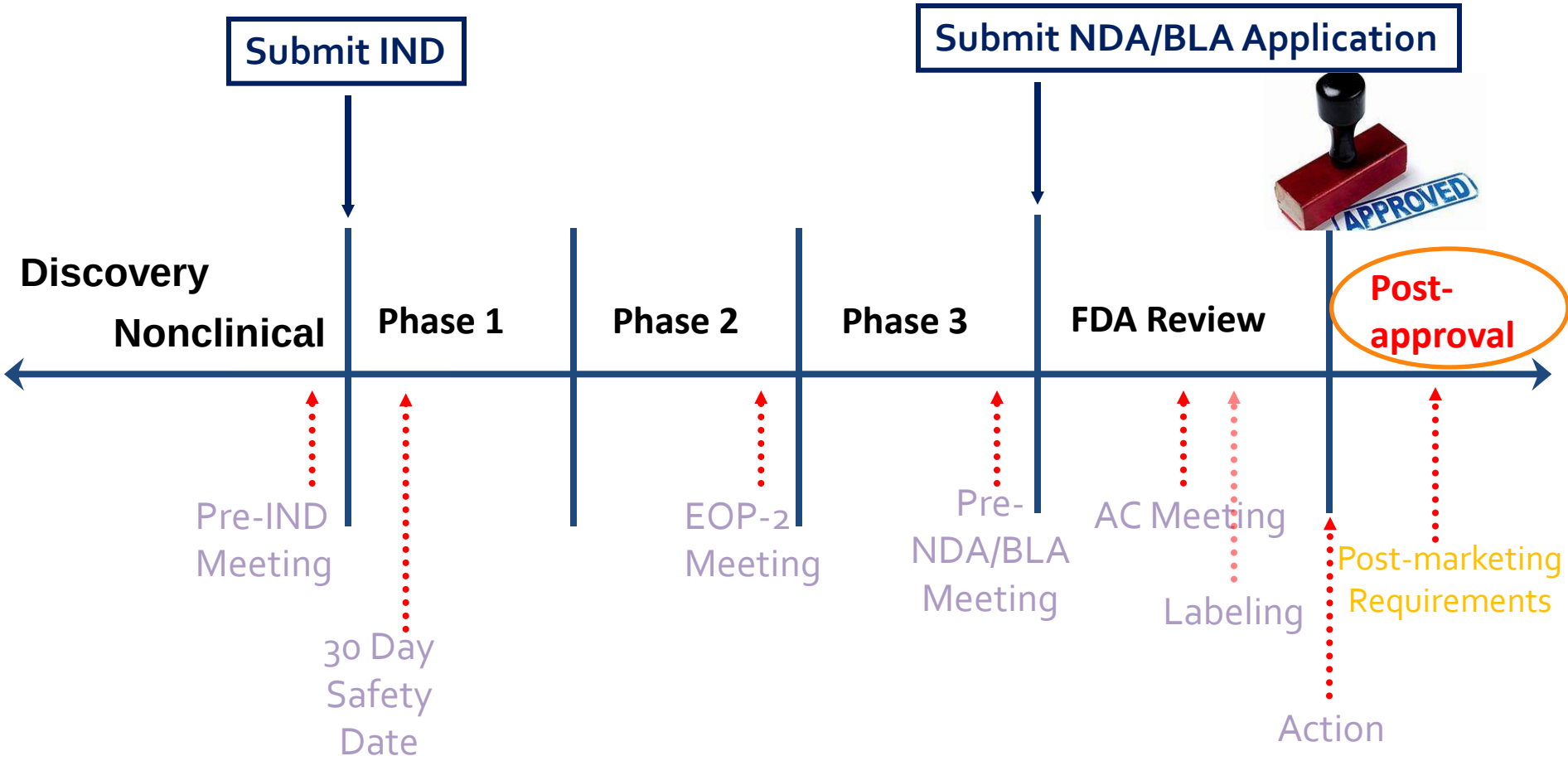


Marketing Application Review

- Filing determination [21 CFR 314.50]
- Scientific (e.g. clinical, biostats, etc.) reviews
- Advisory committee meeting (optional)
- Product labeling discussions
- "Substantial evidence" determination
- Benefit:risk decision
- Final action:
  - "Approval" (applicant can legally market the new drug product)

  or
  - "Complete Response" (more information is needed to establish that the benefits outweigh the risks for the intended use)

