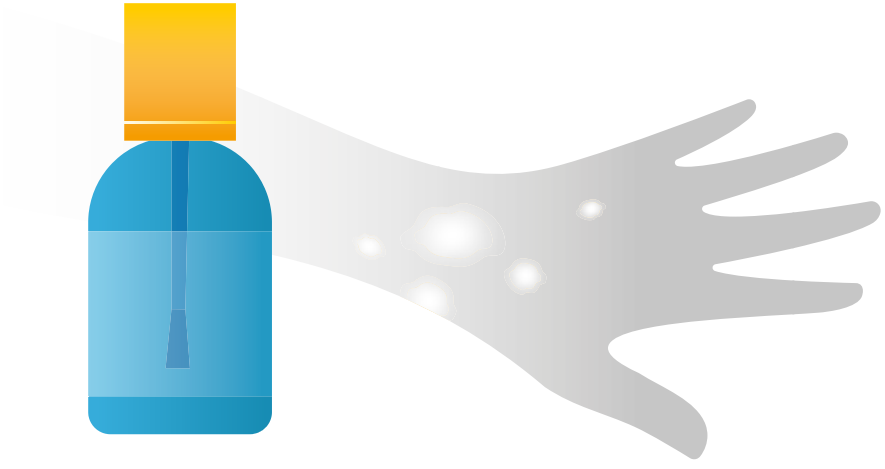
VOL 14 / ANNO 2019 / PAG 67-80

CLINICO ECONOMICS

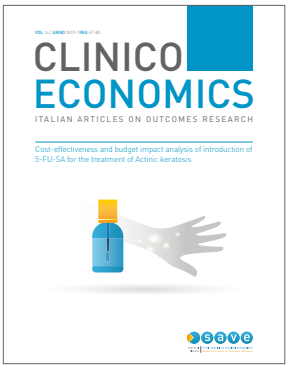
ITALIAN ARTICLES ON OUTCOMES RESEARCH

Cost-effectiveness and budget impact analysis of introduction of 5-FU-SA for the treatment of Actinic keratosis



save

CENTRO DI RICERCA | STUDI ANALISI VALUTAZIONI ECONOMICHE
Health Economics & Outcomes Research



ClinicoEconomics è una rivista peer-reviewed di farmacoeconomia e di outcomes research sulle conseguenze economiche e di politica sanitaria di dispositivi medici e strategie farmacologiche.
Obiettivo della Rivista è quello di pubblicare in modo rapido e conciso lavori sull'impatto clinico ed economico in tutte le principali aree terapeutiche, valutazioni in tema di sicurezza, di efficacia nella pratica clinica, di costo-efficacia, di costo-utilità e di costo-beneficio nell'uso sostenibile dei farmaci e dei dispositivi medici.
www.clinicoeconomics.eu

Progetto grafico e impaginazione
newattitude comunicazione

CENTRO DI RICERCA | STUDI ANALISI VALUTAZIONI ECONOMICHE Health Economics & Outcomes Research

www.savestudi.it

Volume n. 14 / 2019 alla Pubblicazione peer-reviewed open access
ClinicoEconomics Italian Articles on Outcomes Research (Print ISSN 2282-8087; Online ISSN 2282-8095) è una rivista annuale pubblicata da S.A.V.E. Studi Analisi Valutazioni Economiche S.r.l. via G. Previati 74, 20149 Milano, Italia - www.clinicoeconomics.info
Registrazione del Tribunale di Milano n. 368 del 14/07/2011

CLINICO ECONOMICS

Cost-effectiveness and budget impact analysis of introduction of 5-FU-SA for the treatment of Actinic keratosis

G.M. Bruno [1] | **S. Di Matteo** [1] | **M.C. Valentino** [1] | **C. Martinotti** [1] | **G.L. Colombo** [1,2]

[1] S.A.V.E. Studi Analisi Valutazioni Economiche S.r.l., Milan, Italy

[2] Department of Drug Sciences, University of Pavia, Italy

E-mail:
giacomo.bruno@savestudi.it
sergio.dimatteo@savestudi.it
chiara.valentino@savestudi.it
chiara.martinotti@savestudi.it
giorgio.colombo@savestudi.it

Corresponding author:
Giorgio L. Colombo – giorgio.colombo@unipv.it
via G. Previati 74, 20148 Milano | tel: +39 0248519230

ABSTRACT EN

BACKGROUND

Actinic keratosis, also called solar keratosis, is a skin disease that manifests itself with rough or scaly spots or lesions in areas of the body exposed to the sun that can take on pink, red, brown or the same color as the skin. Due to the comparable efficacy of 5-FU-SA with diclofenac sodium, ingenol mebutate and imiquimod as treatment for AK multiple lesions, we carried out a cost-effectiveness of the four alternatives.

METHODS

A cost-effectiveness analysis comparing 5-FU-SA with diclofenac sodium, ingenol mebutate and imiquimod was performed. The simulation model was created with Microsoft Excel® software. The main focus of the model is to evaluate the cost-effectiveness of 5-FU-SA in relation to comparators in the treatment of actinic keratosis (AK). The model time horizon is set to 1 year. The perspective of the public payer (National Health Service, NHS) so only direct costs are included. Italy (ITA) is the reference country (base-case)

ABSTRACT ITA

INTRODUZIONE

La cheratosi attinica, chiamata anche cheratosi solare, è una malattia della pelle che si manifesta con macchie o lesioni ruvide o squamose in aree del corpo esposte al sole che possono assumere colore rosa, rosso, marrone o lo stesso colore della pelle. Vista l'efficacia comparabile di 5-FU-SA con diclofenac sodium, ingenolo mebutato e imiquimod come trattamento delle lesioni multiple dovute a cheratosi attinica, è stata svolta una analisi di costo efficacia delle quattro alternative.

METODI

È stata eseguita un'analisi economica di costo efficacia che confronta 5-FU-SA con diclofenac sodio, ingenolo mebutato e imiquimod. Il modello di simulazione è stato creato con il software di Microsoft Excel®. L'obiettivo principale del modello è quello di valutare l'efficacia in termini di costi di 5-FU-SA in relazione ai comparatori nel trattamento della cheratosi attinica (AK). L'orizzonte temporale del modello è impostato su 1 anno. La prospettiva del Servizio Sanitario Nazionale (SSN)

for the model. A budget impact analysis was also performed.

