



photonamic



A dermal application of 5-ALA for photodynamic therapy (PDT)

to see. to know. to heal.



photonamic

The indication: Actinic keratosis

Actinic keratosis in the EU

- Actinic keratosis (AK) = pre-cancerous lesion/SCC in situ
- More than 42 million people affected

Current treatment modalities

- Cryosurgery
- Topical creams (Effudix, Aldara, Solaraze)
- Photodynamic therapy

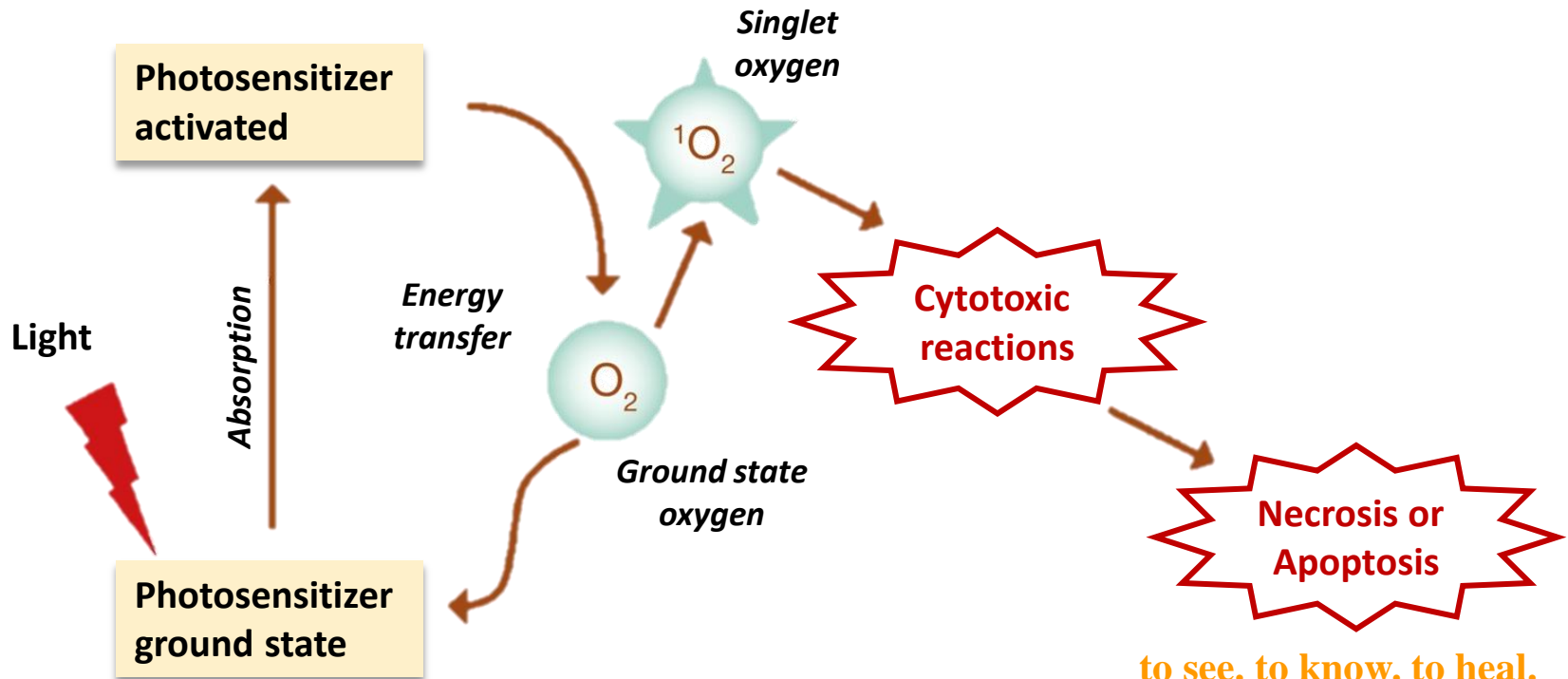
to see. to know. to heal.



Photodynamic Therapy (PDT)

photonamic

- Therapeutic use of a photochemical reaction
- First clinical application 1903 in Munich
- PDT mechanism:



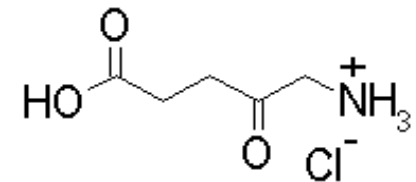
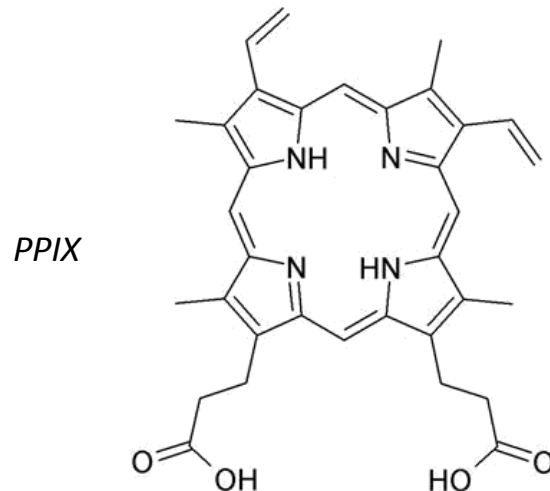
to see. to know. to heal.



photonamic

PDT with 5-ALA HCl

- **5-ALA HCL = 5-Aminolevulinic acid hydrochloride**
 - produced naturally in the body
 - an early intermediate stage in the synthesis of haem
 - surplus of 5-ALA HCl lead to selective accumulation of protoporphyrin IX (PPIX) in diseased cells
 - PPIX: actual photosensitizer