The Drug Development Process



Post-Approval

- Adverse events reports [21 CFR 314.80]
- FDA Sentinel system
- Post-marketing requirements/commitments [21 CFR 314.81(b)(2)(vii)]
  - Pediatric Research and Equity Act (PREA)
  - Food & Drug Administration Amendments Act (FDAAA)
- Investigate new indications [21 CFR 314.70]

Basic Concepts in Rare Disease Drug* Development and Review

Kathryn O'Connell, MD PhD
Rare Diseases Program
Office of New Drugs/CDER/FDA

for this talk, the word "drug" refers to new drugs and original biological products regulated in FDA's Center for Drug Evaluation and Research (CDER)

What do 'rare' and 'orphan' mean?

- A **rare disease** is defined in the **Orphan Drug Act** as a disease/condition that affects <200,000 people in the US

  note: prevalence can be >200,000 people if "no reasonable expectation" of recovering development & marketing costs

- An **orphan drug** is a drug (or biological product) used for the prevention, diagnosis or treatment of a rare disease in the US

The 1983 Orphan Drug Act (ODA)

- Enacted to stimulate product development for rare disease/condition diagnosis, prevention or treatment

- **Financial incentives**
  - ✓ tax credits up to 50% of qualified clinical trial costs
  - ✓ waiver of FDA User Fees

    note: the fee *is* applied if application includes an indication other than the rare disease for which the drug was designated
  - ✓ seven years of marketing exclusivity

The ODA *does not* alter the statutory standard for drug approval

The regulatory requirements and process for obtaining marketing approval are the same for drugs granted orphan designation as for common disease drugs

Patients affected by rare diseases deserve the same level of quality, safety, and efficacy

Flexibility is part of FDA regulations and is frequently used in evaluation of rare disease drug development programs

Special standards for orphan drugs are unnecessary because the regulations at 21 CFR 314.105 (Applications for FDA Approval to Market a New Drug) provide for flexibility and judgment in applying the standards

US approval essentials

- ✓ Substantial evidence of effectiveness for treatment of the proposed indication
- ✓ Demonstration that the benefits of the drug outweigh its risks for the patient population for which the drug is indicated (21CFR 314.50)
- ✓ Manufacturing that ensures product identity, strength, quality (purity)
- ✓ Evidence-based drug labeling that adequately guides providers and patients to use the drug safely and effectively

The regulatory requirement for approval in the US

- Demonstration of **substantial evidence** of effectiveness requires studies designed well enough "to distinguish the effect of a drug from other influences, such as spontaneous change… placebo effect, or biased observation"
- "The benefits exceed the risks under the conditions stated in the labeling"
- The usual approval standard is two **adequate and well-controlled** studies

21CFR 314.50 and 21CFR 314.126

How much evidence is enough?

FDA Modernization Act (FDAMA)

(1997)

Amended Section 505(d) of the Food, Drug, and Cosmetic Act to clarify that FDA may consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute substantial evidence

FDA Guidance 1998
Providing Clinical Evidence of Effectiveness for Human Drug & Biological Products

- For many scientific reasons reliance on a single study is generally limited to
  - a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a **serious** disease
  - situations where confirmation in a second trial is not feasible
- Reliance on a single study is a judgment call

Safety evidence for approval

The adequacy of safety data to support marketing approval is a judgment call based on the overall assessment of benefit-risk within the context of the disease

- Demonstration of substantial evidence of effectiveness
- The benefits must exceed the risks under the conditions stated in the labeling

There are TWO pathways in the US

traditional (regular or "full") **approval**

and

accelerated approval

the statutory standards are the same for both

demonstration of substantial evidence based on adequate and well-controlled clinical study(ies)