RESULTS

Results of the cost effectiveness analysis shown the use of 5-FU-SA as a dominant strategy. Patients receiving 5-FU-SA incurred in lower costs and more QALYs than patients receiving imiquimod, ingenol mebutate and diclofenac sodium. Budget impact analysis results' shown that treatment with 5-FU-SA would result in a total savings of 2.07% in the first year, equal to € 314.574, which would become 4.14% in the second year with a saving of € 635.377. Finally, the third year the introduction of 5-FU-SA in the market would generate savings for € 962.410 (6.21%).

CONCLUSIONS

The economic assessment carried out shows that therapy with 5-FU-SA involves an improvement in the quality of life of patients and overall represents in Italy a cost-effective treatment option for the treatment of patients affected by actinic keratoses.

in modo che siano inclusi solo i costi diretti. L'Italia (ITA) è il paese di riferimento (caso di base) per il modello. È stata inoltre eseguita un'analisi dell'impatto del budget.

RISULTATI

I risultati dell'analisi dell'efficacia dei costi hanno mostrato l'uso di 5-FU-SA come strategia dominante. I pazienti che hanno ricevuto 5-FU-SA hanno sostenuto costi inferiori ottenendo QALYS maggiori rispetto ai pazienti che ricevono imiquimod, mebutato ingenolo e diclofenac sodium. I risultati dell'analisi di budget impact hanno mostrato che il trattamento con 5-FU-SA comporterebbe un risparmio totale del 2,07% nel primo anno, pari a 314.574 euro, che diventerebbe 4,14% nel secondo anno con un risparmio di 635.377 euro. Infine, nel terzo anno, l'introduzione di 5-FU-SA sul mercato genererebbe risparmi pari 962.410 euro (6,21%).

CONCLUSIONI

La valutazione economica effettuata mostra che la terapia con 5-FU-SA comporta un miglioramento della qualità della vita dei pazienti e nel complesso rappresenta in Italia un'opzione di trattamento conveniente per il trattamento dei pazienti affetti da cheratosi attinica.

KEYWORDS: Actinic keratosis, 5-FU-SA pharmacoeconomic, budget impact, cost effectiveness.

INTRODUCTION

Actinic keratosis, also called solar keratosis, is a skin disease that shows itself with rough or scaly spots or lesions in areas of the body that are in contact with the sun that can take on pink, red, brown or identical pigment of the skin. Chronic exposure to the sun is the cause of almost all lesions of actinic keratoses.[1]

A short period of exposure to the sunlight is added to the total of a lifetime because the damage due to sun exposure is cumulative. Actinic keratosis (AK) is a clinical status represented from keratinocytic dysplastic lesions of the epidermis, that affects people who expose themselves chronically to the sun, particularly with phototypes I–II according to the Fitzpatrick scale.[2]

Current estimates of the incidence of actinic keratosis indicate that more than 10 million Americans are affected. People with fair complexions, red or blonde hair and blue, green or gray eyes, if exposed to the sun for long periods of time, have a high probability of developing, as they age, one or more of these common forms of precancerous. In this case, the place where you live plays a particularly important role: in fact, the more you live near the equator the greater the probability of developing actinic keratoses. The incidence of this disease is slightly higher in men, as they tend to stay longer in the sun applying less sunscreen. African Americans, Hispanics, Asians and, in general, people with dark complexions do not present the same risk of developing actinic keratoses as the Caucasians. Regarding the incidence Actinic keratosis affects about one in three men over 70 years (18 percent for women). It is a precancerous skin disease caused by continuous exposure to the sun, some scholars consider it as the initial form of squamous cell carcinoma 40-60 percent of squamous cell carcinomas originate from untreated actinic keratoses and may progress by invading the surrounding tissues. From 2 to 10 percent of squamous cell carcinomas can spread to internal organs and become lethal.

As an initial phase of cell spino carcinoma, an invasive tumor with high metastatic potential, AK represents a sensitive risk for the health of affected individuals. Approximately 10 percent of immunocompetent patients and 40 percent of those immunosuppressed with AK may develop an invasive SCC.

Due to several studies about AK's natural history, it is clear that up to 10% of lesions can worsen until it becomes invasive squamous cell carcinoma (SCC), with the risk increasing as time passes.[3] Subclinical lesions of the photo-damaged area may degenerate as well in SCC according to the concept of "field cancerization."

The primary objective of the treatments of actinic keratosis is to reduce the number of injuries and thus prevent the risk of progression in invasive squamous cell carcinoma (SCC), as well as to relieve symptoms such as itching and sensitivity.

The treatments used for actinic keratosis can be:

- targeted to the lesion, that is directed towards one or a few clinically visible lesions;
- targeted to the "cancer field", the so-called Field Directed Treatments, used to treat clinically evident lesions and surrounding photodamaged skin at the same time.

Drug's therapy are therapies are of three types:

- physical treatments (cryotherapy, laser therapy, diathermocoagulation, surgical excision, curettage);
- photodynamic or PDT therapy (aimed at both the "field" and the individual lesions) carried out by a photosensitizing agent, 5-methylaminolevulinate (MAL) or aminolevulinic acid hydrochloride (ALA) and subsequent exposure to red light;
- topical treatments (ingenol mebutare gel applied one time per day for 2/3 days in a row, chemical peeling diclofenac sodium 3% gel applied twice a day for at least 60-90 days, imiquimod 5% cream applied 3 times a week for 4- 8 weeks).[4]

AK is primarily treated to prevent progression to SCC, for cosmetic reasons, and to eliminate symptoms such as itching and pain. With an approach focused on the photo-damaged skin instead of single lesions, topical therapies have the benefit, if compared with surgical

or ablative treatments, of curing subclinical lesions furthermore. Recent studies have shown that the latter is moreover capable of degenerating into SCC.[5] Diclofenac sodium has a mechanism of action that particularly articulated. The scientific literature has shown that arachidonic acid metabolites are an active part in the response of keratinocytes to exposure to ultraviolet (UV) rays and to skin irritation. Furthermore it has been shown that the hyperactivation of cyclooxygenase enzymes (in particular COX-2) is carcinogenic.[6] Diclofenac causes apoptosis of neoplastic cells, angiogenesis downregulation,[7] and receptor activation activated by the peroxisome proliferator (PPAR) which decrease the receptors the proliferation of neoplastic cells.[8] An additional topical treatment that is often used is Ingenol mebutate, for AK derived from the Euphorbia peplus plant. it induces necrosis of tumor cells by activating the immune system with a dual mechanism of action: initially it induces necrosis of the lesion substantially through a cascade of proinflammatory cytokines and then subsequently activates neutrophils.[9]

Imiquimod, an immune modulator, is part of the family of imidazoquinolone drugs, its action causes it to bind to the Toll-like receptor 7 which is present on dendritic cells, macrophages and monocytes, with a subsequent immune response and induction of the receptor Fas on tumor cells.[10]

Various therapeutic approaches are available that are useful for the direct treatment of the AK lesion and / or the surrounding area; these are not always appropriate for all patients and there is a need for alternative therapies that can reduce recurrence rates, a phenomenon that remains an unmet need in treatment.