5-ALA HCl

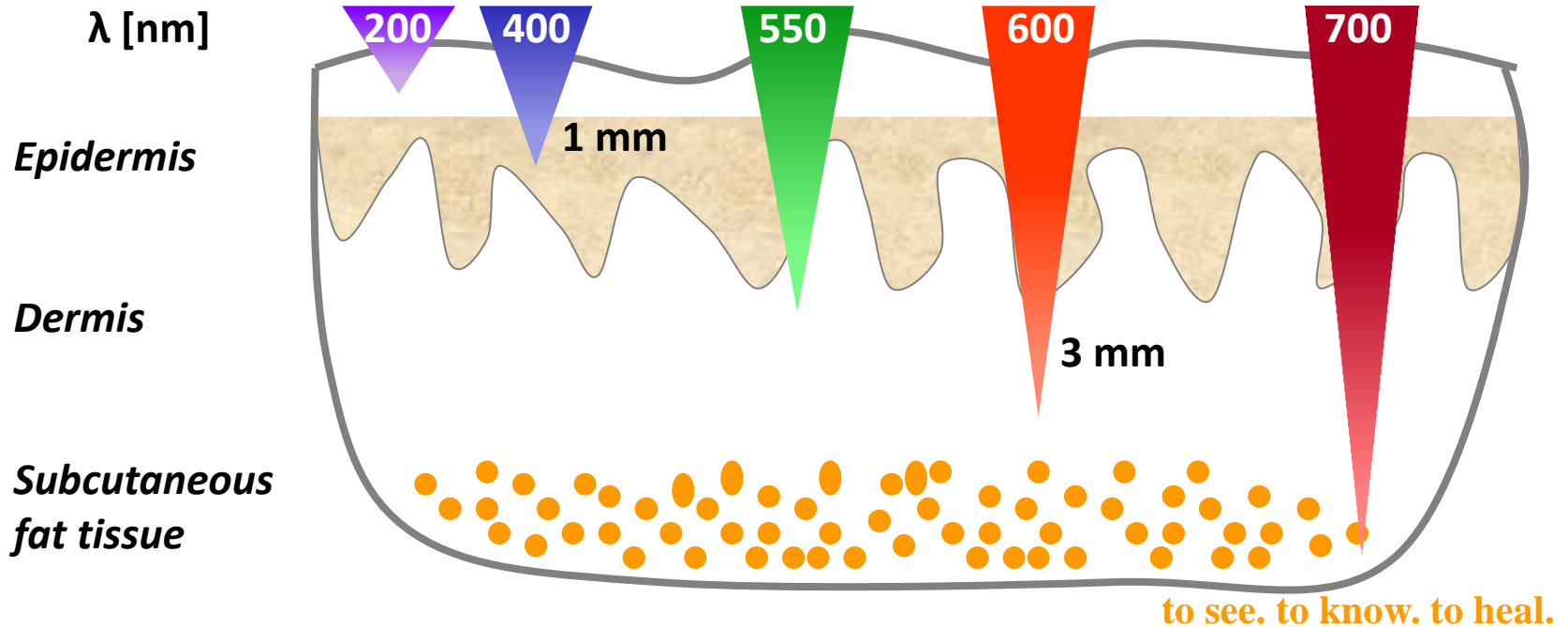
to see. to know. to heal.



photonamic

Penetration of light into skin

PPIX absorption bands





photonamic

Photodynamic Therapy

Current topical PDT procedures involve ...

- Preparation of the lesion(s) by curettage
- Application of the precursor in semiliquid formulation
- Occlusion with clingfilm
- Light protective measures
- Incubation
- After incubation: Cleaning of lesion(s)
- Illumination

to see. to know. to heal.



photonamic

Alacare[®] 8 mg medicated plaster

Product profile Alacare[®]

- Easy and convenient handling in a few steps
 - *Apply, remove, illuminate!*
 - No extra light protection necessary
 - Time saving for doctors and nurses as compared with standard PDT
- Defined dosage of the active ingredient
- Stable at room temperature (achieved: 3 years)
- Potential self application by patient
- Patent protected

to see. to know. to heal.



photonamic

Alacare[®]: Pharmaceutical Development

- **Development of formulation**
 - Manufacturing principle
 - Polymer
 - Particle size
 - Loading
- **Development of analytical methods**
- **Development of manufacturing process**
- **Stability studies**

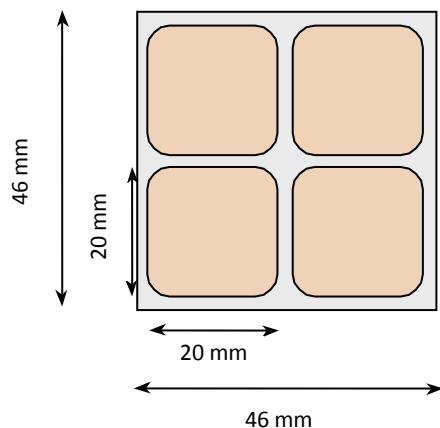
to see. to know. to heal.



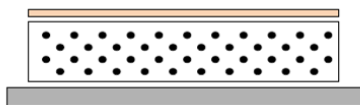
photonamic

Alacare[®] 8 mg medicated plaster

View on the release liner

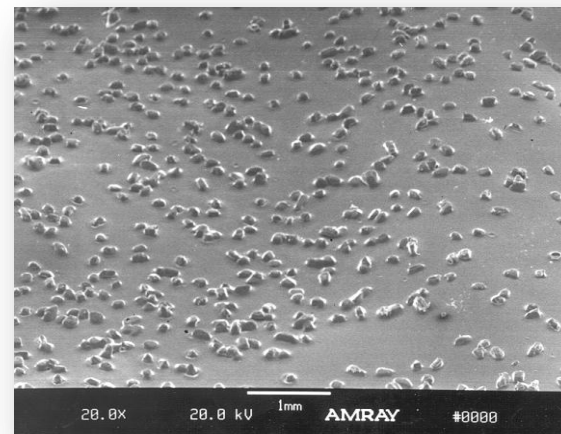


Cross section through a single STS



- Skin coloured backing
- Polymer matrix with susp. of 5-ALA-HCl
- Release liner

5-ALA HCl crystals suspended in the polymer matrix



to see. to know. to heal.