Accelerated approval: a pathway to speed regulatory approval

- Drug must provide a meaningful advantage over available therapies to treat a **serious** condition, generally irreversible morbidity or mortality
- Relies on a **more readily measured surrogate** (or intermediate clinical) **endpoint**
- A post-approval confirmatory study evaluating a **direct clinical endpoint** is generally required

Clinical vs. surrogate endpoints

- **Direct clinical** endpoint: characteristic or variable that *directly* measures a therapeutic effect - how a patient feels, functions, or survives

- **Surrogate** endpoint for accelerated approval: marker *thought to predict* clinical benefit; not itself a measure of benefit

A note about historical controls

- Historically controlled studies can be adequate and well controlled studies in appropriate cases

HOWEVER

Such studies have ***many*** interpretability issues

THEREFORE

- Placebo or active controlled trials remain the goal for rare (and common) diseases whenever ethically and practicably feasible

A note about expanded access programs

- Expanded access is use of an **investigational** (has not been approved by FDA) medical product **outside** of a clinical trial
- Whenever possible, patient enrollment in a clinical research trial is preferable because trials generate data that may lead to FDA approval and wider availability
- When trial enrollment is not possible (patient is not eligible or there is no trial), a patient *may* be able to receive the product, when appropriate, through expanded access
  - for the diagnosis, monitoring, or treatment of a **serious disease or condition if** necessary conditions are met

Guidance for Industry - Expanded Access to Investigational Drugs for Treatment Use – Questions and Answers (June, 2016)

Expanded access process

- **Safeguards for patients**: FDA review, informed consent, institutional review board (IRB) review, safety reporting requirements
- FDAs **Office of Health and Constituent Affairs** staff can provide information and assistance
  - webpage includes the Expanded Access request form (designed to be completed in <45 min), Q&A, information pages for patients and physicians

http://www.fda.gov/ForHealthProfessionals/ExpandedAccess/default.htm

- More than 99% of expanded access applications received by FDA have been allowed to proceed
- FDA requested changes to protect participants for 11% of the applications

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Challenges in Clinical Trial Design for Erythropoietic Protoporphyria

Elisabeth Minder, MD
Stadtspital Triemli, Porphyria Outpatient Clinics,
Zürich, Switzerland

October 24, 2016

Conflict of interest statement

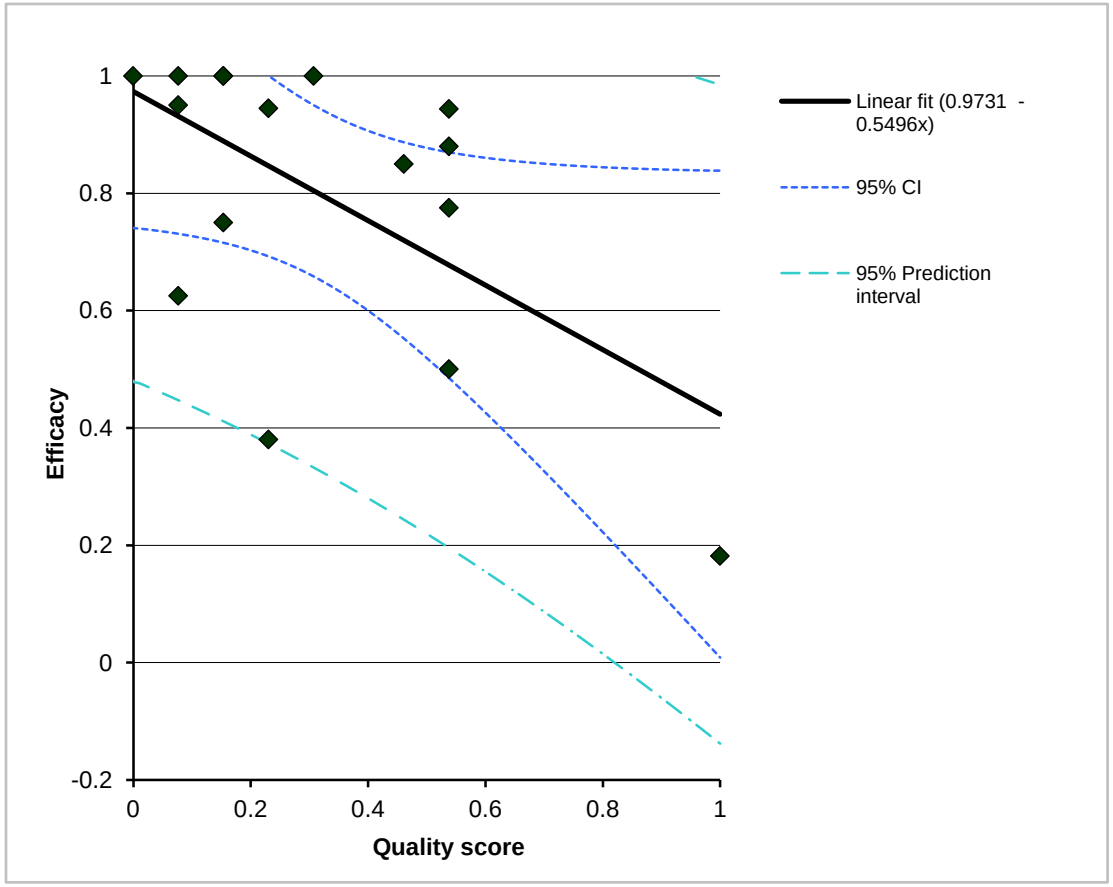
- PI in two trials of afamelanotide
- Two grants by Clinuvel Pharmaceuticals to our institution:
  - immunogenicity of afamelanotide in EPP: $ 5000;
  - training of young porphyria experts: $1000)
- Expert consultation to European Medicines Agency (EMA) and Gemeinsamer Bundesausschuss (German Authority)
- Acted several times as consultant on behalf of Clinuvel Pharmaceuticals at EMA and national authorities (all without honorarium)