Actikerall® (5-Fluorouracil 0.5% and Salicylic Acid 10%, 5-FU-SA) 25 ml pack for topical treatment of actinic keratosis (AK); it can only be used upon prescription by the dermatologist specialist with a repeatable limitative recipe.[11]

Literature data suggest that Actikerall is a more effective treatment option than currently available treatments for both histological outcomes, complete clearance of lesions, reduced relapse rate and good tolerability profile. Indeed thanks to its mechanism of action, the combination of 5-fluorouracil (5-FU) 0.5 percent /10 percent salicylic acid applied once a day is a topical and effective treatment for lesions and for treatment local (up to 25 cm^2) of actinic keratosis and hyperkeratotic lesions of grades I and II.

Actikerall® allows to treat up to 10 individual injuries simultaneously, treatment is performed until the lesion disappears, the maximum duration allowed is 12 weeks. 5-fluorouracil is a cytostat with antimetabolite effect and prevents the formation and use of thymine, thus inhibiting the synthesis of DNA and RNA and determining the inhibition of cell growth, topical salicylic acid has keratolytic effect and reduces the hyperkeratosis associated with actinic keratosis.

Due to the comparable efficacy of Actikerall® (combination of 0.5% 5-Fluorouracil and 10% salicylic acid) Solaraze® (diclofenac), Picato® (ingenol mebutate), and Zyclara® (imiquimod) in treating AK multiple lesions, a pharmacoeconomic evaluation of cost-effectiveness of the four treatments was needed.

MATERIAL AND METHOD

A cost-effectiveness analysis comparing 5-FU-SA with diclofenac sodium, ingenol mebutate and imiquimod was performed. The simulation model was created with Microsoft Excel® software.

The main focus of the model is to evaluate the cost-effectiveness of 0. 5-FU-SA in relation to comparators in the treatment of actinic keratosis (AK). The model time horizon is set to 1 year. The perspective of the public payer so only direct costs are included (National Health Service, NHS). Italy (ITA) is the reference country (base-case) for the model. The model gives the possibility to shift the results for every Italian region.

In the model 5-FU-SA has three predefined comparators:

1. Solaraze® gel (3% diclofenac sodium)
2. Picato® gel (ingenol mebutate, 150 µg/g)
3. Zyclara® cream (3,75% imiquimod)

The model was built using a decision tree approach.

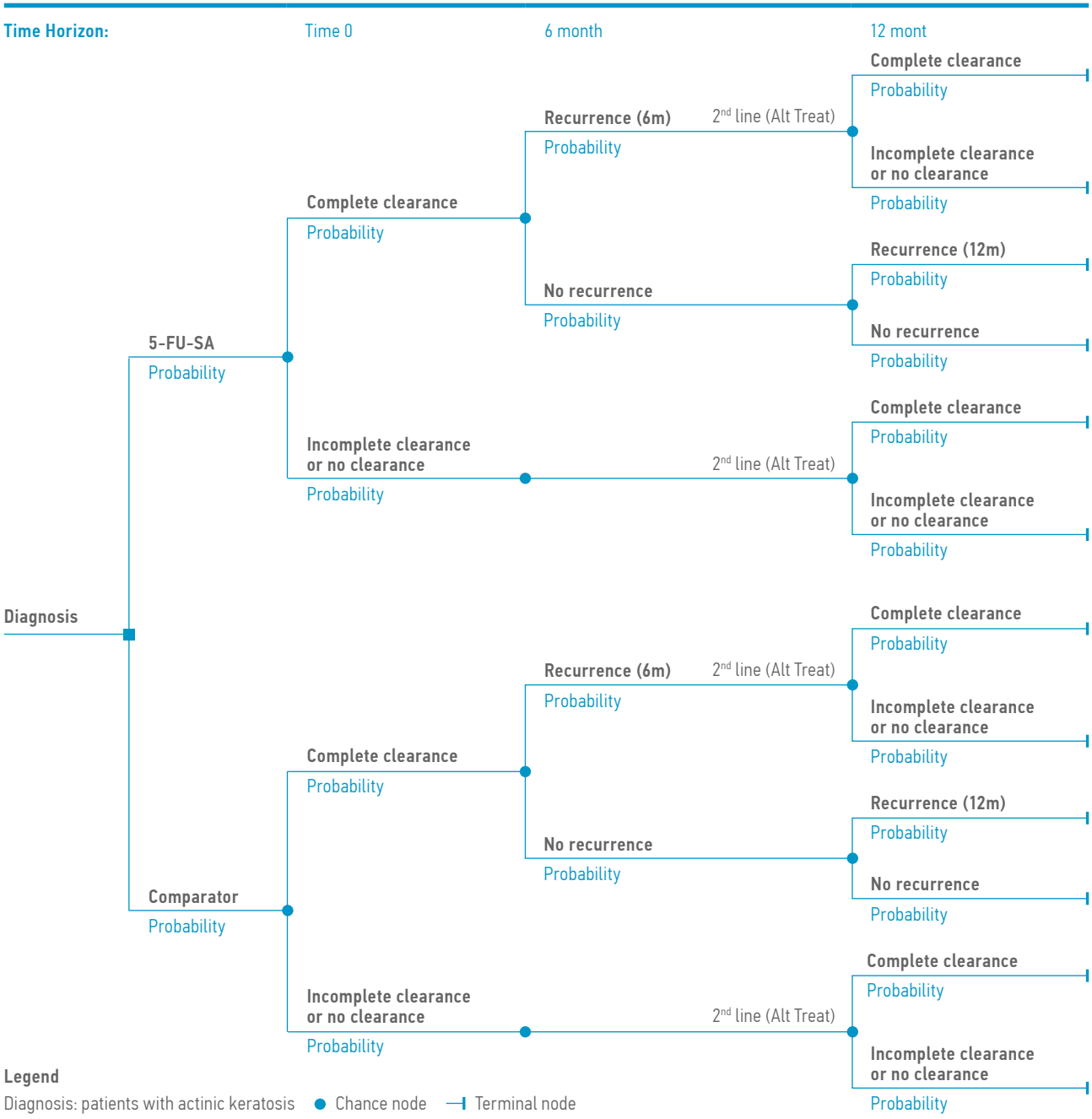
This is in line with the previous SMC submission and AK models in literature.