photonamic

Alacare[®]: Manufacturing process

Excipients

- Plaster:
 - Polyacrylic pressure sensitive adhesive
- Backing film:
 - Pigmented polyethylene Aluminium vapour coated polyester
- Release liner (polyethylene terephthalate film) which is removed prior to application



photonamic

Alacare[®]: Manufacturing process

Packaging

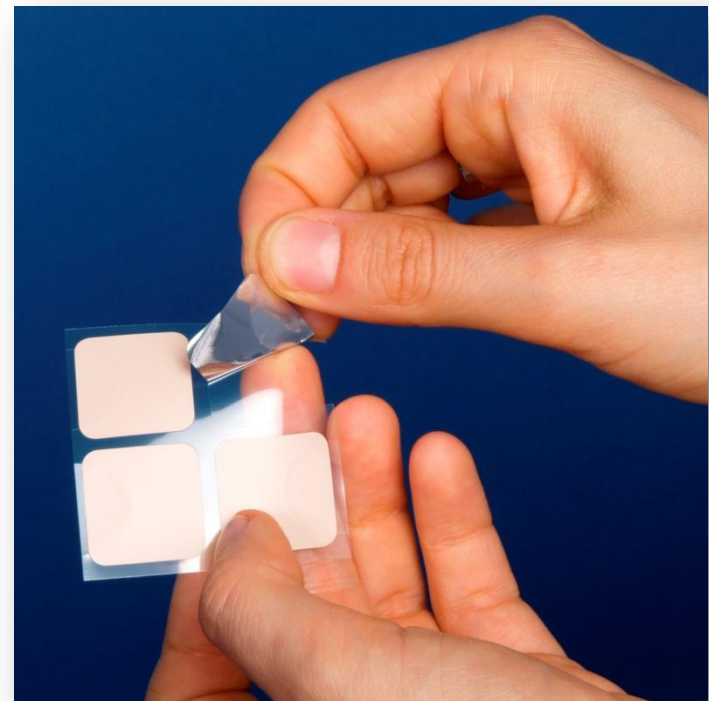
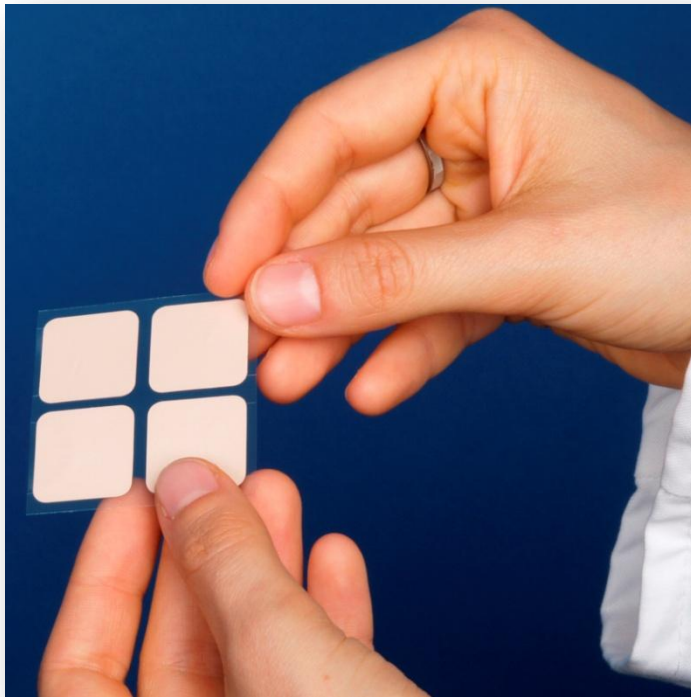
- 4 medicated plasters sealed in protective sachets consisting of 4 layers: paper (outer layer), polyethylene LDPE, aluminium, ethylene copolymer (inner layer)
- Pack sizes of 4 or 8 medicated plasters (1 or 2 protective sachet(s)).

to see. to know. to heal.



photonamic

Alacare[®] 8 mg medicated plaster



to see. to know. to heal.



photonamic

Alacare[®] 8 mg medicated plaster



to see. to know. to heal.



Alacare[®]: Nonclinical development

photonamic

Non-clinical experiments

photonamic has performed

- safety pharmacology tests
- systemic general toxicity tests, including toxicokinetics and genotoxicology tests for 5-ALA and
- local tolerance tests for Alacare[®]

Preclinical pharmacodynamic tests

- have not been performed by photonamic as the principle of 5-ALA-PDT is well-known
- instead, literature data have been summarized in the CTD

to see. to know. to heal.



photonamic

Alacare[®] : Clinical development

Indication under investigation in clinical trial program

- Mild to moderate actinic keratosis of head and face*
- Maximum of 8 lesions per patient (package size)
- No pre-treatment of lesions (debulking) prior to patch application
- Single treatment (in conjunction with red light)
- Follow-up periods 8 weeks to 12 months
- Primary endpoint: lesion-based clearance rate
- Secondary endpoint: patient-based clearance rate

*Cockerell CJ. Histopathology of incipient intraepidermal squamous cell carcinoma ("actinic keratosis").
J Am Acad Dermatol 2000; **42**:11–7

to see. to know. to heal.



photonamic

Severity grade acc. to Cockerell

Grade	Definition according to Cockerell
Mild (grade I)	Flat, pink maculae or patch on sun-damaged skin, background mottling, no roughness or hyperkeratosis
Moderate (grade II)	Pink to red papule or plaque with rough, hyperkeratotic surface, variable induration
Severe (grade III)	Red, scaly indurated plaques on sun-damaged skin; may be pigmented; very thick

to see. to know. to heal.