Our expertise in Porphyria

- Since 1980, I work as a researcher and clinician in the field of porphyria
- We care for 500 Swiss porphyria patients
- Patients from European (Germany, France, Belgium, Austria, Luxembourg, Poland) and non-European countries (Jordan, USA) had requested visits in our outpatient clinics
- Since the 1990's focus in erythropoietic protoporphyria
- Member of the European Porphyria Initiative, Member of EPNET (European Porphyria network), organizers of the International Congress of Porphyrins and Porphyrias 2013
- Laboratory fully certified (ISO 17025, ISO 15189)
- Genetic laboratory certified by Swiss national authory

The importance of high trial quality in EPP

(example betacarotene – low quality>high efficacy, high quality>low efficacy)



Minder EI, et al. 2009

First challenge: Definition of EPP

- Phototoxic episodes since infancy or early childhood (in neonatal period not affected)
- Significantly increased (>5 times) metal-free protoporphyrin in Ec
- [Heterozygous mutation in FECH combined *in trans* with IVS3-48c>t polymorphism, rare compound-heterzygous or homozygous cases or heterozygous activating ALAS2 mutation]

Congenital erythropoietic porphyria (or hepatoerythropoietic porphyria) may manifest with

- Symptomatic as newborsn, burns by phototherapy
- Recurrent blisters
- Extended scars

(s. case 3 Tu el al. JAMA dermatology 2016; 13. July)

Second challenge: rational of a treatment

- Skin-barrier against light activation of PPIX (increase of pigmentation or colouring compound at 410nm-550-700nm, visible light): dihydroxyacetone*, betacarotene*, afamelanotide***, Ti-di-oxid/Zn-oxide containing suncreens*, UVB treatment**
- Scavenging of oxygen radicals or other inflammatory compounds: betacarotene*, afamelanotide***, cysteine*, antihistaminics*
- Mitigation of local skin-inflammation, prosurvival activity: afamelanotide***
- Inhibition of ALAS2 (iron-deprivation^{O}, cimetidine$^{?}$)

* No clinical effect observed by our team; ** marginally effective, not tolerated by many patients; *** highly effective; ^{O}limited by adverse effects; $^{?}$insufficient preclinical evidence

Modulating (liver) ALAS

Marcus DL, 1984; biochemical pharmacology 33: 2005.