The primary outcome is the incremental cost per QALY. Other results of cost and effectiveness are also presented, the costs are also subdivided into sub-categories in order to facilitate their interpretation.

The main sources of data for comparative efficacy in the model are head-to-head (H2H) trials or indirect naive comparisons.[12-17] The model structure is represented by the present schematic decision tree. Each branch represents the patient's possible pathway in the treatment of actinic keratosis (**Figure 1**).

Events are sorted from left to right. Different events are shown using shapes called "nodes". A decision node

FIGURE 1
Decision tree structure



(square) indicates a choice for the decision maker. A probabilistic node (circle) represents an event with possible results and that is not under the control of the decision maker. A terminal node (triangle) represents the end point of a scenario. The branches of a probabilistic node represent the set of possible results of an event.

The paths are identical for 5-FU-SA and for the comparator arms, but the proportion of patients in each node is different due to the different effectiveness.

STRUCTURE OF THE MODEL

The pharmacoeconomic model takes into consideration the adult population over the age of 45, which in Italy is equal to 31.502.460 people.[18]

The model shows a prevalence rate of 1.4% among people over 45 years.[19]

Therefore patients with actinic keratosis are 441,034. Patients eligible for topical product for AK are 39% (N 172.003). The model also takes into account the incidence of patients treated with topical products that is 1%. This data leads patients treated with topical products for actinic keratosis at 173.723.

The model gives the possibility to choose the comparator to compare with. If the first-line treatment is not successful, a second-line treatment will take place. Those % are assumption based on the market from IQVIA data. Subsequent treatments are distributed as follows in the following tables (**Tables 1, 2, 3, 4**).

TABLE 1
Distribution of subsequent treatments: 5-FU-SA

DICLOFENAC	70%
IMIQUIMOD	4%
INGENOL MEBUTATE	26%

TABLE 2
Distribution of subsequent treatments: ingenol mebutate

5-FU-SA	20,0%
DICLOFENAC	75,2%
IMIQUIMOD	4,8%

TABLE 3
Distribution of subsequent treatments: diclofenac

5-FU-SA	20,0%
IMIQUIMOD	11,7%
INGENOL MEBUTATE	68,3%

TABLE 4
Distribution of subsequent treatments: imiquimod

5-FU-SA	20,0%
DICLOFENAC	58,4%
INGENOL MEBUTATE	21,6%

CLINICAL DATA

Regarding clinical efficacy, the model considers the percentage of complete clearance, the 6-month recurrence rate, the 12-month recurrence rate of all 4 drugs that are compared in the analysis. The following table shows the % of the clinical data (**Table 5**).

The sources of efficacy data for each drug of the analysis are explained below.

By analyzing 5-FU-SA for complete clearance the source data is Phase II trial, Simon et al. 2014; 6 month recur-

TABLE 5
Efficacy data

5-FU-SA	%
% complete clearance	56,50%
6 month recurrence rate	21,00%
12 month recurrence rate	33,00%
DICLOFENAC	%
% complete clearance	32,90%
6 month recurrence rate	30,60%
12 month recurrence rate	34,70%
IMIQUIMOD	%
% complete clearance	39,90%
6 month recurrence rate	31,29%
12 month recurrence rate	55,87%
INGENOL MEBUTATE	%
% complete clearance	54,50%
6 month recurrence rate	33,00%
12 month recurrence rate	53,90%

rence rate and 12 month recurrence rate the source is Stockfleth et al. 2012,[8] phase III trial H 10056002.

As regards to diclofenac, the source of % complete clearance is Table 14.2.20 Integrated report: Study on the efficacy of Verrumal® compared to placebo and Solaraze® in the treatment of actinic keratosis grade I to II. Instead considering 6 month recurrence rate and 12 month recurrence rate the source is Stockfleth 2009,[20] H1005 6002-0702 report addendum final.pdf: 11.4.7 Efficacy Summary, p. 34.

The source for the data for ingenol mebutate referring to % complete clearance, 6 month recurrence rate and 12 month recurrence rate is Lebwohl et al. 2012, p. 1015. [21]

Focusing on imiquimod the source of data appears to be Vegter et al. 2014, Table 2 [22] for % complete clearance and Hanke et al. 2011,[23] Table 1 for 6 month recurrence rate and 12 month recurrence rate.

The estimated utilities represent health states at different time intervals of the model.

Legend for estimated utilities (representing health status at different model time intervals) are available in **Table 6**. The source for the utilities is Wilson et al. 2010 (**Table 7**). [24]

COST DATA

Costs taken into account in the analysis are € 40,74 for 5-FU-SA (Source Almirall), € 41,27 for Diclofenac (average weighted on real consumption; € 58,23 for Imiquimod and € 61,40 for ingenol mebutate. The source for the last three prices is the Software Tunnel®, Farmadati Italy.[25] In particular drug acquisition costs were derived from official national price lists and ex-factory prices were used (with -5%,-5% mandatory rebates).[25]

TABLE 7
Utilities

Utility	Value
Utility 0cc6r12cc	0.993
Utility 0cc6r12nc	0.990
Utility 0cc6nr12r	0.997
Utility 0cc6nr12nr	1.000
Utility 0nc6nc12cc	0.990
Utility 0nc6nc12nc	0.986

SENSITIVITY ANALYSIS AND BUDGET IMPACT

To assess the importance of the assumptions of the model and the variability of the data used, it was decided to carry out a budget impact analysis in order to evaluate the robustness of the analysis. It was decided to check the potential savings following the entry of 5-FU-SA into the market with hypothetical market shares of 10% for the 1st year, 20% for the 2nd year and 30% for the 3rd year. There is an increasing acknowledgement that a comprehensive economic assessment of a new health-care intervention at the time of launch needs both a cost-effectiveness analysis (CEA) and a budget impact analysis (BIA).[26] Introduction Definition and Intended Use BIAs are increasingly required by reimbursement authorities, along with a Cost Effectiveness Analysis, as part of a listing or reimbursement submission. A budget impact analysis estimates the financial consequences of the adoption of a new intervention in the health care system. Another use of a BIA