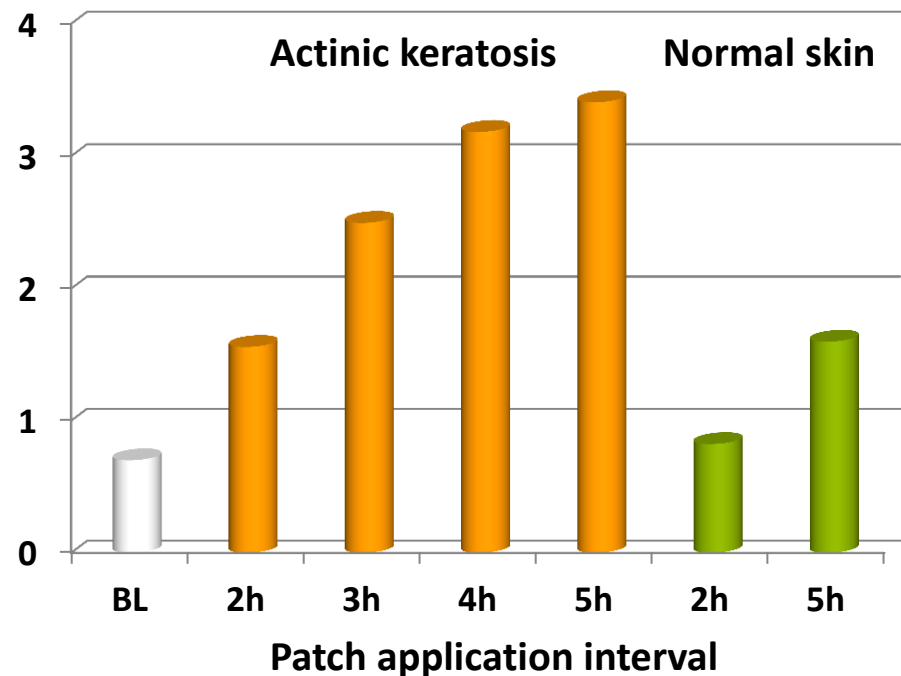


photonamic

Alacare[®] application interval: AK 01

- Fluorescence analysis study (no illumination)
- PPIX specific fluorescence in AK lesions steered by patch application duration
- No significant increase of fluorescence at time of patch removal between 4h and 5h application
- Application safe and well tolerable

Rel. Fluorescence



Fauteck JD, Ackermann G, Birkel M et al., Arch Dermatol Res 300, 2008: 53-60

to see. to know. to heal.

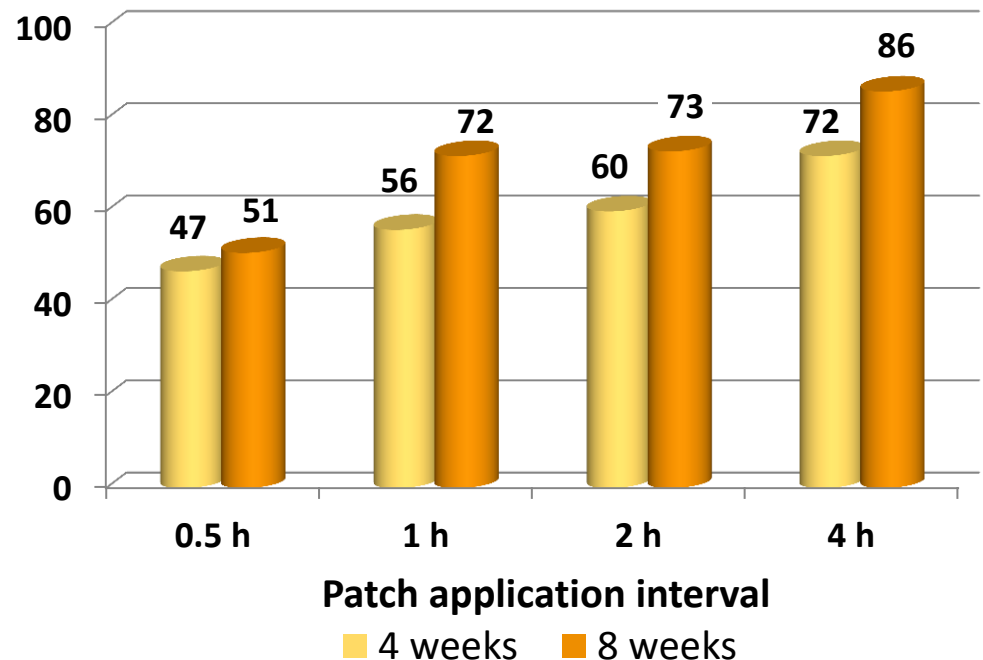


photonamic

Alacare[®] application interval: AK 02

- Dose finding study (illumination with red light after patch removal)
- Lesion clearance rate after 8 weeks: 86% with 4h patch application
- 4h group statistically superior to the other arms

% CCR (lesions)



Hauschild A, Popp G, Stockfleth E et al., *Exp Dermatol* 18 (2), 2009: 116-121

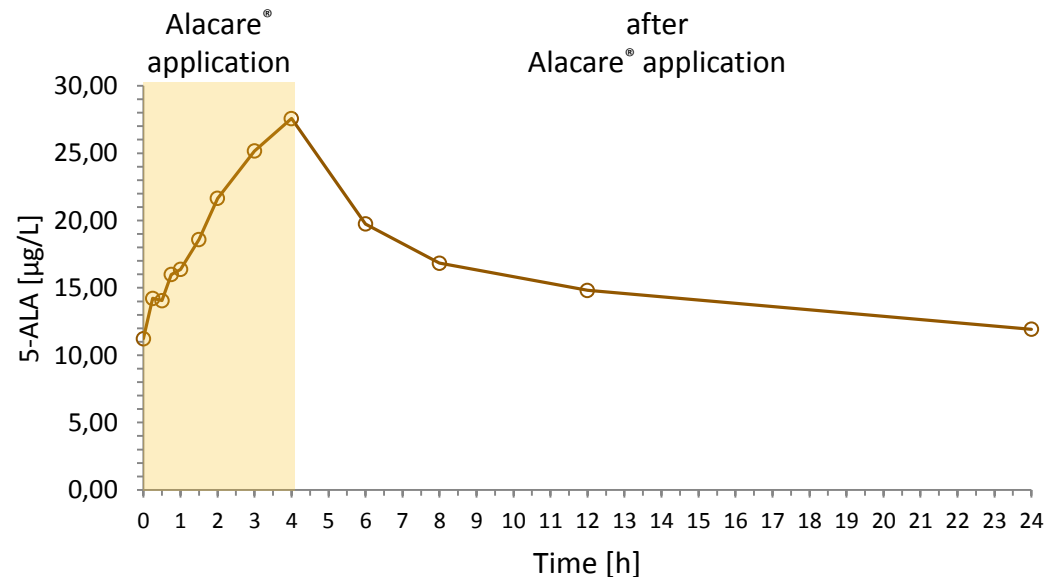
to see. to know. to heal.