In vivo

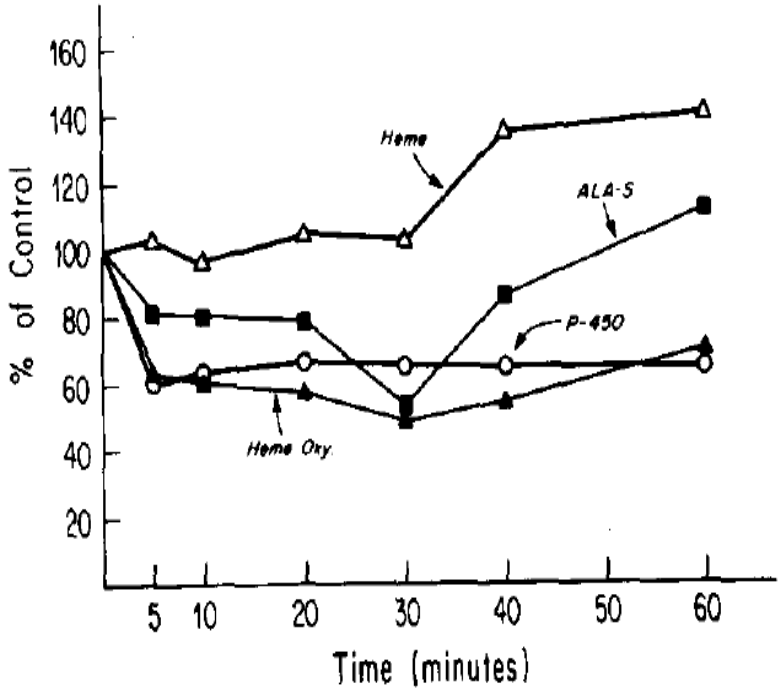


Fig. 3. Time course of the effect of cimetidine on the components of the heme regulatory pathway. Rats were treated with cimetidine, and the enzymes were assayed as in Fig. 2. Key: (△) microsomal heme; (■) ALA-S; (○) cytochrome P-450; and (▲) heme oxygenase. Each point represents the value obtained for pooled livers from three rats.

In vitro

Table 1. Effect of cimetidine on the *in vitro* determination of ALA-S, heme oxygenase and cytochrome P-450*

	Percent control activity remaining		
	ALA-S	Heme oxygenase	Cytochrome P-450
No addition (control)	100	100	100
Cimetidine			
10^{-2} M	96.7	48.0	82.5
10^{-3} M	103.2	54.0	80.0
10^{-4} M	95.5	78.0	94.5
10^{-5} M	96.7	114.0	95.0
10^{-6} M	93.8	108.0	95.0
10^{-7} M	103.2	104.0	102.8

* Each enzyme was prepared, incubated with the indicated concentration of cimetidine for 30 min at 37° and then assayed according to Materials and Methods.

As shown in Fig. 1, 50% inhibition of ALA-S activity occured after a dose of 20 mg of cimetidine/100 g body wt was administered 30 min prior to sacrifice. Table 1 shows that there is no direct *in vitro* effect of cimetidine on the activity of this enzyme through the entire concentration range tested. The

Third challenge: limitations of evidence-based medicine decisions in rare diseases

- Complexity of disease (affects outcome measurements)
- High variablility of symptoms even in «monogenic» diseases (reduction of statistical significance)
- Adaptation and disease coping (initial overstimation of QoL)
- Minor positive changes may be significant for the patient's life quality («common sense» clinical efficacy may be misleading)
- Lack of qualified instruments for outcome measurements (without an effective therapy an outcome instrument cannot be validated)

Complexity of disease

EPP ≠ «sunlight-sensitivity»

irradiance ≠ extent of phototoxic damage

Complexity of disease: more than sunlight sensitivity

- Patients are sensitive to
  - Direct sunlight
  - Sunlight passing through windows
  - Sunlight reflections (beach, snow, glass)
  - Bright sunshine less offending than overcast sky, «white light», «greyish sky», fog
  - Indirect light in the shadow (outdoors, in rooms)
  - Artificial light, especially last-generation «energy-saving» bulbs (LED, halogen, fluorescent)
  - Wind
  - Temperature
  - Air humidity