TABLE 6
Legend for estimated utilities

Time intervals (months)	0	6	12
0cc6r12cc	Complete clearance	Relapse	Complete clearance
0cc6r12nc	Complete clearance	Relapse	Partial clearance or no clearance
0cc6nr12r	Complete clearance	No relapse	Relapse
0cc6nr12nr	Complete clearance	No relapse	No relapse
0nc6nc12cc	Partial clearance or no clearance	No clearance	Complete clearance
0nc6nc12nc	Partial clearance or no clearance	No clearance	Partial clearance or no clearance

is the budget or resource planning. The BIA can stand alone or together with a CEA in an integrated health economic assessment.[27]

RESULTS

Results regarding costs and health state of 5-FU-SA compared to diclofenac, ingenol mebutate and imiquimod in the treatment of AK were estimated for a time frame of 1 year. The results of the incremental cost and QALYs are shown below.

COST-EFFECTIVENESS RESULT 5-FU-SA VS INGENOL MEBUTATE

Use of 5-FU-SA was a dominant strategy ie, patients receiving 5-FU-SA incurred in lower costs and more) QALYs than patients receiving ingenol mebutate. Indeed: the comparison with ingenol mebutate shows better results both in terms of costs (-€ 21.83 compared to ingenol mebutate) which in terms of total QALYS (ingenol mebutate 0.992 vs 5-FU-SA 0.993), therefore 5-FU-SA is a dominant strategy when compared with ingenol mebutate (**Table 8**, **Figure 2**).

Use of 5-FU-SA was a dominant strategy i.e., patients receiving 5-FU-SA incurred in lower costs and more QALYs than patients receiving diclofenac. In fact, the comparison with diclofenac shows better results both in terms of costs (-€ 16.29 compared to diclofenac) and in terms of total QALYS (diclofenac 0.991 vs 5-FU-SA 0.993), therefore 5-FU-SA is dominant strategy when compared with diclofenac (**Table 9**, **Figure 3**).

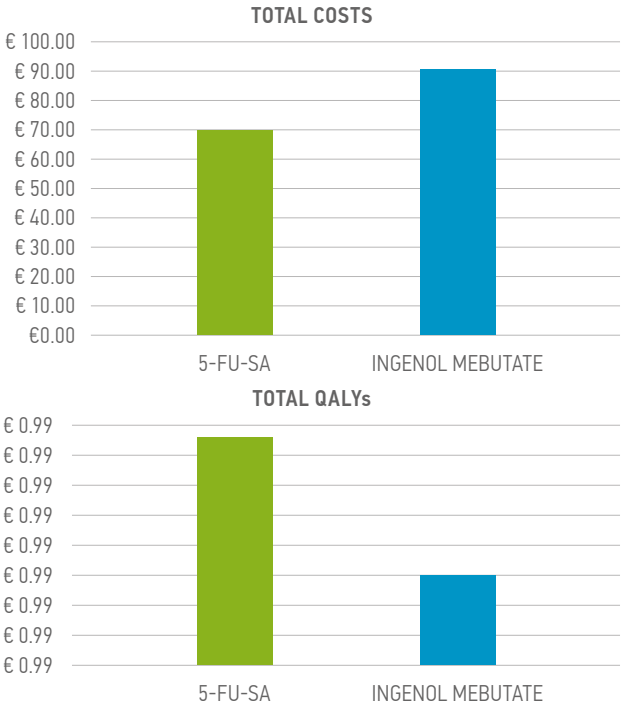
COST-EFFECTIVENESS RESULT 5-FU-SA VS IMIQUIMOD

Use of 5-FU-SA was a dominant strategy, patients receiving 5-FU-SA incurred in lower costs and more QALYs than patients receiving imiquimod. In fact, the comparison with imiquimod shows better results both in terms of costs (-€ 24.92 compared to imiquimod) and in terms of total QALYS (imiquimod 0.991 vs 5-FU-SA 0.993), therefore 5-FU-SA is dominant strategy when compared with imiquimod (**Table 10**, **Figure 4**).

TABLE 8
Cost-effectiveness result 5-FU-SA vs ingenol mebutate

	TOTAL COSTS	TOTAL QALYs
5-FU-SA	€ 69,41	0,993
INGENOL MEBUTATE	€ 91,25	0,992
Incremental costs:	-€ 21,83	
Incremental QALYs:	0,001	
ICER:	Dominant	

FIGURE 2
Total Costs and total QALYs 5-FU-SA vs ingenol mebutate



RESULTS OF THE SIMULATION OF BUDGET IMPACT, A SENSITIVITY ANALYSIS

A budget impact simulation was then carried out to test the real use and robustness of the results of the cost effectiveness analysis for Italian National Health Service.

In the budget impact model (BIM) two different settings are compared: a) without 5-FU-SA introduction, and b) with the introduction of 5-FU-SA simulating market share changes over time. Both the modeling framework and methods are consistent with the recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research's Task Force on Good Research Practices.[26,27] The results are shown below.

TABLE 9
Cost-effectiveness result 5-FU-SA vs diclofenac

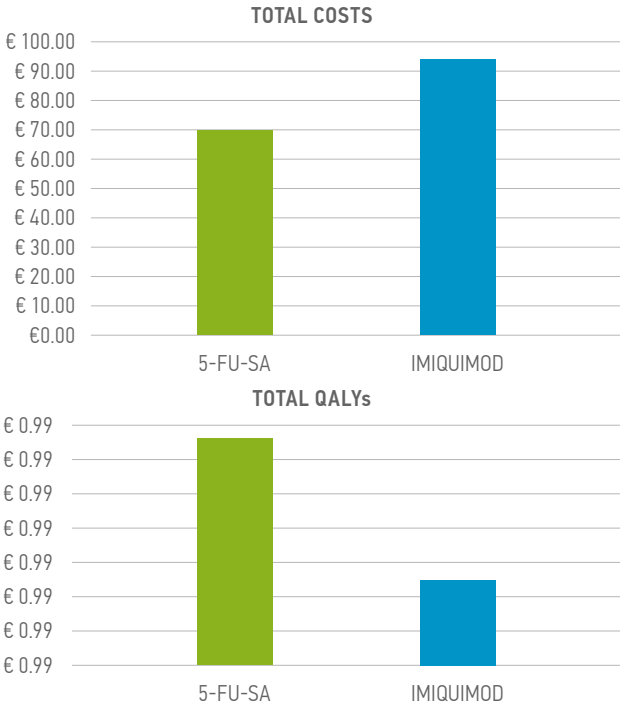
	TOTAL COSTS	TOTAL QALYs
5-FU-SA	€ 69,41	0,993
DICLOFENAC	€ 85,71	0,991
Incremental costs:	-€ 16,29	
Incremental QALYs:	0,002	
ICER:	Dominant	