Alacare[®] pharmacokinetics: AK 05

photonamic

- PK study (no illumination)
- 12 patients with 8 plasters (4h)
- 10/12 patients show maximum 5-ALA plasma levels greater than 1.5 x baseline
- Maximum plasma level: 3.7 x baseline values
- No detection of PPIX in plasma
- Application safe and well tolerable



Fauteck JD, Ackermann G, Birkel M et al., Arch Dermatol Res 300, 2008: 53-60

to see. to know. to heal.



photonamic

Confirmative phase III studies

AK 03:

- Alacare-PDT versus placebo-PDT (superiority design)
- Observer-blinded randomised parallel group comparison

AK 04:

- Alacare-PDT versus cryosurgery (non-inferiority design) and placebo-PDT
- Randomised parallel group comparison

to see. to know. to heal.



photonamic

Confirmative Phase III Studies

Number of patients

- 449 patients treated (2537 study lesions)
 - AK 03: 103 patients (587 lesions)
 - AK 04: 346 patients (1950 lesions)



Study treatments

- Comparison of treatment efficacy 12 weeks after therapy
- Follow-up until 12 months
- PDT: 4 h patch application plus standardized illumination protocol (37 J/cm² at λ 630 ± 3 nm; red light)
- Cryosurgery: 5-10 sec after ice ball formation (mean: 7.3 sec)

to see. to know. to heal.



photonamic

Study populations AK 03 & AK 04

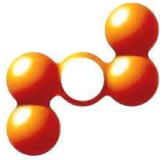
AK 03 (vs. Placebo)

- ***Lesions***
 - 44% mild, 56% moderate
 - 52% forehead, 26% scalp, 12% cheek
- ***Patients***
 - Mean age 70.7 years
 - 82% male
 - 92% skin type I or II*
 - Mean 5.7 AK study lesions

AK 04 (vs. Cryosurgery)

- ***Lesions***
 - 44% mild, 56% moderate
 - 45% forehead, 29% scalp, 15% cheek
- ***Patients***
 - Mean age 70.5 years
 - 72% male
 - 83% skin type I or II*
 - Mean 5.6 AK study lesions

*remaining: skin type III
to see. to know. to heal.

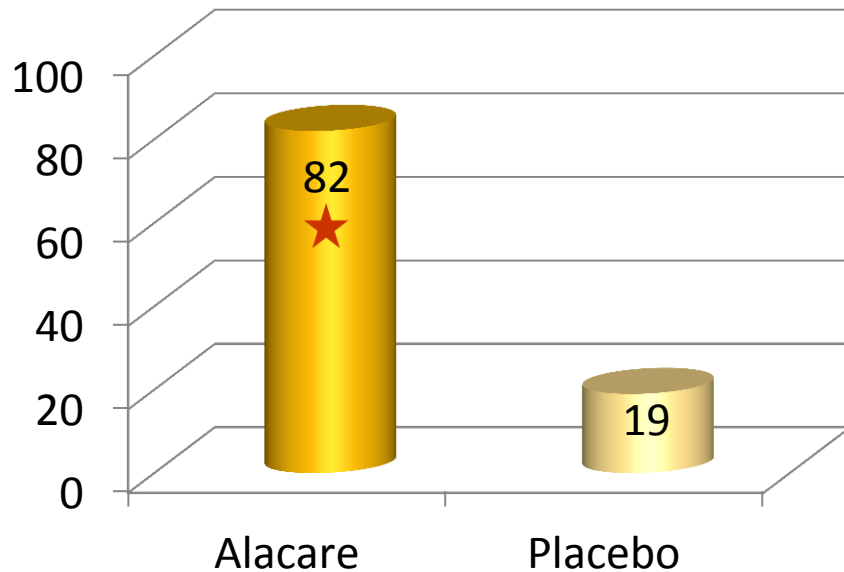


photonamic

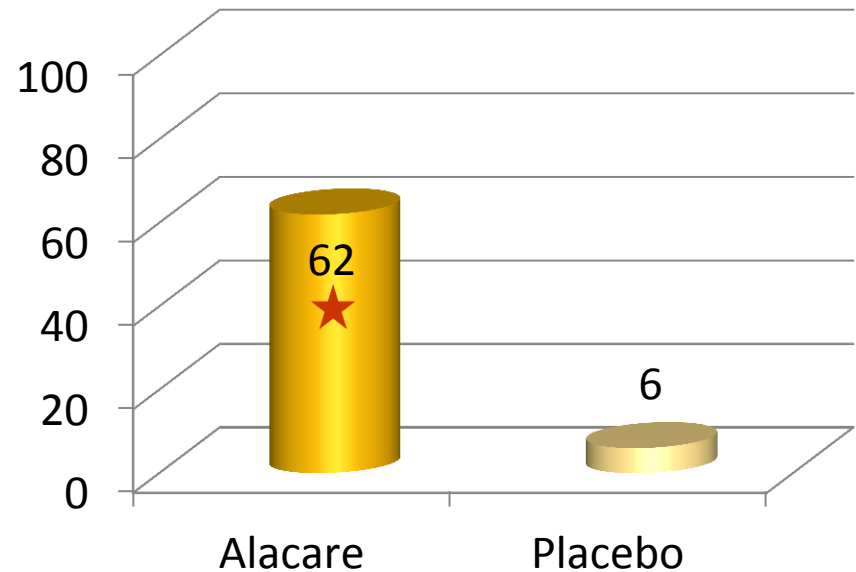
AK 03: Clear superiority over placebo

Clearance rate 12 weeks after therapy [%]

Lesion based



Patient based



★ Statistically significantly superior to placebo ($p < 0.0001$)

to see. to know. to heal.