Complexity of disease – offending wavelength

- Exact wavelenght(s) of symptom provocation unknown
  - Blue light
  - Red light
  - Some patients UV
  - IR? (Patients report heat intolerance at least during phototoxic attacks)

Complexity of disease – lack of correlation of irradiance and extent of photodamage

- Effect of latitude
  - In tropical areas and even in desertic areas some patients have less symptoms than in temperate zones.
  - Some patients report within temperate zones to have more symptoms in higher latitudes than in lower ones

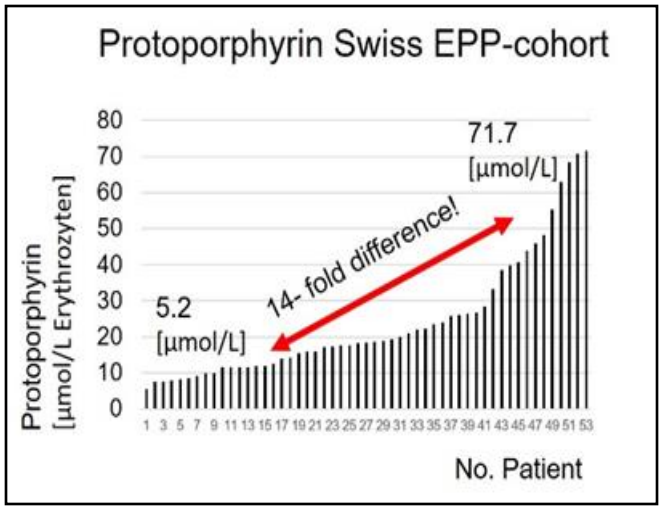
Complexity of disease - phototoxicity

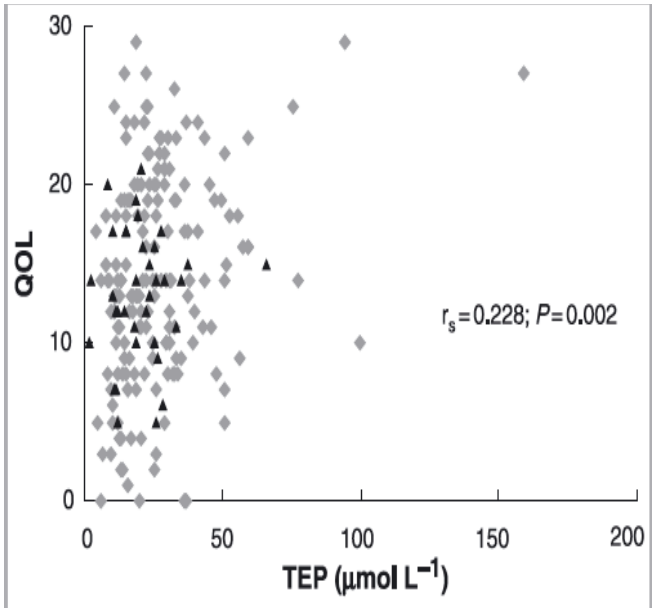
- It is not only acute phototoxicity on a day-to-day basis: Photodamage accumulates
  - priming phenomenon,
  - «light account»: Accumulation of augmented light sensitivity over days

Complexity of disease - variability

- Protoporphyrin levels vary widely between patients (In Swiss patients without liver complications 14-times). Skewed distribution, no subgroups!

- DLQI-QoL is (positively) correlated with protoporphyrin levels, correlation being weak (Home SA 2006).