TABLE 10
Cost-effectiveness result 5-FU-SA vs imiquimod

	TOTAL COSTS	TOTAL QALYs
5-FU-SA	€ 69,41	0,993
IMIQUIMOD	€ 94,34	0,991
Incremental cost:	-€ 24,92	
Incremental QALYs:	0,002	
ICER:	Dominant	

FIGURE 3
Total Costs and total QALYs 5-FU-SA vs diclofenac

FIGURE 4
Total Costs and total QALYs 5-FU-SA vs imiquimod



Following the introduction of 5-FU-SA, comparing with ingenol mebutate in the first year the use of 5-FU-SA in a percentage of 10% vs 90% of ingenol mebutate would lead to a saving of € 379.309. In the second year, going to a percentage equal to 20% of 5-FU-SA would come to have a saving of € 766,204. In the third year, the savings that would be generated following the use of 5-FU-SA equal to 30%, would be € 1,160,799. The total savings would be € 2,036.311 (**Table 11**).

As shown in Table 11 comparing with imiquimod, in the first year the use of 5-FU-SA in a percentage of 10% vs 90% of imiquimod would lead to a saving of € 432.977. In the second year, going to a percentage equal to 20% of 5-FU-SA would come to have a saving of € 874.614. In the third year, the savings that would be generated following the use of 5-FU-SA equal to 30%, would be € 1,325,040 for a total of € 1,263,631.

In comparison with diclofenac, in the first year the use of 5-FU-SA in a percentage of 10% vs 90% of diclofenac would lead to a saving of € 283,082. In the second year, going to a percentage equal to 20% of 5-FU-SA would get to save € 571,826. In the third year, the savings that would be generated following the use of 5-FU-SA equal to 30%, would be € 866,316 for a total of € 1.721,224 (Table 11).

TABLE 11
Result of the sensitivity analysis

Treatment	Scenario WITHOUT 5-FU-SA			Scenario WITH 5-FU-SA		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
5-FU-SA				10.0%	20.0%	30.0%
DICLOFENAC	69.7%	69.7%	69.7%	62.8%	55.8%	48.8%
INGENOL MEBUTATE	25.9%	25.9%	25.9%	23.3%	20.7%	18.1%
IMIQUIMOD	4.4%	4.4%	4.4%	4.0%	3.5%	3.1%
TOTAL	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**
Treatment	Scenario WITHOUT 5-FU-SA			Scenario WITH 5-FU-SA		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
5-FU-SA				17,372	35,089	53,149
DICLOFENAC	121,142	122,341	123,541	109,028	97,873	86,479
INGENOL MEBUTATE	44,920	45,365	45,810	40,428	36,292	32,067
IMIQUIMOD	7,661	7,737	7,813	6,895	6,190	5,469
TOTAL	**173,723**	**175,444**	**177,164**	**173,723**	**175,444**	**177,164**
Treatment	Scenario WITHOUT 5-FU-SA			Scenario WITH 5-FU-SA		
	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
5-FU-SA				€ 1.205,880	€ 2.435,640	€ 3.689,278
DICLOFENAC	€ 10.382,927	€ 10.485,728	€ 10.588,530	€ 9.344,634	€ 8.388,583	€ 7.411,971
INGENOL MEBUTATE	€ 4.098,887	€ 4.139,470	€ 4.180,053	€ 3.688,998	€ 3.311,576	€ 2.926,037
IMIQUIMOD	€ 722,732	€ 729,887	€ 737,043	€ 650,459	€ 583,910	€ 515,930
TOTAL	**€ 15.204,546**	**€ 15.355,086**	**€ 15.505,626**	**€ 14.889,971**	**€ 14.719,708**	**€ 14.543,216**
Delta				€ -314,574	€ -635,377	€ -962,410
				-2.07%	-4.14%	-6.21%

As shown in Table 11, treatment with 5-FU-SA would result in a total savings of 2.07% in the first year, equal to € 314.574, which would become 4.14% in the second year with a saving of € 635.377. Finally, the third year the introduction of 5-FU-SA in the market would generate savings for € 962.410 (6.21%).

DISCUSSION

The actinic keratosis is a growing incidence worldwide, is the second type of cancer that covers the skin most commonly diagnosed. It is defined as squamous cell carcinoma in situ (SCS) of the skin. Within the recent past, we have seen for the first time that starting from a mechanism of differentiation of origin, also the lesions of AK I have a potential risk of direct progression towards an invasive squamous cell carcinoma. For this reason, early treatment of AK of all severity is recommended.[28]

Actinic keratoses (AK) are defined as dysplastic lesions limited to epidermal keratinocytes and fall into squamous cell carcinomas in situ. The AKs mostly affect subjects who expose themselves chronically to sunlight, especially those with skin types 1 or 2 on the scale of the Fitzpatrick skin type.[29]

DNA mutations induced by UVB light cause the suppression of tumor suppressor proteins such as P53, whose mutation appears to be the main cause of clonal expansion of keratinocytes, which leads to AK.[30]

Single or, more commonly, multiple actinic keratoses are slow-growing papules or plaques that are usually <1 cm in diameter, dry, of the same color as the skin

or erythematous, teleangectasic, with some covered in yellowish or brown scales.[31]

Despite the paucity of studies on the natural history of AK, it is clear that up to 10% of lesions can degenerate over time into invasive squamous cell carcinoma (SCC), that this risk increases over time, and that subclinical lesions in the photo-damaged area can also degenerate into SCC, in accordance with the concept of "field cancerisation".[16,31,32]

Actinic keratoses are primarily treated in oder to not progress towards SCC, but also for cosmetic purposes and to remove symptoms like pain and itching.