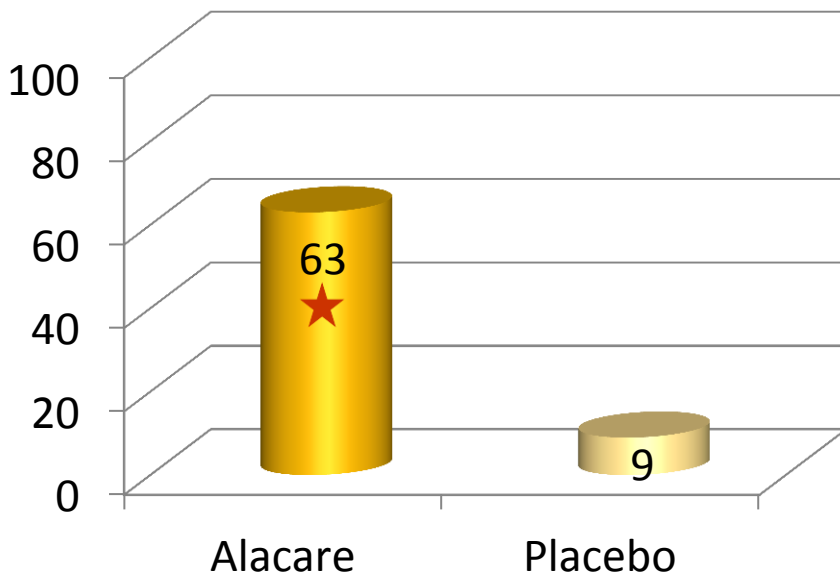


AK 03: Clear superiority over placebo

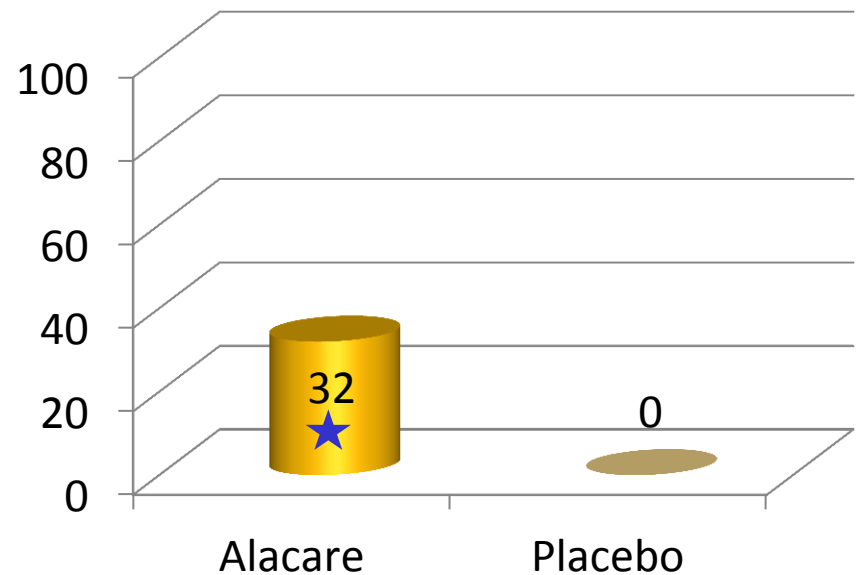
photonamic

Clearance rate 12 months after therapy [%]

Lesion based



Patient based



★ Statistically significantly superior to placebo ($p < 0.001$)
★ No statistical test possible

to see. to know. to heal.