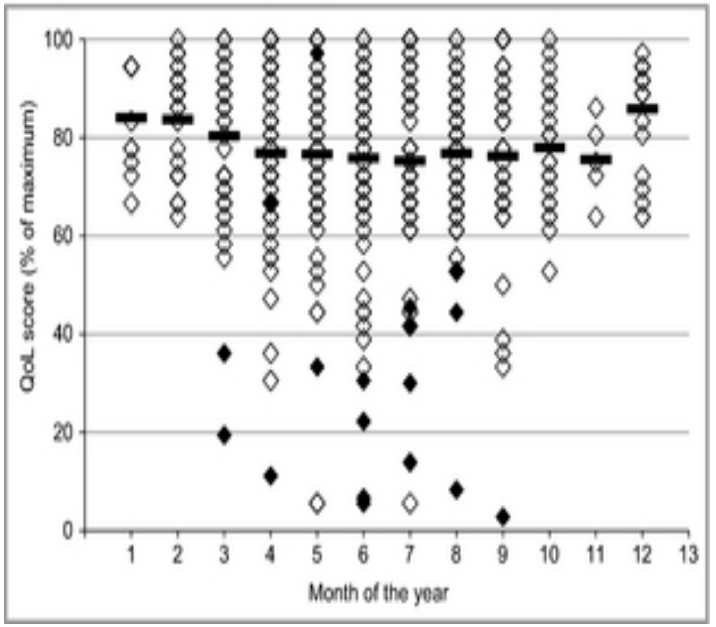
Fourth challenge: trial endpoints

without an effective treatment, sensitivity of efficacy determinations cannot be validated

- Sunlight exposure
- Pain intensity

Complementary endpoints, measuring only one of them results in loss of sensitivity

- Protoporphyrin concentration (if intended to be influenced by treatment)
- Quality of life
  - ~~DLQI,~~
  - ~~SF36,~~
  - EPP-QoL: Disease-specific!!!
    - Good discrimination between treated and untreated patients
    - High sensitivity (seasonal effect visible)