Although some SCC lesions are clinically indistinguishable from AK lesions,[31] certain clinical features raise suspicion of SCC and warrant biopsy. These include bleeding, ulceration, hardening of the lesion, diameter >1 cm, rapid increase in volume and erythema.[33,34]

Treatments for AK can be divided into self-applied topical therapies and surgical or ablation therapies. Surgical or ablation therapies are indicated for single lesions but are not effective on areas of field cancerisation.

Among the topical therapies that treat an entire area of the affected skin, there are currently: diclofenac sodium gel, 5-fluorouracil cream, 5-fluorouracil and acetylsalicylic solution, imiquimod cream and ingenol mebutate gel.

All actinic keratoses and the field of cancerization must be treated. There are medical treatments with scientifically proven efficacy and tolerability as far as their action mechanism, pharmacological characteristics and radically different approval status are concerned. The knowledge of the characteristics of the single therapies and the needs of the individual patients allow individualizing the treatment, optimizing compliance and therefore obtaining the best therapeutic result.[35]

Since in recent times there are more and more treatment options for AK, the choice that is made of one treatment regimen rather than another must take into account the patient's preferences, in relation to the therapeutic program, to the tolerance of side effects and must also take treatment costs into account. Among the critical aspects are the characteristics of the AK lesions such as distribution, number and thickness, furthermore there is the past history of each patient of treatment and relapses.[36]

5-FU-SA, is indicated for the topical treatment of slightly palpable and/or moderately thick hyperkeratotic actinic keratosis (grade I/II) of the face, forehead, and balding scalp in immunocompetent adult patients.

Literature data suggest that 5-FU-SA is an option more effective treatment compared to currently available treatments for both histological outcomes, complete clearance of lesions, reduced relapse rate and good tolerability profile.

Various clinical trials have shown the efficacy and safety of 3% diclofenac in both immunocompetent and immunosuppressed patients, ingenol mebutate, and of 3.75% imiquimod. One important factor to consider is the duration of treatment, with a short course of therapy that may reduce the burden of treatment and increase patients' adherence.

The present pharmacoeconomic analysis denotes that in the Italian health care service, with comparable efficacy, 5-fluorouracil 0.5% and salicylic acid 10.0% is as effective and less expensive than either ingenol mebutate or imiquimod, or diclofenac sodium. There are few limitations in this study: the most important regards the short time horizon of the analysis. In the BIA, according to the INHS perspective, only direct costs are included. Considering the impact on the productivity of these diseases, the potential savings, if we consider the big impact these diseases have on productivity, would certainly be higher if indirect costs were included. It would therefore be important to define the total costs, differentiating how the direct costs are composed and demonstrating what the real burden is for Italian society and for patients. Although the sensitivity analysis confirmed the robustness of results, real world evidence could further confirm our assumptions and results in future.

Factors to be taken into account when deciding a patient's treatment: Treatment preferences, Immunosup-

pression status, age, manual capacity, need of a caregiver, wish of cosmesis, motivations for treatment.[37] The inferior cost associated with 5-fluorouracil 0.5% and salicylic acid 10.0% treatment and the improvement in QALYS should be an important consideration to take into account when choosing the right therapy for the patient.

In conclusion, the economic assessment carried out shows that therapy with 5-FU-SA involves an improvement in the quality of life of patients and overall represents in Italy a cost-effective treatment option for the treatment of patients affected by actinic keratoses.

FUNDINGS

This analysis was funded by Almirall, Italy.

CONFLICT OF INTERESTS

GLC, GMB, SDM, CV, MO, CM are employees of S.A.V.E. S.r.l and consultants for Almirall. GLC has received research and educational grants from Amgen, Abbott, Eisai, Novonordisk, Menarini Ricerche, Otzuka, JazzPharma.

REFERENCES

1. Annabel Dodds, Alvin Chia, Stephen Shumack, *Actinic Keratosis: Rationale and Management.* Dermatol Ther (Heidelb) (2014) 4:11–31.
2. Samrao A, Cockerell J, *Pharmacotherapeutic management of actinic keratosis: focus on newer topical agents.* Am J Dermatol. 2013;14:273–7.
3. Werner RN, Stockfleth E, Connolly SM et al., (2015) *Evidence- and consensus-based (S3) guidelines for the treatment of actinic keratosis: International League of Dermatological Societies in cooperation with the European Dermatology Forum: Short version.* Journal of the European Academy of Dermatology and Venereology 29(11): 2069–2079.
4. D. de Berker, *British Association of Dermatologists' guidelines for the care of patients with actinic keratosis* 2017.
5. Stockfleth E, Ortonne JP, Alomar A, (2011) *Actinic keratosis and field cancerisation.* European Journal of Dermatology 21(Suppl. 1): 3–12.
6. Buckman SY, Gresham A, Hale P et al., (1998) *COX-2 expression is induced by UVB exposure in human skin: Implications for the development of skin cancer.* Carcinogenesis 19: 723–729.
7. Fecker LF, Stockfleth E, Braun FK et al., (2010) *Enhanced death ligand-induced apoptosis in cutaneous SCC cells by treatment with diclofenac/hyaluronic acid correlates with downregulation of c-FLIP.* Journal of Investigative Dermatology 130(8): 2098–2109.
8. Stockfleth E, Ferrandiz C, Grob JJ et al., (2008) *Development of a treatment algorithm for actinic keratoses: A European consensus.* European Journal of Dermatology 18(6): 651–659.
9. Lebwohl M, Swanson N, Anderson LL et al., (2012) *Ingenol mebutate gel for actinic keratosis.* New England Journal of Medicine 366(11): 1010–1019.
10. Navi D, Huntley A, (2004) *Imiquimod 5 percent cream and the treatment of cutaneous malignancy.* Dermatology Online Journal 10(1): 4.
11. Gazzetta ufficiale del 25 settembre 2018 come aggiornamento della nota 95 dell'Agenzia Italiana del Farmaco.
12. Stockfleth E et al., *Phase IV head-to-head randomized controlled trial comparing ingenol mebutate 0·015% gel with diclofenac sodium 3% gel for the treatment of actinic keratosis on the face or scalp.* Br J Dermatol. 2018;178(2):433-442.
13. Swanson N et al., *Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: results of two placebo-controlled studies of daily application to the face and balding scalp for two 2-week cycles.* J Am Acad Dermatol 2010;62:582-90.
14. Wolf JE et al., *Topical 3.0% diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratoses.* Int J Dermatol. 2001 Nov;40(11):709-13.
15. Krawtchenko N et al., *A randomised study of topical 5% imiquimod vs. topical 5-fluorouracil vs. cryosurgery in immunocompetent patients with actinic keratoses: a comparison of clinical and histological outcomes including 1-year follow-up.* Br J Dermatol 2007; 157 Suppl: 34–40.
16. Stockfleth E et al., *Reduction in lesions from Lmax: a new concept for assessing efficacy of field-directed therapy for actinic keratosis.* Results with imiquimod 3.75%. Eur J Dermatol 2014;24:23-7.