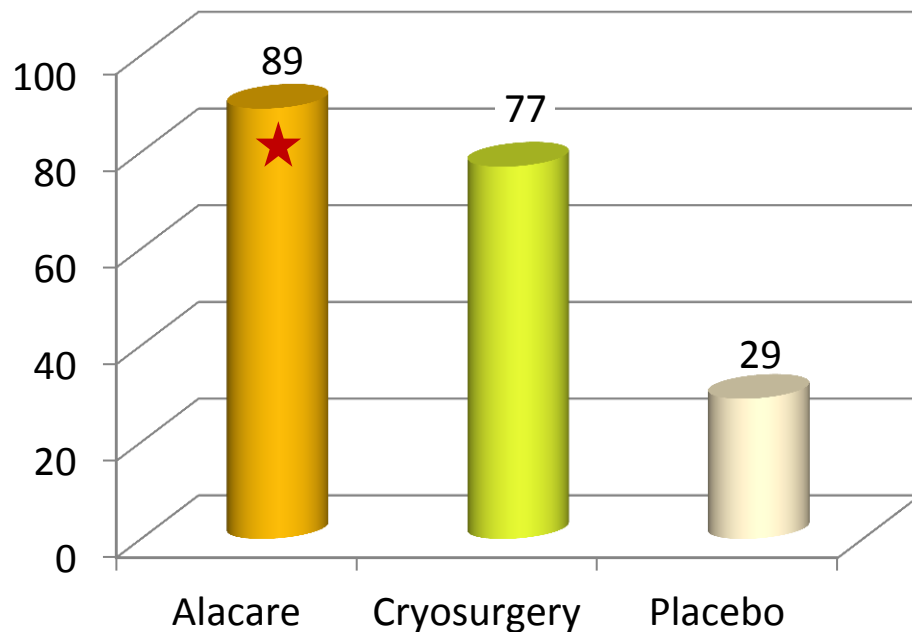


photonamic

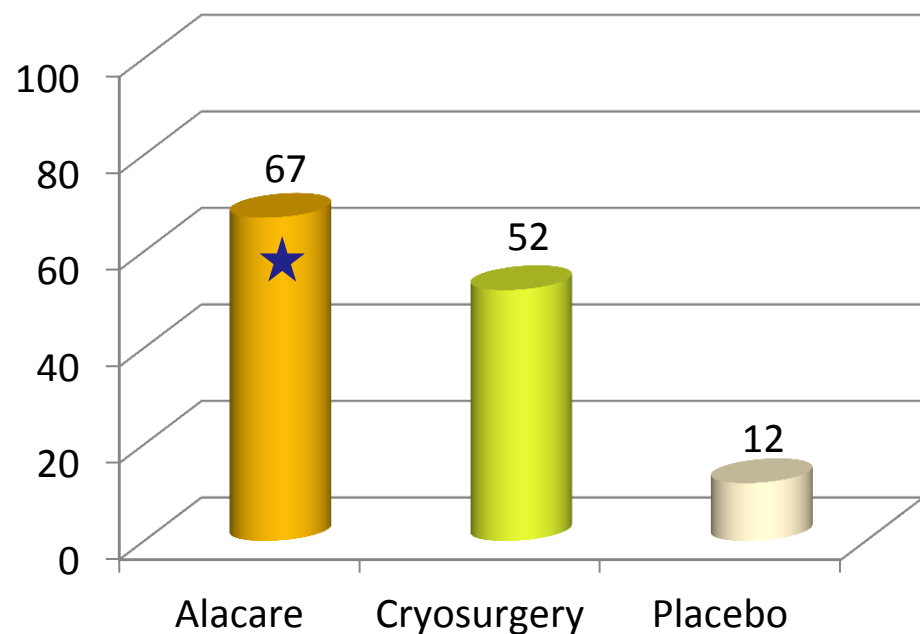
AK 04: Clearance rates after PDT prove superior to cryosurgery

Clearance rate 12 weeks after therapy [%]

Lesion based



Patient based



★ Statistically significantly superior to cryosurgery ($p=0.007$) and placebo ($p<0.001$)

★ Statistically significantly superior to cryosurgery ($p=0.02$) and placebo ($p<0.0001$)

to see. to know. to heal.

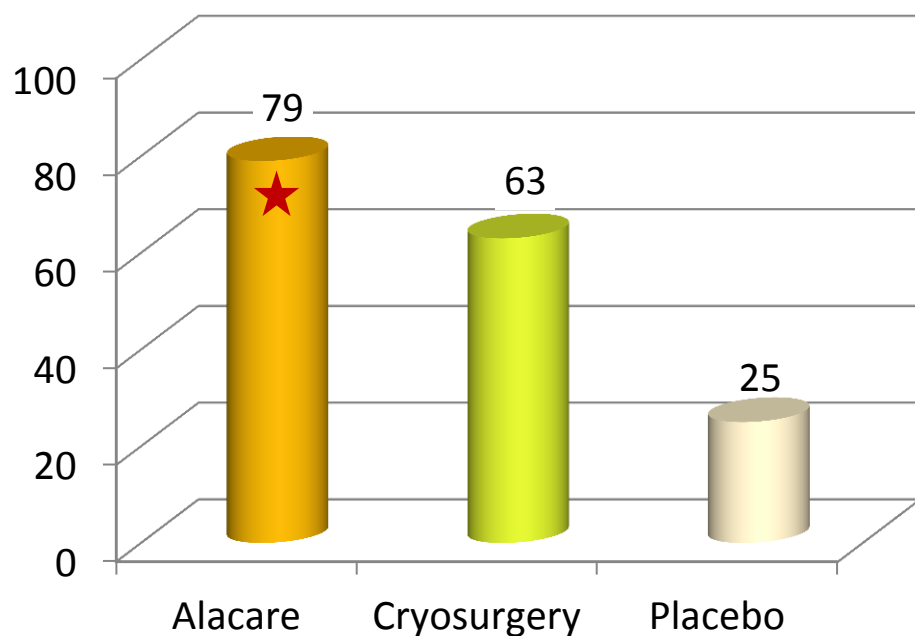


photonamic

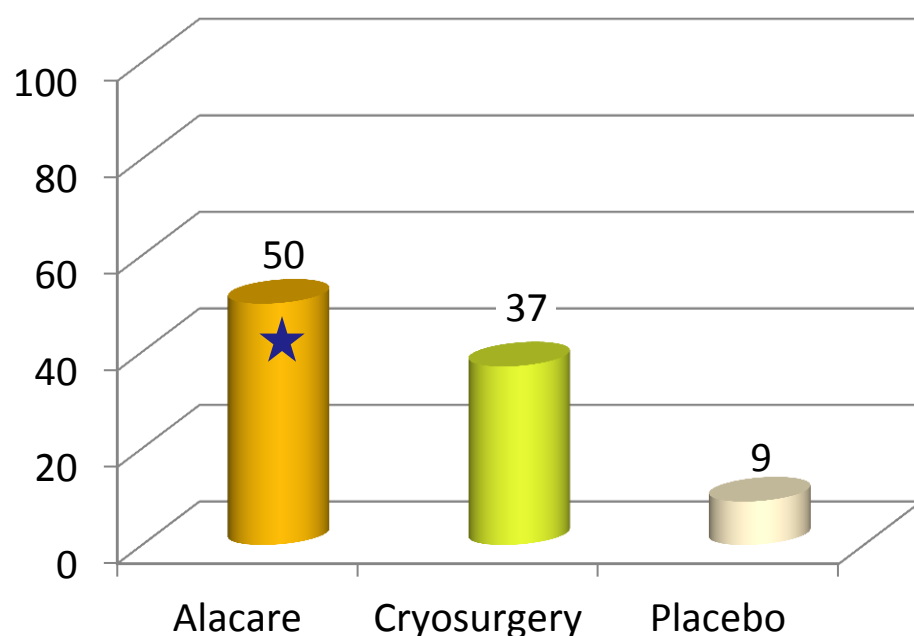
AK 04: Clearance rates after PDT prove superior to cryosurgery

Clearance rate 12 months after therapy [%]

Lesion based



Patient based



★ Statistically significantly superior to cryosurgery and placebo ($p < 0.001$)

★ Statistically significantly superior to cryosurgery ($p = 0.027$) and placebo ($p < 0.001$)

to see. to know. to heal.



Alacare[®]-PDT: Summary of tolerability

photonamic

Adverse reactions involving the treatment site:*

- *Very common*: Erythema, exfoliation, irritation, pain, pruritus, scab
- *Common*: Bleeding, desquamation, discharge, discomfort, erosion, hyper/hypopigmentation, oedema, reaction, swelling, vesicles, pustules

Adverse reactions not involving the treatment site:*

- *Common*: Headache

*Based on a safety meta analysis of all Alacare[®] efficacy studies (*unpublished data*)

to see. to know. to heal.