Complementary endpoints: sunlight exposure and pain intensity

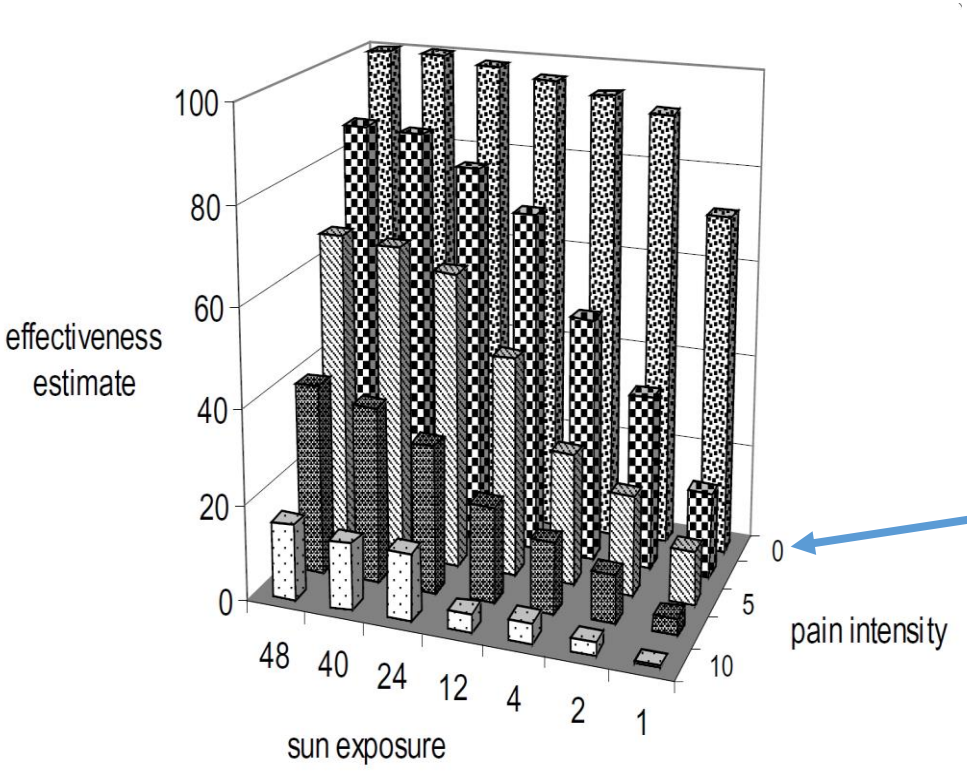


Figure 1 The effect of sunlight exposure time and pain on effectiveness estimate. The means of 490 estimates of effectiveness are plotted against both pain levels and sunlight exposure time. The pain scores are: 0 = no pain, 2 = mild pain, 5 = moderate pain, 8 = strong pain, 10 = intolerable pain. Exposure times are expressed as "multiples of 15 minutes", e.g. 1 = 15 min, 10 = 2.5 hours, 48 = 12 hours etc. The effectiveness ratings are in percent between 0 and 100. It is evident, that pain has a higher influence on the effectiveness rating than sunlight exposure time.

Minder et al, 2010

Best estimate practically: sunlight exposure without pain (Langendonk et al. NEJM 2015)

Afamelanotide versus placebo:
69.4h vs 40.8h p=0.04, n=89 (US trial)
6.0h vs 0.8h p=0.005 n=74 (EU trial)

Unblinding by skin pigmentation or coloring may induce a bias in double-blind trials

- Using diaries in a randomized, double-blind trial Corbett found 1977 no effect of betacarotene compared to placebo, despite unblinding by high dose betacarotene: Diary registration are apparently not affected by unblinding.
- In contrast, Norris found 1995 a high placebo effect using N-acetyl-cysteine. He used retrospective questionnaires.
- Diaries are therefore the reliable option to prevent unblinding related bias.

Last challenge: statistical efficacy and clinical efficacy

- Clinical efficacy is not a scientific term, it is «common sense» of healthy persons
- If no validated comparator exists, statistical efficacy should be taken as clinical efficacy
- Averaging per day is a misleading term (rainy days, staying inside because of work, habit and life-long conditioning reduce the effect)
- Validation of clinical efficacy in EPP treatment:
  - Judgement of effectiveness by patients
  - Patients' own share to receive treatment
  - Treatment adherence (8% discontinuation to non-compelling reasons in long-term application (Biolcati 2015))

Thank you for your interest

Discussion Topics

- Considerations when defining EPP trial population
- Choosing appropriate endpoints:
  - Endpoints that can be reliably measured and interpreted
  - Endpoints that can demonstration clinically meaningful benefit
  - Types of measures (e.g., patient reported outcomes, lab measures)
- Other clinical trial design considerations:
  - Choice of control, e.g. placebo, active comparator, dose response
  - Trial duration
  - Potential for unblinding due to side effects, e.g., pigmentary changes)
  - Use of photoprovocation
- Patient and caregiver experiences in clinical trials

Have you or your loved one ever participated in any type of clinical trial studying experimental treatments for EPP?

A. Yes

B. No

If you or your loved one had the opportunity to participate in a clinical trial to study an experimental treatment, would you consider participating?

A. **Yes:** It would depend on many factors, but I am generally willing to consider participating

B. **No:** I would probably not consider participating

C. **Maybe:** I am not sure whether I would be generally willing to consider participating or not

What are the biggest factors you would take into account if you had the opportunity to consider participating in a clinical trial for an experimental EPP treatment? *Please choose up to three factors.*

A. Complexity of study requirements
B. Eligibility criteria (such as exclusion requirements)
C. Location of study site
D. Concerns about side effects
E. Placebo as a control
F. Need to stop current medications
G. Trial duration
H. Informed consent procedures
I. Other

Experts: Of the following factors, which are the most significant to address in designing a robust and feasible clinical trial? *Please choose up to three factors.*

A. Understanding natural history of EPP
B. Appropriately defining trial population
C. Choosing endpoints that are meaningful to patients
D. Choosing endpoints that can be reliably measured and interpreted
E. Choosing an appropriate control
F. Selecting an appropriate trial duration
G. Complexity of study protocol and requirements
H. Recruiting and retaining trial participants
I. Other

Discussion Topics

- Considerations when defining EPP trial population
- Choosing appropriate endpoints:
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Closing Remarks

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Center for Drug Evaluation and Research
U.S. Food and Drug Administration

October 24, 2016