17. Stockfleth E et al., *Efficacy and Safety of 5-Fluorouracil 0.5%/Salicylic Acid 10% in the Field-Directed Treatment of Actinic Keratosis: A Phase III, Randomized, Double-Blind, Vehicle-Controlled Trial.* Dermatol Ther (Heidelb). 2017;7(1):81-96.).
18. Geodemo DATA ISTAT.
19. Naldi et al, *Prevalence of Actinic Keratoses Italian Study Arch Dermatol.* 2006 Jun;142(6):722-6
20. Stockfleth *Topical management of actinic keratosis and field cancerisation.* G Ital Dermatol Venereol. 2009 Aug;144(4):459-62.
21. Lebwohl et al. *Ingenol Mebutate Gel for Actinic Keratosis* N Engl J Med 2012; 366:1010-1019.
22. Vegter S, Tolley K.A *network meta-analysis of the relative efficacy of treatments for actinic keratosis of the face or scalp in Europe.* PLoS One. 2014 Jun 3;9(6):e96829. doi: 10.1371/journal.pone.0096829. eCollection 2014.
23. Hanke et al. C*omplete clearance is sustained for at least 12 months after treatment of actinic keratoses of the face or balding scalp via daily dosing with imiquimod 3.75% or 2.5% cream.* J Drugs Dermatol. 2011 Feb;10(2):165-70.
24. Wilson et al., *Cost Effectiveness of Imiquimod 5% Cream Compared with Methyl Aminolevulinate-Based Photodynamic Therapy in the Treatment of Non-Hyperkeratotic, Non-Hypertrophic Actinic (Solar) Keratoses A Decision Tree Model*. November 2010, Volume 28, Issue 11, pp 1055–1064.
25. Software Tunnel®, Farmadati Italy.
26. Sullivan SD, Mauskopf JA, Annemans L et al., *Principles of Good Practice for Budget Impact Analysis: Report of the ISPOR Task Force on Good Research Practices - Budget Impact Analysis.* Value Health 2007; 10:5:336-47.
27. Sean D. Sullivan, Josephine A. Mauskopf, Federico Augustovski, J. Jaime Caro, Karen M. Lee, Mark Minchin, Ewa Orlewska, Pete Penna, Jose-Manuel Rodriguez Barrios, Wen-Yi Shau, *Budget Impact Analysis - Principles of Good Practice: Report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force, Value in Health, Volume 17, Issue 1*, 2014, Pages 5-14, ISSN 1098-3015.
28. U. Reinhold, *Low-dose 5-fluorouracil in combination with salicylic acid for the treatment of actinic keratoses on the hands and/or forearms - results of a non-interventional study.* JEADV 2016.
29. WHO: Skin cancers. 2016, http://www.who. int/uv/faq/skincancer/en/index1.html (accessed July 30, 2016.
30. Nomura T, Nakajima H, Hongyo T, Taniguchi E, Fukuda K, Li LY, Kurooka M, Sutoh K, Hande PM, Kawaguchi T, Ueda M, Takatera H, *Induction of cancer, actinic keratosis, and specific p53 mutations by UVB light in human skin maintained in severe combined immunodeficient mice.* Cancer Res. 1997 Jun 1;57(11):2081-4.
31. Rossi R, Mori M, Lotti T, *Actinic keratosis.* Int J Dermatol. 2007 Sep;46(9):895-904.
32. Criscione VD, Weinstock MA, Naylor MF, Luque C, Eide MJ, Bingham SF; Department of Veteran Affairs Topical Tretinoin Chemoprevention Trial Group. *Actinic keratoses: Natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial.* Cancer. 2009 Jun 1;115(11):2523-30.
33. Werner RN, Stockfleth E, Connolly SM, Correia O, Erdmann R, Foley P, Gupta AK, Jacobs A, Kerl H, Lim HW, Martin G, Paquet M, Pariser DM, Rosumeck S, Röwert-Huber HJ, Sahota A, Sangueza OP, Shumack S, Sporbeck B, Swanson NA, Torezan L, Nast A; International League of Dermatological Societies; European Dermatology Forum. *Evidence- and consensus-based (S3) Guidelines for the Treatment of Actinic Keratosis - International League of Dermatological Societies in cooperation with the European Dermatology Forum - Short version.* J Eur Acad Dermatol Venereol. 2015 Nov;29(11):2069-79.
34. Quaedvlieg PJ, Tirsi E, Thissen MR, Krekels GA, *Actinic keratosis: how to differentiate the good from the bad ones?* Eur J Dermatol. 2006 Jul-Aug;16(4):335-9.)
35. Dirschka T, Gupta G, Micali G, *Real-world approach to actinic keratosis management: practical treatment algorithm for office-based dermatology.* J Dermatolog Treat. 2017 Aug;28(5):431-442.
36. G. L. Colombo, S. Chimenti, S. Di Matteo, M. C. Fargnoli, P. Frascione, V. Silipo, K. Peris, *Cost-effectiveness analysis of topical treatments for actinic keratosis in the perspective of the Italian health care system*, G Ital Dermatol Venereol 2010;145.
37. Calzavara-Pinton P, Zane C, Pacou M, Szeimies RM, *Bucher's indirect comparison of daylight photodynamic therapy with methyl aminolevulinate cream versus diclofenac plus hyaluronic acid gel for the treatment of multiple actinic keratosis.* Eur J Dermatol 2016; 26: 487–92.

CENTRO DI RICERCA | STUDI ANALISI VALUTAZIONI ECONOMICHE
Health Economics & Outcomes Research

www.clinicoeconomics.eu | www.savestudi.it | www.savedigital.it