Publications in peer reviewed journals

photonamic

- **Fluorescence analysis study and PK study**

Fauteck JD, Ackermann G, Birkel M, Breuer M, Moor AC, Ebeling A, Ortland C. "Fluorescence characteristics and pharmacokinetic properties of a novel self-adhesive 5-ALA patch for photodynamic therapy of actinic keratoses." *Arch Dermatol Res*. 2008 Feb;300(2):53-60

- **Dose finding study**

Hauschild A, Popp G, Stockfleth E, Meyer KG, Imberger D, Mohr P, Itschert G, Kaufmann R, Neuber K, Frambach Y, Gollnick H, Brunnert M, Stocker M, Ortland C, Karrer S. "Effective photodynamic therapy of actinic keratoses on the head and face with a novel, self-adhesive 5-aminolaevulinic acid patch." *Exp Dermatol*. 2009 Feb;18(2):116-21

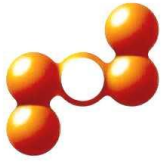
- **Phase III studies: 12 weeks data**

Hauschild A, Stockfleth E, Popp G, Borrosch F, Brünig H, Dominicus R, Mensing H, Reinhold U, Reich K, Moor AC, Stocker M, Ortland C, Brunnert M, Szeimies RM. "Optimization of photodynamic therapy with a novel self-adhesive 5-aminolaevulinic acid patch: results of two randomized controlled phase III studies." *Br J Dermatol*. 2009 May;160(5):1066-74

- **Phase III studies: 12 months data**

Szeimies RM, Stockfleth E, Popp G, Borrosch F, Brünig H, Dominicus R, Mensing H, Reinhold U, Reich K, Moor AC, Stocker M, Ortland C, Brunnert M, Hauschild A. „Long-term follow-up of photodynamic therapy with a self-adhesive 5-aminolaevulinic acid patch: 12 months data." *Br J Dermatol*. 2010 Feb 1;162(2):410-4

to see. to know. to heal.

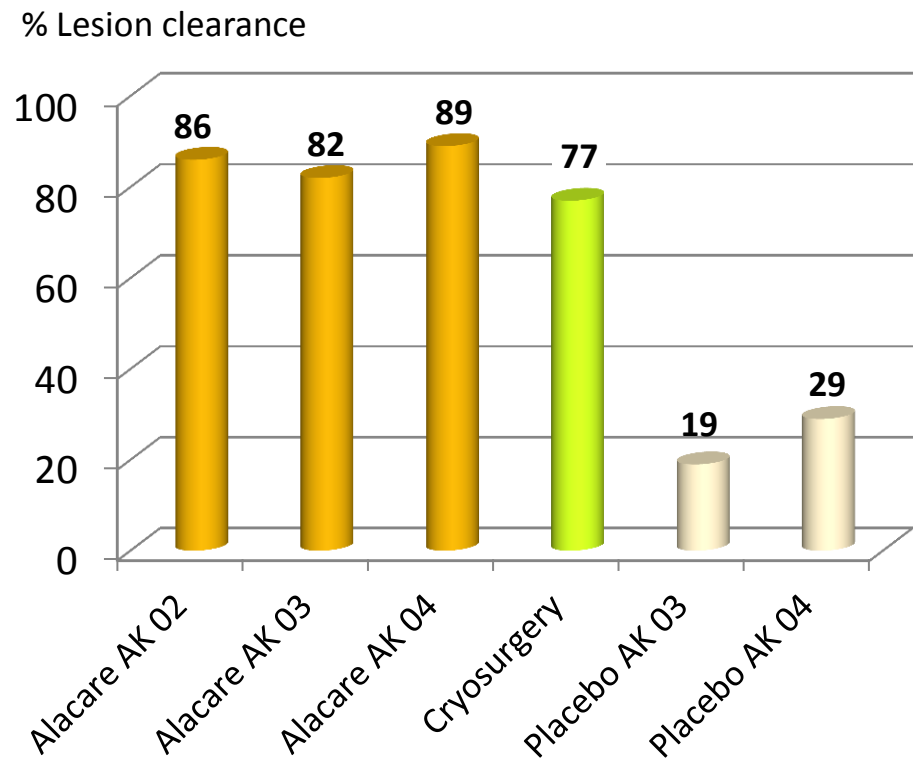


photonamic

Alacare[®] 8 mg medicated plaster: Advantageous product profile

Summary

- Consistently high clearance rates after Alacare-PDT in 3 independent studies (82% to 89%) with a total of 1392 lesions treated with Alacare-PDT in 252 patients
- Clinical efficacy of Alacare superior to cryosurgery (and placebo) over a 12 months follow-up period



to see. to know. to heal.



photonamic

Alacare[®] 8 mg medicated plaster: Advantageous product profile

- Excellent cosmetic results without scarring or altered pigmentation (superiority over cryosurgery)
- Simple, quick and convenient procedure
 - No debulking prior to Alacare application
 - No extra occlusion by clingfilm
 - No light protection
 - Cosmetically compatible plaster
 - No rinsing of the treated area after Alacare removal
 - *“Simply apply it, remove it, illuminate it”*

to see. to know. to heal.



photonamic

Alacare[®] 8 mg medicated plaster: Advantageous product profile

- Patient independent from doctor's office during Alacare application interval
- Product potential: Self-administration by patient
- Defined 5-ALA dosage in each Alacare plaster
- Alacare suitable for difficult-to-treat areas (e.g. nose, ear)
- Larger areas (field cancerization; up to 32 cm²) can be treated by applying Alacare plasters adjacently

to see. to know. to heal.



photonamic

Alacare®: Status

- Registered in 2009 (European Decentralised Procedure) for PDT of up to 6 mild actinic keratoses lesions with a maximum diameter of 1.8 cm on the face and scalp (hairless areas)
- Marketed in Europe by Galderma



to see. to know. to heal.



photonamic

Alacare[®]: Status

Alacare[®]-PDT has the potential to become first-line treatment in the therapy of Actinic Keratosis.

to see. to know. to heal.



photonamic

Thank you!



to see. to know. to heal.